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EDITORIAL

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Managing Editor Tamara C. Faggen:

Cover Impressions

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DEPARTMENTS

JMCP Peer Reviewers, 2005

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Wolfgang A. Ritschel, PhD, has been chosen as the cover artist for JMCP’s annual issue featuring artists with a pharmaceutical or medical background. Ritschel worked in the medical sciences for more than 40 years before deciding to spend all of his time on his artwork. “I am happy and thankful to be able to devote my full time and energies to a life as an Expressionist painter and sculptor. My wife and I travel a lot in our van across beautiful America to catch impressions of our great land and its people. Other travels take us overseas, and I always return enriched and inspired, with numerous sketches and paintings to be completed in my studio in downtown Cincinnati,” he says.

Born in Trautenau, Bohemia, and reared in Vienna, Austria, Ritschel has had a passion for art since he was a child. His older sister was an artist whose work inspired the young Ritschel. The other notable artist in his family was his great-grandfather, a wood carver at the Imperial Court in Vienna. Ritschel began his formal training in fine art and art history as an undergraduate at the University of Vienna, where he received a doctorate degree in philosophy. He also studied painting with Professor Anton Boehm at the Art Academy of Vienna. Ritschel continued his studies, this time in the medical field, receiving a doctorate degree in pharmacology from the University of Strasbourg, France, and a doctorate degree in medicine and a magister degree in pharmacy from the University of Innsbruck, Austria. Ritschel, www.wolfgangritschel.com. He loves teaching and has given numerous art lectures and demonstrations at diverse locations, including national and international health science meetings. Ritschel maintains a studio at the Pendleton Art Center in downtown Cincinnati.

Ritschel’s ability to unite his medical and art careers is related to two studies that he conducted in the Andes Mountains during the late 1990s. His first study, which was accomplished with the help of researchers from the University of Chile in Santiago, concerned the effects of medication upon subjects who either live at high altitudes or live at sea level and travel to high altitudes. His second study was about the perception of increased color intensity encountered at high altitudes. Ritschel’s evaluation revealed that color appears to be brighter and more intense at higher altitudes primarily because of the lack of dust and water particles in the air. This revelation has greatly influenced his artwork. “My signature style is characterized by the Fauvistic use of bright colors, strong defining contours, and sharp contrasts of light and shadow,” Ritschel says.

“Vibrant, metropolitan cities are among his favorite subjects. In To Be Together, Ritschel has captured the vibrancy of the Montmartre hill in Paris in brilliant jewel tones, yet the scene conveys a peaceful mood at the same time. The painting’s focus is a couple strolling down the street hand in hand, silhouetted by glowing streetlights. “The beauty and romanticism of a couple being partners in life and caring for each other—undertaking the journey of life together—these are the elements that were the inspiration for my composition,” he says.

Truly a modern “Renaissance man,” Ritschel possesses talents and skills in many disciplines. During his academic career, he wrote 14 books and published more than 450 articles. He now enjoys tremendous success as an artist, with more than 60 solo exhibitions to his credit in the United States, Europe, and South America, and approximately 250 group exhibitions worldwide. Ritschel’s art can be found at the Pendleton Art Center Gallery Studio 713 in Cincinnati, the Ward-Nasse Gallery in New York City, and the Art Museum Store in the Art Museum of Las Vegas. His colorful online gallery can be seen on his Web site, Expressionist Paintings & Sculpture: Wolfgang A. Ritschel, www.wolfgangritschel.com. He loves teaching and has given numerous art lectures and demonstrations at diverse locations, including national and international health science meetings. Ritschel maintains a studio at the Pendleton Art Center in downtown Cincinnati.

Sheila Macho
Cover Editor

COVER CREDIT
Wolfgang A. Ritschel, PhD, To Be Together, acrylic on canvas, 61 x 46 cm, Code FR-132, Cincinnati, Ohio. Copyright© 2003. (Private collection of Dr. Greg Kearns and Dr. Kathleen Neville, Platte City, Missouri.)

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Interview with the artist www.wolfgangritschel.com.
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- abstract: no more than 500 words
- keywords: follows the abstract
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- tables and figures (generally no more than a total of 6). Submit referenced tables and figures on separate pages with titles (and captions, as necessary) at the end of the manuscript, match symbols in tables and figures to explanatory notes, if included. May use 10-point font
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REFERENCE

A 30-Month Evaluation of the Effects on the Cost and Utilization of Proton Pump Inhibitors From Adding Omeprazole OTC to Drug Benefit Coverage in a State Employee Health Plan

DONNA S. WEST, RPh, PhD; JILL T. JOHNSON, PharmD, BCPS; and SONG HEE HONG, PhD

ABSTRACT

OBJECTIVE: On March 1, 2004, the state employee health plan began covering omeprazole OTC (over the counter) at a $5 copayment. Reimbursement to pharmacy providers for omeprazole OTC increased by $10.50 per claim, from $2.50 to a $13 dispensing fee. Initially, neither generic omeprazole prescription (Rx) nor brand omeprazole Rx was covered because omeprazole OTC was available in the same strength as the Rx products at a lower cost, but an omeprazole OTC shortage necessitated coverage of generic omeprazole Rx at a $10 copay. The objective of this study was to evaluate the long-term financial impact of a drug benefit policy change on a mid-size state employee health plan and its beneficiaries associated with the addition to coverage of omeprazole OTC.

METHODS: The pharmacy claims database for the employee benefits division (EBD) was used to examine utilization and cost data for beneficiaries who received proton pump inhibitors (PPIs). Pharmacy claims for the 30-month period for dates of service from December 1, 2002, through May 31, 2005, were extracted from the database, yielding a preperiod of 15 months and a postpolicy change period of 15 months.

RESULTS: In the 15-month postperiod, the number of PPI claims per member per month (PMPM) decreased by 3.9%, but the days of PPI therapy PMPM increased from 1.71 to 1.82 (6.4%). Price as measured by the allowed charge per day of drug therapy decreased from $4.25 to $2.74 (35.6%) despite an increase of $1.89 (76%) in the average dispensing paid per PPI claim to pharmacies, from $2.49 to $4.38. The average beneficiary copayment decreased by $0.50 (2.0%) per PPI claim, from $2.50 in the preperiod to $2.46 per claim in the postperiod. Therefore, the net health plan cost for PPIs decreased by $2.20 PMPM (37.6%) during the 15-month postperiod, from $5.84 to $3.64 PMPM, producing savings of $4,207,350, or annualized savings of $3,365,880, in this employee benefit plan during the 15-month postperiod, from $5.84 to $3.64 PMPM, producing savings of $4,207,350, or annualized savings of $3,365,880, in this employee benefit plan of 127,495 members.

CONCLUSION: A change in policy to include coverage of omeprazole OTC and an increase in pharmacy reimbursement for omeprazole OTC resulted in 38% net savings to a state employee health plan. The large decrease in drug acquisition cost between omeprazole OTC and the other Rx-only PPIs made it possible to implement a program intervention that provided financial benefit to pharmacists, beneficiaries, and the drug plan sponsor despite a 6% increase in PPI utilization.

KEYWORDS: Proton pump inhibitors, OTC medications, Rx copayments, Rx utilization

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In recent years, there has been an increase in the number of products switched from prescription (Rx)-only to over-the-counter (OTC) status, increasing the potential for coverage of OTC products in Rx drug benefits. Specifically, the availability of omeprazole (Prilosec) OTC in the same strength as omeprazole Rx, presents a potential opportunity for health plans to cover an OTC product. As a class, proton pump inhibitor (PPI) products ranked second in overall retail sales, at $11.9 billion in 2002 and nearly $12.8 billion in 2003. The patent on omeprazole Rx expired in October 2001, but litigation kept generic omeprazole off the market until December 2002, and the price of generic omeprazole Rx has not been significantly less than brand-name omeprazole Rx.

The U.S. Food and Drug Administration (FDA) announced on October 31, 2003, that it had approved omeprazole OTC for sale in the popular 20 mg strength, and by July 2004, omeprazole could be purchased for $0.63 per tablet for a 42-day supply, less than 20% of the price of the alternative PPIs. Thus, health plans have considered covering the less-expensive omeprazole OTC with the opportunity to treat 5 patients with omeprazole OTC for the same cost as treating 1 patient with an alternative brand PPI.

We initially reported on the Arkansas State Employee Benefits Division’s (EBD, Little Rock) decision to cover omeprazole OTC beginning in March 2004. The EBD covered approximately 129,500 members with Rx benefits and had an annual drug budget of $74.6 million in 2003. PPIs represented 12% ($8.9 million) of the pharmaceutical costs for the EBD in 2003. Using clinical evidence from systematic literature reviews, the Drug Utilization Evaluation (DUE) Committee for the EBD concluded that all PPIs were therapeutically equivalent in efficacy and safety. Based on cost considerations, the DUE Committee recommended making omeprazole OTC the preferred drug among PPIs. The EBD was paying, on average, more than $90 per prescription PPI (e.g., average brand omeprazole Rx cost to the EBD was $123.40 and average generic omeprazole Rx cost was $91.71 in February 2004). Because the average wholesale price (AWP) was significantly lower for omeprazole OTC, it was estimated that the OTC product would save more than $40 per claim. The EBD administrator adopted the benefit change to cover omeprazole OTC, effective March 1, 2004.

Based on the results of the first 2 months of omeprazole OTC coverage, we projected that the EBD would save approxi-
approximately $3,978,240 annually for an average eligible membership of 127,500.\textsuperscript{7} This initial projection was based on the original benefit design that included OTC coverage but not coverage of generic omeprazole Rx. However, because of the shortage of omeprazole OTC, the benefit design was later modified, effective October 1, 2004, to include coverage of both omeprazole OTC and generic omeprazole Rx.

### Methods

The purpose of this study was to evaluate the longer-term financial impact of the Arkansas State EBD policy change on the health plan and its beneficiaries by examining the utilization and cost of PPIs during the 15 months prior to and 15 months following implementation of omeprazole OTC coverage on March 1, 2004.

### The Pharmacy Benefit Design for PPIs

Prior to omeprazole OTC coverage in March 2004, generic omeprazole Rx was covered in the first tier with a $10 copayment; rabeprazole, esomeprazole, and brand omeprazole Rx were covered in the second tier with a $25 copayment; and lansoprazole and pantoprazole were covered in the third tier with a $50 copayment (Table 1). EBD reimbursement to pharmacies was based upon a product (ingredient) cost rate of AWP minus 13\% plus a $2.50 dispensing fee for single-source brand PPI drugs and generic omeprazole Rx.

The DUE Committee for the EBD not only recommended making omeprazole OTC the preferred drug but also changed the beneficiary copayment and pharmacy reimbursement structure to encourage use of omeprazole OTC. The EBD administrator adopted these policy recommendations, as outlined in Table 1. The OTC-tier copayment and reimbursement structure changes became effective March 1, 2004. To allow time for the benefit change to be communicated to all stakeholders, the copayment changes for the Rx PPI drugs were implemented 2 weeks later, on March 15, 2004. As noted in Table 1, coverage of generic omeprazole Rx was discontinued initially, except that a $25 copayment was permitted for the 10 mg (capsule) strength. Neither generic omeprazole Rx nor brand omeprazole Rx was covered because omeprazole OTC was available in the same strength as the Rx products, at a significantly lower cost.

The benefit was designed with the intent to provide a beneficiary incentive to switch from Rx-only PPIs to omeprazole OTC and to facilitate pharmacy participation. The financial incentive for the beneficiary was significant. Not only did the new omeprazole OTC have a $5 copay per Rx but it also provided longer days of therapy per Rx (i.e., 42- vs. 30-days supply). A 42-day supply of omeprazole was provided because of the OTC product packaging. Since only 9 omeprazole OTC claims (of 42 units each) would be necessary per PPI-utilizing member per year, there was an expected reduction of 3 PPI
claims per year per beneficiary switched from an Rx PPI to omeprazole OTC. To encourage pharmacists to facilitate the switch from an Rx PPI to omeprazole OTC, a $13 dispensing fee per claim for omeprazole OTC was implemented. The purpose of this larger dispensing fee was to ensure that switching beneficiaries from an Rx to OTC product would be at least revenue-neutral and perhaps revenue-favorable for the pharmacy provider. With the $13 dispensing fee, the dollar gross margin for omeprazole OTC would be similar to the other PPIs. The higher dispensing fee was also perceived as helping to compensate pharmacists for the extra work in switching patients, which involved calling prescribers to obtain an Rx for omeprazole OTC but thereby avoided the need for a physician office visit.

Within 2 months of implementation of the policy changes, there was a shortage of omeprazole OTC. Reacting to the marketplace and considering product availability, the EBD modified the PPI benefit design. Effective June 1, 2004, generic omeprazole Rx was covered at a $10 copay for a 30-day supply, and pharmacies were reimbursed AWP-13% + $2.50 for generic omeprazole Rx. On October 1, 2004, the EBD changed its pharmacy benefit manager (PBM), and the reimbursement structure for generic omeprazole Rx changed to the lesser of AWP-13% + $2.50 or maximum allowable cost (MAC) + $2.50. The MAC price was set at $1.49 per capsule.

There was originally an appeals process for physicians on behalf of a plan beneficiary to request a brand Rx PPI at a lower copayment ($25). Receipt of an Rx PPI at a lower copayment required verification of the diagnosis of Zollinger-Ellison (ZE) syndrome or other hypersecretory condition. The physician had to inform the EBD of the patient’s condition and request approval for the higher-cost PPI at a lower copayment. Although omeprazole is effective and approved by the FDA for ZE syndrome and other hypersecretory conditions, there were insufficient data to directly compare the effectiveness of omeprazole to the other PPIs so these diagnoses were originally established as sufficient criteria for a successful appeal. Although several appeals were submitted, none met the criteria and were therefore denied. At this time, a diagnosis of ZE or other hypersecretory condition is no longer accepted as the basis for appeal since all PPI drugs are still available to each member, at a higher copay.

The Rx claims database for the EBD was used to examine utilization and cost data for beneficiaries who received Rxs for PPIs. Summary data included the number of Rxs for each PPI, total ingredient cost, total dispensing fee, total allowed charge, total copayment, and total amount paid by the EBD (net EBD cost). Data for claims with dates of service from December 1, 2002, to May 31, 2005, were extracted from the database, reflecting the 15 months prior to policy implementation and the 15 months following policy implementation. March 1, 2004, was considered the start date of OTC coverage, although the entire benefit change was phased in over a 2-week period, as previously mentioned. These data were assessed to determine market share changes after policy implementation and the resulting shifts in ingredient costs, dispensing fees, amount paid by the plan, and amount paid by the beneficiary (copayment). Prescriptions per member per month (PMPM), days of therapy PMPM (days PMPM), charge PMPM, charge per prescription,
charge per day, copay per prescription, net PMPM, and net cost per days of therapy were then calculated. Frequencies and derived measures are reported.

Results
Within a month of the policy decision, omeprazole OTC accounted for more than 55% of all PPI pharmacy claims, eliminating almost all of the omeprazole Rx claims (Figure 1). Further, the implementation of the omeprazole OTC coverage cut the Rx market share of esomeprazole in half and even replaced one third of all other brand Rx PPI claims. As a result, the initial financial impact of the policy change amounted to the savings of $40.86 per PPI claim or $270,440 per month.7 However, the initial savings of that magnitude were undercut by the shortage of omeprazole OTC immediately following the OTC coverage decision. The EBD put generic omeprazole Rx into the first tier of copayment in a prompt response to the OTC shortage. The preferential treatment of generic omeprazole Rx allowed the generic to recover most of its share lost to omeprazole OTC while compromising the potential for omeprazole OTC to save the plan money. By November 2004, the market share of generic omeprazole Rx had increased to approximately 28% from 0% in April 2004. On the other hand, the share for omeprazole OTC was more than 50% in April 2004 but decreased to about 28% in November 2004. As the shortage eased, omeprazole OTC gradually regained some of its lost share, to about 41% of the Rx share of PPIs by the end of the 15-month follow-up period (Figure 1).

The share that omeprazole OTC captured of the PPI market was translated into dollar savings (Figure 2). The amount paid by the plan showed a sharp drop in the first month of the OTC coverage benefit. The plan paid about $700,000 per month for all PPI claims before the implementation but paid less than $400,000 immediately following the implementation. Although the paid amounts increased to about $500,000 per month during the OTC shortage, they gradually began to decrease as the shortage eased around November 2004. Savings were realized without shifting costs to providers or beneficiaries. Following the OTC coverage decision, the fees for pharmacist dispensing had increased, and the out-of-pocket costs for beneficiaries had decreased. However, the trend of paid amounts by the EBD showed a direct relationship to total ingredient costs; total ingredient costs and paid amounts moved together throughout the study period.

### TABLE 2

| 3-Month Periods | Member-Months | Rxs | Days Supply | Days/Rx | Ingredient Cost ($)† | Dispensing Fee ($)‡ | Allowed Charge ($)§ | Copayment ($) | EBD Cost ($)|| |
|------------------|---------------|-----|-------------|---------|----------------------|--------------------|---------------------|---------------|-----------------|
| Preperiod        |               |     |             |         |                      |                    |                     |               |                 || |
| Dec. 02-Feb. 03  | 385,824       | 20,267 | 611,166     | 30.2    | 2,523,198           | 46,817             | 2,570,015           | 523,682    | 2,048,571       || |
| Mar. 03-May 03   | 377,196       | 21,537 | 650,250     | 30.2    | 2,702,482           | 51,462             | 2,753,944           | 532,433    | 2,223,882       || |
| Jun. 03-Aug. 03  | 367,427       | 22,219 | 671,186     | 30.2    | 2,810,632           | 54,802             | 2,865,434           | 545,813    | 2,322,108       || |
| Sep. 03-Nov. 03  | 373,686       | 21,254 | 642,783     | 30.2    | 2,703,263           | 53,590             | 2,756,859           | 527,503    | 2,231,766       || |
| Dec. 03-Feb. 04  | 383,556       | 21,471 | 650,256     | 30.3    | 2,690,087           | 59,120             | 2,749,207           | 546,164    | 2,205,483       || |
| Preperiod total  | 1,887,689     | 106,748 | 3,225,641 | 30.2    | 13,429,662          | 265,797            | 13,695,459          | 2,675,595  | 11,031,810      || |
| Postperiod       |               |     |             |         |                      |                    |                     |               |                 || |
| Mar. 04-May 04   | 387,615       | 20,424 | 706,356     | 34.6    | 1,508,718           | 130,278            | 1,638,996           | 444,615    | 1,196,575       || |
| Jun. 04-Aug. 04  | 376,318       | 19,743 | 667,830     | 33.8    | 1,658,204           | 114,400            | 1,772,604           | 480,918    | 1,293,880       || |
| Sep. 04-Nov. 04  | 378,583       | 20,871 | 684,402     | 32.8    | 1,936,187           | 82,277             | 2,018,464           | 532,149    | 1,487,231       || |
| Dec. 04-Feb. 05  | 384,706       | 21,425 | 706,233     | 33.0    | 1,992,011           | 67,707             | 2,059,718           | 548,118    | 1,511,798       || |
| Mar. 05-May 05   | 385,210       | 21,444 | 714,218     | 33.3    | 1,965,334           | 60,424             | 2,025,758           | 546,339    | 1,479,644       || |
| Postperiod total | 1,912,432     | 103,907 | 3,479,039  | 33.5    | 9,060,454           | 455,086            | 9,515,540           | 2,552,139  | 6,969,128       || |
| Change           | 24,743        | -2,841 | 253,398     | 10.9    | -4,369,208          | 189,289            | -4,179,919          | 123,456    | -4,062,682      || |
| % change         | -1.3%         | -2.7%  | 7.9%        | 10.9%   | -32.5%              | 71.2%              | -30.5%              | 4.6%       | -36.8%          || |

* P values could not be calculated for these summary data for the population of all EBD beneficiaries.
† Drug ingredient cost reimbursement to pharmacies is average wholesale price-13%.
‡ Dispensing fee may be greater than set reimbursement rate of $2.50 because of generic incentive programs that pay a higher dispensing fee in this state employee health plan.
§ Allowed charge is the sum of the pharmacy professional fee plus the drug ingredient cost.
|| Net EBD costs are slightly higher than the allowed charge minus copayment because the net EBD cost includes the administrative fee paid to the pharmacy benefits manager for processing the pharmacy claims.
EBD = employee benefits division; OTC = over the counter; PPI = proton pump inhibitor; Rx = prescription.
A 30-Month Evaluation of the Effects on the Cost and Utilization of Proton Pump Inhibitors
From Adding Omeprazole OTC to Drug Benefit Coverage in a State Employee Health Plan

The number of PPI claims for the 15 months following policy implementation decreased by 2,841 (2.7%) over the prior 15-month period (Table 2). The number of claims likely decreased because of the omeprazole OTC commercial packaging, which allowed the beneficiary to receive a 42-day supply, thereby reducing the number of prescriptions needed per utilizing member per year. In fact, the average days of therapy per prescription increased by 10.9% (from an average of 30.2 days per PPI claim in the preperiod to 33.5 days per PPI claims in the postperiod). Utilization of PPIs adjusted for membership changes decreased by 3.9%, from 0.057 Rxs PMPM to 0.054 but increased by 6.5% in days of PPI therapy PMPM, from 1.71 in the preperiod to 1.82 in the postperiod (Table 3).

Price, as measured by the average allowed charge (drug cost plus pharmacy dispense fee) per PPI claim, dropped by 28.6% ($36.72), from $128.30 in the 15-month preperiod to $91.58 in the 15-month postperiod. Adjusted for change in days supply, the price per PPI day of therapy dropped by 35.6% ($1.51), from $4.25 in the preperiod to $2.74 in the postperiod. After consideration of the average $0.50 (2.0%) decrease in member cost-share per PPI claim (from $25.06 to $24.56), the net plan cost per day of PPI drug therapy dropped by 41.4% ($1.42 per day) to $2.00 in the postperiod. Adjusted for membership, the net plan cost PMPM decreased by $2.20 (37.6%) to $3.64 PMPM in the postperiod compared with $5.84 in the preperiod (Table 3). Therefore, during this 15-month period of omeprazole OTC coverage, net EBD costs for PPIs decreased by 37.6%, or $4,207,350, for the 1,912,432 member-months of eligibility (Table 2) in the postperiod. Annualized savings for an average of 127,495 eligible members were $3,365,880 in 2004-2005 dollars, unadjusted for inflation.

While the average copayment for all PPI pharmacy claims dropped by only 2.0% ($0.50), the member copayment for a claim for omeprazole OTC was 90% less compared with the copayment amount for the 4 single-source brand PPIs and 50% less than the copayment for generic omeprazole Rx. Drug plan members did not realize all of this potential in lower out-of-pocket costs since omeprazole OTC ultimately accounted for only about 41% of all PPI claims by the end of the 15-month postperiod (Figure 1), resulting in a small increase in the average member cost-share for all PPI claims, from 19.5% ($25.06/$128.30) in the preperiod to 26.8% ($24.56/$91.58) in the postperiod (derived from data presented in Table 2).

The average pharmacy dispensing fee for PPI drugs increased by $1.89 (76%) per claim to $4.38 in the 15-month postperiod compared with $2.49 in the 15-month preperiod (derived from data presented in Table 2).

### Discussion

During the first 15 months of omeprazole OTC coverage in the period ended May 31, 2005, this state employee health plan of 127,495 members saved $4,207,350 on spending for PPI drugs, or annualized savings in 2004-2005 dollars of $3,365,880, which would be larger by 5% or more after adjustment for price

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**Table 3: Cost and Utilization Measures for PPI Drugs in 3-Month Periods**

<table>
<thead>
<tr>
<th>Derived Measures</th>
<th>Rxs PMPM</th>
<th>Days PMPM</th>
<th>Charge PMPM ($)</th>
<th>Charge/Rx ($)</th>
<th>Charge/Day ($)</th>
<th>Copay/Rx ($)</th>
<th>Net/Rx ($)</th>
<th>Net/Day ($)</th>
<th>Net PMPM ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preperiod</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec. 02-Feb. 03</td>
<td>0.053</td>
<td>1.584</td>
<td>6.66</td>
<td>126.81</td>
<td>4.21</td>
<td>25.84</td>
<td>101.08</td>
<td>3.35</td>
<td>5.31</td>
</tr>
<tr>
<td>Mar. 03-May 03</td>
<td>0.057</td>
<td>1.724</td>
<td>7.30</td>
<td>127.87</td>
<td>4.24</td>
<td>24.72</td>
<td>103.26</td>
<td>3.42</td>
<td>5.90</td>
</tr>
<tr>
<td>Jun. 03-Aug. 03</td>
<td>0.060</td>
<td>1.827</td>
<td>7.80</td>
<td>129.46</td>
<td>4.27</td>
<td>24.57</td>
<td>104.51</td>
<td>3.46</td>
<td>6.32</td>
</tr>
<tr>
<td>Sep. 03-Nov. 03</td>
<td>0.057</td>
<td>1.720</td>
<td>7.38</td>
<td>129.71</td>
<td>4.29</td>
<td>24.82</td>
<td>105.00</td>
<td>3.47</td>
<td>5.97</td>
</tr>
<tr>
<td>Dec. 03-Feb. 04</td>
<td>0.056</td>
<td>1.695</td>
<td>7.17</td>
<td>128.04</td>
<td>4.23</td>
<td>25.44</td>
<td>102.72</td>
<td>3.39</td>
<td>5.75</td>
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<tr>
<td>Preperiod average</td>
<td>0.057</td>
<td>1.709</td>
<td>7.26</td>
<td>128.30</td>
<td>4.25</td>
<td>25.06</td>
<td>103.34</td>
<td>3.42</td>
<td>5.84</td>
</tr>
<tr>
<td>Postperiod</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mar. 04-May 04</td>
<td>0.053</td>
<td>1.822</td>
<td>4.23</td>
<td>80.25</td>
<td>2.32</td>
<td>21.77</td>
<td>58.59</td>
<td>1.69</td>
<td>3.09</td>
</tr>
<tr>
<td>Jun. 04-Aug. 04</td>
<td>0.052</td>
<td>1.775</td>
<td>4.71</td>
<td>89.78</td>
<td>2.65</td>
<td>24.36</td>
<td>65.54</td>
<td>1.94</td>
<td>3.44</td>
</tr>
<tr>
<td>Sep.04-Nov. 04</td>
<td>0.055</td>
<td>1.808</td>
<td>5.33</td>
<td>96.71</td>
<td>2.95</td>
<td>25.50</td>
<td>71.26</td>
<td>2.17</td>
<td>3.93</td>
</tr>
<tr>
<td>Dec. 04-Feb. 05</td>
<td>0.056</td>
<td>1.836</td>
<td>5.35</td>
<td>96.14</td>
<td>2.92</td>
<td>25.58</td>
<td>70.56</td>
<td>2.14</td>
<td>3.93</td>
</tr>
<tr>
<td>Mar. 05-May 05</td>
<td>0.056</td>
<td>1.854</td>
<td>5.26</td>
<td>94.47</td>
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<td>25.48</td>
<td>69.00</td>
<td>2.07</td>
<td>3.84</td>
</tr>
<tr>
<td>Postperiod average</td>
<td>0.054</td>
<td>1.819</td>
<td>4.98</td>
<td>91.58</td>
<td>2.74</td>
<td>24.56</td>
<td>67.07</td>
<td>2.00</td>
<td>3.64</td>
</tr>
<tr>
<td>Change</td>
<td>-0.002</td>
<td>0.110</td>
<td>-2.28</td>
<td>-36.72</td>
<td>-1.51</td>
<td>-50.0</td>
<td>-36.27</td>
<td>-1.42</td>
<td>-2.20</td>
</tr>
<tr>
<td>% change</td>
<td>-3.9%</td>
<td>6.5%</td>
<td>-31.4%</td>
<td>-28.6%</td>
<td>-35.6%</td>
<td>-2.0%</td>
<td>-35.1%</td>
<td>-41.4%</td>
<td>-37.6%</td>
</tr>
</tbody>
</table>

Rx = prescription; PMPM = per member per month; PPI = proton pump inhibitor.
infrastructure in PPI drugs during this time period. Actual net plan cost savings were $4,062,682 prior to adjustment for changes in membership.

Initial savings for this employee health plan were projected to be $2.56 PMPM based upon the experience in the first 2 months of the benefit change, which included an Rx share of 55% for omeprazole OTC.7 Actual savings after 15 months of follow-up were lowered by 14% to $2.20 PMPM attributable almost entirely to the supply shortage of omeprazole OTC (Figure 1). The final Rx share for omeprazole OTC in the last 3-month period of this study was 39.6%.

The present study not only extended the follow-up period to 15 months from 2 months but it also increased the preperiod from 2 months to 15 months. Based upon this expanded analysis, the initial price savings on all PPI charges declined from $1.82 (43.7%) per day in the earlier analysis to $1.51 (35.6%) per day savings in the present analysis. The lower price savings on all PPI claims, before copayment but including pharmacy dispensing fees, were offset somewhat in the present analysis by a smaller increase in PPI utilization. In the 2-month analysis, PPI utilization in days of therapy PMPM was estimated to have increased by 17.2%, from 1.63 in the preperiod to 1.91 in the postperiod. The extended analysis over 30 months showed a smaller increase in days of PPI therapy, 6.5% higher in the 15-month postperiod, 1.82 days PMPM versus 1.71 days PMPM in the 15-month preperiod. This is an anticipated outcome given the larger 42-days supply for omeprazole OTC packaging.

One can only speculate about the financial impact on this state employee health plan absent the supply shortage of omeprazole OTC. It seems that the initial 55% share of all PPI claims would have been maintained and perhaps increased to 60% or more. Nevertheless, this multifaceted change in drug benefit policy to include a financial incentive for members and a financial incentive for pharmacists produced 38% net costs savings on expenditures for all PPI drugs. Certainly, net plan savings would have been larger, as much as 80%, had coverage been eliminated for all PPI alternatives to omeprazole OTC. Due to the supply shortage of omeprazole OTC that occurred almost immediately after the benefit policy change in March 2004, a closed formulary approach would have necessitated coverage of a PPI alternative to omeprazole OTC at least in nonpreferred status, to maintain continuity of care.

This analysis focused on the financial effects, including utilization changes in the PPI class of drugs. The somewhat surprising market share resilience of the nonformulary PPIs with an average copayment of $50 per claim for the 4 brand-only PPIs (esomeprazole, lansoprazole, pantoprazole, and rabeprazole) is no doubt attributable to several factors, including direct-to-consumer advertising and drug manufacturer promotion of PPIs to physicians. There were also anecdotal stories of beneficiaries who did not like receiving a box of omeprazole OTC in a package where each tablet had to be punched out, some opting instead for generic omeprazole capsules over omeprazole OTC tablets. Another obvious explanation is that education of plan beneficiaries and their prescribers was less than optimally successful. Future studies should identify factors associated with these prescribing trends.

The opportunity for additional cost savings from the more than 60% Rx share of PPIs that is not yet dispensed as omeprazole OTC has caused the EBD to consider other plan design changes. In August 2005, the EBD adopted an additional policy for the PPI drug class whereby the plan will pay up to $0.90 per capsule for any brand or generic Rx PPI. For 1 capsule a day (a 31-day supply), the plan reimbursement will therefore be no more than $27.90 for any PPI claim, and the plan beneficiary is responsible for the difference between the MAC of $0.90 per unit (capsule or tablet) reimbursement and the allowed pharmacy charge. It will be interesting to observe if this policy change impacts market share of brand Rx PPIs. Coverage of omeprazole OTC coverage continues as does the $13 dispensing fee for pharmacy providers for each omeprazole OTC claim. From this multifaceted intervention, it is difficult to determine the relative influence of copayment incentives for beneficiaries versus favorable pharmacy reimbursement in the shift to omeprazole OTC and the significant drug cost savings for the state employee health plan.

When reviewing the data from this 15-month postperiod, the cost of generic omeprazole Rx has gradually decreased (the net EBD cost for generic omeprazole Rx claim in February 2004 was $91.71 and in June 2005 was $58.15). As the generic omeprazole price decreases, it is important for the EBD to continually assess the marketplace and evaluate the benefit plan design. There will likely be a time in the future when generic omeprazole Rx will be priced comparably with the OTC product. In June 2005, the average cost to the EBD after subtraction of member cost-share was $0.87 per day for omeprazole OTC ($32.32 for an average supply of 37 days) compared with $1.82 per day for generic omeprazole Rx ($58.15 for an average supply of 30 days), $3.18 per day for esomeprazole ($95.51 for an average supply of 30 days), or $3.26 per day for lansoprazole ($97.94 for an average supply of 30 days). These average costs per day of PPI therapy and per pharmacy claim reflect the reason for continuation of omeprazole OTC coverage since significant cost savings can be realized as market share is shifted to the OTC product.

It might be argued that the $13 dispensing fee is no longer necessary, nearly 2 years after adoption of this financial incentive for pharmacies to dispense the preferred, OTC product. However, the EBD continues to support pharmacist involvement in dispensing the preferred, much-lower-cost OTC product by maintenance of the $13-per-claim dispensing fee, judged to make the pharmacy dollar revenue nearly the same for dispensing omeprazole OTC and the PPI alternatives. The EBD also intends to continue to engage pharmacists in other pharmacy benefit
interventions in the future and maintains this visible financial support, in part, as a matter of good will. To some observers, the dispensing fee differential of $10.50 ($13.00 vs. $2.50) for each omeprazole claim may seem large, but in fact, it is less than 15% of the average net cost differential between brand PPIs and omeprazole OTC.

The success of this multifaceted intervention in pharmacy benefits management begs the obvious question of what similar opportunities exist for other drugs classes with OTC equivalents. For the low-sedating antihistamines (LSAs), also known as second generation antihistamines, one study suggested that a substantial decrease in utilization and cost occurred even for plan sponsors who did not cover loratadine OTC when it became available. The health plans that did not cover loratadine OTC experienced cost savings, in part, by shifting costs to the beneficiaries to pay for the OTC drug out of pocket. Meissner et al. found that the use of LSAs, and the therapeutic alternative nasal steroids, was resilient to a $10 (47%) increase in member cost-share. Utilization of LSAs and nasal steroids increased by 8.9%, but net health plan costs decreased for allergic rhinitis drugs, all drugs used by allergic rhinitis patients, and all drugs used by continuously enrolled health plan members. Further studies of the utilization and cost effects of benefit design changes to encourage the use of drugs for treatment of allergic rhinitis are warranted.

The statin drugs may be another target of Rx-to-OTC switching in the future. The first OTC statin was introduced to the market in the United Kingdom in August 2004 as Zocor Heart-Pro. While not yet available in the United States, Richards, Blumenfield, and Lyon found generally favorable opinions among pharmacy and medical officers in managed care organizations (MCOs) and PBMs regarding the possible introduction of lovastatin OTC to the U.S. market. However, there was a curious lack of PBM support, and only small MCO support, for changing the formulary status of other statins if coverage was expanded to an OTC statin. The findings of this study suggest that a multifaceted intervention with substantial member financial incentive is necessary to attain maximum value from the availability of an OTC therapeutic alternative.

The drug benefit plan design adopted by the EBD and implemented in March 2004 reduced costs for both the plan and for beneficiaries. If the EBD had not covered the OTC product and kept the original benefit design for PPIs, it is likely that the shift to the OTC product would have been gradual, if it occurred at all. By covering the OTC product, in a multifaceted intervention, the EBD received the immediate financial benefit of beneficiaries switching to a less-expensive product. Cost savings would have been larger absent the product shortage of omeprazole OTC and under larger financial incentives for plan beneficiaries to use the preferred (OTC) drug. The adoption of the therapeutic MAC for PPI drugs, effective for the EBD and Arkansas state employees and their beneficiaries in August 2005, was intended to realize more of the cost-savings opportunity that exists in this class of drugs from the use of omeprazole OTC as a therapeutic alternative to other PPIs.

When drug products are determined to be therapeutically equivalent based on clinical evidence, strategies to reduce costs should be considered when there is a low-cost therapeutic alternative in the class. Once a preferred drug product is selected, the Rx benefit should be designed to encourage use of the preferred drug(s). In the present study, this meant encouraging beneficiaries to switch to the preferred drug and modifying pharmacy reimbursement to facilitate use of the preferred drug. Community pharmacists are in a position to identify beneficiaries eligible for switching and to communicate with beneficiaries and physicians about cost-effective options within a particular benefit plan.

Limitations

This was a cost-outcome analysis and did not consider clinical or service outcomes (e.g., either beneficiary or pharmacist satisfaction with the program) other than the overall 2% average decrease in member cost-share for all PPI drugs. This study did not measure the incidence or costs of medical visits, which would presumably decrease with increasing use of the OTC drug. Additionally, the study did not include assessment of the administrative costs associated with implementing the policy.

Conclusion

This multifaceted strategy of extending coverage to omeprazole OTC saved the drug benefit plan sponsor 38% in the net cost of all PPI drugs after 15 months despite an interruption in the supply of the preferred OTC drug and the consequent need to cover generic omeprazole at a $10 copayment. The significant cost savings were achieved with near-maximum choice of PPIs for drug plan members and no copayment increase for 2 of the 4 brand-only PPIs. The net savings were $2.20 PMPM after consideration of lower average member cost-share and higher average pharmacy dispensing fee reimbursement, yielding total savings of $4,207,350 over the first 15 months of coverage of omeprazole OTC. Annualized savings for this state health plan of approximately 127,500 members was $3,365,880.

ACKNOWLEDGMENTS

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DISCLOSURES

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and design were contributed primarily by author Jill T. Johnson, with input from West and author Song Hee Hong. Data collection was the work of West and Hong; data interpretation was primarily the work of West, with input from Hong and Johnson. Drafting of the manuscript and its critical revision was primarily the work of West, with input from Hong and Johnson.

REFERENCES

Analysis of the Effectiveness and Cost Benefit of Leukotriene Modifiers in Adults With Asthma in the Ohio Medicaid Population

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ABSTRACT

OBJECTIVE: The objectives of this research were to (1) determine the association of the use of leukotriene modifiers (LMs) with 3 clinical outcome measures that can serve as proxy measures of effectiveness: subsequent emergency room visits, hospitalizations, and steroid bursts, and (2) estimate whether LM use compared with nonuse is cost beneficial from a Medicaid payer perspective.

METHODS: This was a retrospective, longitudinal study of asthma patients in the fee-for-service Ohio Medicaid program. The study population included 5,541 adult patients who were identified as having a claim containing an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for asthma (code 493.xx, excluding 493.2x) in 2001. Logistic regression, controlling for selection bias through the use of propensity scores, was used to determine the association of LM use on 3 outcome measures: emergency room visits, hospitalizations, and steroid bursts. An oral steroid burst was defined as a pharmacy claim for oral prednisone in the date range from 1 day before to 3 days after an office visit that has an ICD-9-CM code for asthma. A cost-benefit analysis was also performed.

RESULTS: During the prestudy period, the LM users had higher total medical costs of $72.06 per patient per month (PPPM, $170.60 vs. $98.54, P < 0.001). During the outcome period, there was no significant association between LM use and emergency room visits (odds ratio [OR] 1.09; 95% confidence interval [CI], 0.84-1.38), hospitalizations (OR 1.02; 95% CI, 0.66-1.59), or steroid bursts (OR 1.30; 95% CI, 0.89-1.90). Because LM use was not more effective than nonuse and is more expensive than nonuse, a situation of dominance prevails. The mean cost difference in the 3 primary outcome measures between LM users and nonusers was $1.63 PPPM ($34.93 vs. $33.30, P = 0.019).

CONCLUSION: In this study of adult Medicaid asthma patients, users of LMs did not have greater asthma control as measured by emergency room visits, hospitalizations, or steroid bursts. In this cohort of adult asthma patients with at least 1 asthma medication, there does not appear to be any cost offsets to the Ohio Medicaid program associated with the use of LMs. The use of LMs was associated with higher total costs for asthma care.

KEYWORDS: Leukotriene modifiers, Asthma, Medicaid, Cost-benefit analysis, Effectiveness

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Note: An editorial on the subject of this article appears on pages 80-82 of this issue.

Asthma is the most common chronic disorder in industrialized nations. In 2002, about 12 million people in the United States experienced an asthma attack or episode. During this same period, asthma was also responsible for about 13.9 million visits to private physician offices or hospital outpatient departments, 1.9 million emergency room visits, 500,000 hospitalizations, and 4,300 deaths.1 Asthma caused an economic burden on the health care system of approximately $12.7 billion: $7.4 billion in direct costs and $5.3 billion in indirect costs.2 In the United States, the National Asthma Education and Prevention Program Expert Panel, working as a recommending body to the National Heart, Lung, and Blood Institute (NHLBI), defined the guidelines for the diagnosis and management of asthma in Reports I and II.3,4 The pharmacological management of asthma is based upon stepwise treatment according to the level of asthma severity. The goal of therapy is to maintain a patient on a controller medication, requiring low amounts of rescue medication.

The treatment guidelines for both adults and children were updated in May 2002, and the role of leukotriene modifiers (LMs) was further substantiated.6 In patients with mild persistent asthma, inhaled corticosteroids are the preferred treatment, and LMs are listed as an alternative controller medication. In moderate...
persistent asthma, the preferred treatment is to add a long-acting beta2-agonist to low-to-medium doses of inhaled corticosteroids. The alternative treatment is to add an LM or theophylline to inhaled corticosteroids or to double the doses of inhaled corticosteroids.

In placebo-controlled studies, LMs appear to be efficacious.\textsuperscript{7-10} However, studies comparing LMs as monotherapy with inhaled corticosteroids have shown conflicting results.\textsuperscript{11,12} The data are also controversial regarding the effectiveness of LMs added to existing inhaled corticosteroid regimens. At least 2 studies in adults have shown that LMs provide some clinical benefit when added to an existing inhaled corticosteroid regimen.\textsuperscript{13,14} However, a study by Tonelli et al., in which LMs were added to regimens of patients who were unstable on inhaled cortico-

steroids, short-acting beta2-agonists, or oral corticosteroids, showed no statistically significant impact on efficacy.\textsuperscript{15} Other studies show that adding LMs to inhaled corticosteroids is not as effective as adding a long-acting beta2-agonist.\textsuperscript{16-18}

Several studies have examined the cost-effectiveness of LMs and again controversy exists. Some studies show that LMs are cost effective\textsuperscript{19} while others studies do not.\textsuperscript{20-22}

**Purpose of Study**

Because the value of LMs is controversial, this study examined the effectiveness and cost benefit of LM use compared with nonuse. Effectiveness was defined as how well a patient's asthma was controlled. Three variables were selected as measures of asthma control: emergency rooms visits, hospitalizations, and steroid bursts. Thus, the purpose of this study was to determine the difference in risk-adjusted rates of emergency room visits, hospitalizations, and steroid bursts between asthmatic patients who used LMs and asthmatic patients who did not and to evaluate the cost benefit of LMs for these asthmatic patients.

**Methods**

**Study Design**

This study used a retrospective cohort design to compare the outcomes of asthma patients who used LMs with the outcomes of asthma patients who did not. Selection bias was controlled through the use of propensity scores. Drug therapies during a 180-day period and outcomes during the subsequent 90-day period were examined. The “prestudy period” is the 180-day period that was used to classify a patient’s treatment group and to obtain information about variables that were used in the propensity score calculation. The subsequent 90-day period is referred to as the “outcome period.” Ninety days was chosen as the optimum length of time to measure outcomes because it was not so long a period that the outcomes would not be attributable to the drug use during the prestudy period.

**Data Source**

This study utilized prescription, medical service, and institutional claims from the Ohio Medicaid database obtained from the Ohio Department of Jobs and Family Services for the period from October 1, 2000, through June 30, 2002. The Ohio Medicaid fee-for-service program enrolled approximately 1.4 million recipients during this time.

**Patient Selection**

The study included ambulatory fee-for-service recipients who had at least 1 diagnosis for asthma at any time from January 1, 2001, to December 31, 2001, and at least 1 pharmacy claim for an asthma medication in the 6 months prior to their asthma diagnosis. An asthma diagnosis was defined as an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code of 493.xx, any fourth or fifth digit. Patients
with asthma and chronic obstructive pulmonary disease (COPD) (ICD-9-CM 493.xx) were excluded. To further exclude patients with COPD or other respiratory diseases, patients were excluded if they had any prescriptions for inhaled (but not nasal) ipratropium, which does not have a role in asthma therapy, or if they had a diagnosis of emphysema (492.xx) or other respiratory diseases (495.xx-519.xx). Patients were also excluded if they had a diagnosis of cystic fibrosis (277.0), bronchopulmonary dysplasia (770.7), or tracheomalacia (748.3). (Figure 1)

Starting on January 1, 2001, for each recipient we identified the date of the first claim (day 0) that had an asthma diagnosis. The next 180 days (days 1-179) represented the prestudy period for each Medicaid recipient. The subsequent 90 days (days 180-269) represented the outcome period. Day 0 was excluded from the prestudy period calculations because it might cause overweighting for the study period since, by definition, some kind of claim was filed on the asthma identification date.

In order to calculate dose equivalents (see next paragraph), the patient must have been continuously enrolled 90 days prior to the prestudy period and 90 days following the end of the outcome period. When tallying the number of dose equivalents a patient received during a given time, issues arise with regard to date boundaries in 3 cases: (1) A prescription may have been dispensed just prior to the beginning of a patient’s prestudy period. If we ignore this prescription altogether, we are not accounting for the portion of the medication that was taken during the prestudy period. (2) A prescription may have been dispensed a few days prior to the end of the prestudy period and the beginning of the outcome period. It would be misleading to assign the entire quantity dispensed to the patient’s prestudy period, since some of the medicine was consumed during the prestudy period and some was consumed during the patient’s outcome period. (3) A prescription may have been dispensed near the end of the outcome period; clearly, only a portion of such a prescription should be assigned to the patient’s outcome period. To deal with these situations, we developed an algorithm to allocate (or prorate) pharmacy claims across date boundaries. A 90-day window before the prestudy period and after the outcome period was chosen in order to capture prescriptions that fell close to the prespecified date boundaries. Thus, in order to qualify for the study, a patient had to be continuously enrolled 90 days prior to and 360 days after the asthma diagnosis date. If the first asthma date for a recipient did not meet these qualifications but a later asthma date did, the later date was taken as day 0. Patients without 450 days of continuous enrollment (n=18,665) were excluded from the study.

### Dose Calculations

Because many individual medications are available to asthmatics and because patients may receive different drug products within a certain drug class, comparisons were made among drug classes rather than among individual drug products. Patients may have switched products because of formulary changes, physician preferences, cost, or other reasons. Therefore, for the comparisons, quantities of short-acting beta2-agonists, long-acting beta2-agonists, inhaled corticosteroids, and LMs were converted to “dose equivalents,” a common unit of measure within a drug class. This allows for summation of quantities of disparate drug products within the same drug class. For each Medicaid recipient, the sum of the dose equivalents dispensed for each medication class during the presstudy period was divided by 180 to obtain average daily doses in each class.

When attempting to equate use among the inhaled products, the question arose, “Is 1 puff of a particular inhaler equivalent to 1 puff from another product?” The World Health Organization does maintain a system of defined daily doses; however, all inhaled asthma medications have not been assigned conversion factors. Therefore, we calculated conversions for each of the inhaled products. For example, each inhaled corticosteroid pharmacy claim was converted to a beclomethasone equivalent (BME) in which 1 BME equals 1 microgram of beclomethasone. To calculate the BME, the quantity dispensed was divided by the package size, yielding the number of canisters dispensed. The number of canisters was multiplied by the number of puffs per canister. The number of puffs was multiplied by the strength to calculate the total number of micrograms dispensed. Some inhaled corticosteroids are more potent than others. Fluticasone propionate is more potent than beclomethasone dipropionate (which is equal in potency to budesonide) by a ratio of 1 to 0.5. Beclomethasone dipropionate and budesonide, in turn, are more potent than triamcinolone acetonide (which is equal in potency to flunisolide) by a ratio of 0.5 to 0.25. Therefore, the total number of micrograms was multiplied by the following conversion factors: 2 for fluticasone, 1 for beclomethasone and budesonide, and 0.5 for triamcinolone and flunisolide.

For short-acting beta2-agonists, each prescription was converted to albuterol equivalents (AEs). One AE equals 1 puff of albuterol. The calculation of the number of AEs varied depending on the delivery system of the drug. For metered-dose inhalers, the quantity dispensed was divided by the package size to yield the number of canisters. The number of canisters was multiplied by the number of puffs per canister to obtain the total number of puffs. The number of puffs was then multiplied by a conversion factor of 2 for inhaled bitolterol because bitolterol is more potent. No other short-acting beta2-agonist had a conversion factor. For nebulizer solution, the quantity dispensed was multiplied by the conversion factor to approximate the number of puffs or AEs that would be contained in the prescription. The conversion factors were as follows: 7.5 for metaproterenol, 1.25 for albuterol, 0.625 for nebulized bitolterol, and 0.16 for levalbuterol. For albuterol rotahaler, the quantity dispensed was...
multiplied by 2 to equal the number of puffs. For long-acting beta2-agonists, each prescription was converted to a number of salmeterol equivalents (SEs). One salmeterol equivalent equals 2 puffs (42 mcg) of salmeterol.

LMs were converted to an equivalent that represents the recommended dose for 1 day of therapy, i.e., 1 LM equivalent (LME) is equal to 10 mg montelukast, 40 mg zafirlukast, or 2,400 mg zileuton (1 tablet 4 times daily). Patients must have received at least 30 LMEs during the prestudy period, or more than 0.16 LMEs per day (30 LMEs/180 days) to be classified as a leukotriene user.

**Outcome Variables**

Three outcomes (dependent variables) were measured: emergency room visits, hospitalizations, and steroid bursts. Asthma-related hospitalizations and emergency room visits were determined from institutional claims that contained an ICD-9-CM code for asthma. An emergency room visit that led to an immediate hospital admission was considered to be part of the hospitalization event and not an emergency room visit. Oral steroid bursts were used as an indicator of asthma exacerbations. An oral steroid burst was defined as a pharmacy claim for oral prednisone in the date range of 1 day before to 3 days after an office visit that has an ICD-9-CM code for asthma. Since prednisone has many uses, this time restriction increased the likelihood that the drug was being used for an asthma exacerbation. On the other hand, this definition likely underestimated the actual number of oral steroid bursts because it would not capture refill prednisone prescriptions or pharmacy claims for prednisone outside the date range around a medical office visit with an ICD-9-CM code for asthma.

**Propensity Scores**

Propensity scores, which control for the probability of a patient's receiving a particular treatment based on observed baseline characteristics, were used to control for selection bias inherent in observational database research.\(^2^4\) Patients with similar propensity scores have baseline characteristics that are similar enough that their probability of receiving treatment or not receiving treatment is the same. The use of propensity scores can reduce selection bias by 90%.\(^2^5,2^6\) Control of selection bias is important when studying asthma because asthma severity dictates drug treatment.

The propensity score calculation included variables that controlled for demographics, certain comorbidities, and drug use other than LMs. Demographics included race, age, and gender. The ICD-9-CM codes for these diseases were obtained from institutional and medical service claims. Comorbidities that may predict poor asthma outcomes were included in the propensity score model, including obesity\(^2^7,2^8\) (ICD-9 codes 278.xx), depression\(^2^9,3^0\) (296.xx, 311.xx, 309.0, 313.1, 309.4, 309.1, 298.0), allergies (477.xx), sinusitis\(^1^0\) (461.xx, 473.xx), gastroesophageal reflux disease (530.81), status asthmaticus (493.x1), and smoking (472.1, 528.6, 305.1). While there are no data to confirm the validity of all of the coding for these comorbidities, especially smoking, the comorbidities were included in the propensity model in an attempt to achieve equal treatment groups. As long as the validity of coding does not vary by whether or not the patient received LMs, these codes are useful and reliable for identifying potential treatment confounders.

Five different drug classes were covariates in the propensity score since drug use can be used as a predictor of disease severity in asthmatics. High dose short-acting beta2-agonists have been used as a marker of severity; however, high use may reflect lack of control, not severity. The dose of inhaled corticosteroids is a more valid marker of disease severity.\(^2^2\) It is, in part, because of this validity in predicting asthma severity that it was necessary to equate use among inhaled corticosteroid users by calculating dose equivalents. All drug-use variables were continuous—that is, the variables did not simply indicate whether a patient had ever received an asthma drug; instead, they indicated the number of dose equivalents or the number of pharmacy claims. Dose equivalents were calculated for short-acting beta2-agonists, inhaled corticosteroids, and inhaled long-acting beta2-agonists.

Prescription counts (i.e., number of pharmacy claims regardless of quantity) were ascertained for all theophylline, cromolyn, and oral long-acting beta2-agonists (i.e., 4 mg albuterol sulfate).

The propensity score was calculated through logistic regression, with treatment assignment as the binary response and the explanatory variables as covariates. First, a series of \(t\) tests of equality of means for continuous variables and chi-square tests of independence for categorical variables were performed to compare the initial amount of bias between the LM user and the LM nonuser group for each variable. Next, multiple logistic regression was used to calculate the propensity score for each patient. Patients were then separated into quintiles defined by their propensity score to test whether balance, i.e., no remaining statistical differences between the groups, within the quintiles had been achieved.\(^3^3\)

**Statistical Analysis**

Descriptive statistics such as mean, standard deviation, median, and range were calculated for both independent and dependent variables. Logistic regression was used to examine the relationship between the outcome variables and the independent variable, LM use, as a binary variable. Because balance was not achieved in the propensity model for inhaled corticosteroids and short-acting beta2-agonists, the final model had 4 independent variables: inhaled corticosteroids, short-acting beta2-agonists, LM use, and the propensity probability.

**Economic Evaluation**

Cost-benefit analysis is an economic evaluation that compares the benefit, measured in dollars, of 2 alternative programs or
interventions. Cost-benefit analysis usually compares program outcomes or interventions from a societal perspective; therefore, it requires the inclusion of indirect costs. The Medicaid claims database, however, contains provider payment amounts for many direct medical services received by patients, but it does not contain indirect costs. Since the perspective of this study is from that of the third-party payer, Medicaid, we performed a cost-benefit analysis using only direct medical costs.

The program costs were calculated as the difference in mean total asthma costs during the study period between the patients who received LMs and the patients who did not. All asthma drug costs, not only LM costs, were included because of the substitutive nature of drug treatment. Since if one drug is used, another drug may not be used, this offset in utilization needs to be taken into account. We also took nondrug asthma-related utilization, e.g., physician services, laboratory fees, and miscellaneous services, into account (see Table 5). Cost was defined as the actual amount paid by Medicaid, not the amount billed by a provider. The program benefits were the difference in mean costs for expenditures during the study period for the 3 clinical outcome measures: emergency room visits, hospitalizations, and steroid bursts. Costs are expressed in 2001-2002 dollars. We used the Mann-Whitney U test to compare the distribution of costs between the leukotriene users and nonusers.

### Results

#### Patient Selection

After all exclusion and inclusion criteria were applied, we had a cohort of 11,533 recipients aged 18 years or older. Further evaluation of the data revealed that there were 5,992 patients (52%) identified with an asthma diagnosis who did not receive any asthma medications during the 6-month study period. These patients were determined to be either extremely mild asthmatics or miscoded as asthmatic, so we excluded them from the study. This resulted in a final cohort of 5,541 asthma patients (Figure 1).

#### Description of LM Use

Of the final cohort of 5,541 patients, 1,412 (25.5%) received LMs. However, 122 of the patients receiving LMs (8.6%) had use below 30 equivalents during their study period, and these patients were considered LM nonusers. Of the LM users whose use was at least 30 equivalents (n=1,290; 23.3%), the mean equivalent LM use during the 180-day study period was 112.24 (SD 53.88; range, 30-420), and the mean number of LM use was at least 30 equivalents (n=1,290; 23.3%), the mean equivalent LM use during the 180-day study period was 112.24 (SD 53.88; range, 30-420), and the mean number of LM.

#### Propensity Score Calculation

The first step to calculate the propensity score was to determine if there was imbalance, i.e., a statistical difference, among the covariates in the 2 treatment groups. The treatment groups were not balanced in 10 out of 20 variables (Table 1), indicating that there was selection bias. Propensity scores were calculated for each patient by logistic regression (Table 2). After calculating the propensity scores, t tests of equality of means for continuous variables and chi-square tests of independence for categorical variables were performed for each variable within each quintile to determine whether patients were balanced within quintiles. Overall, good balance was achieved; however, short-acting beta₂-agonist use and inhaled corticosteroid use were not suffi-

### TABLE 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 5,541)</th>
<th>Leukotriene Modifier Users (n = 1,290)</th>
<th>Leukotriene Modifier Nonusers (n = 4,251)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean [SD]</td>
<td>40.8 [14.5]</td>
<td>41.2 [13.9]</td>
<td>40.6 [14.6]</td>
<td>0.182</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>40.8 [14.5]</td>
<td>41.2 [13.9]</td>
<td>40.6 [14.6]</td>
<td>0.182</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>81.6 [14.5]</td>
<td>82.2 [13.9]</td>
<td>81.4 [14.6]</td>
<td>0.538</td>
</tr>
<tr>
<td>Other, %</td>
<td>18.4 [14.5]</td>
<td>17.8 [13.9]</td>
<td>18.6 [14.6]</td>
<td>0.538</td>
</tr>
<tr>
<td>Comorbidities,%:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>32.6 [14.5]</td>
<td>33.2 [13.9]</td>
<td>32.5 [14.6]</td>
<td>0.635</td>
</tr>
<tr>
<td>Status asthmatican</td>
<td>6.4 [14.5]</td>
<td>8.5 [13.9]</td>
<td>5.8 [14.6]</td>
<td>0.001</td>
</tr>
<tr>
<td>Drug utilization, mean [SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td>487.1 [568.8]</td>
<td>560.3 [702.5]</td>
<td>465.0 [519.6]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>beta₂-agonist†‡</td>
<td>0.06 [0.52]</td>
<td>0.08 [0.59]</td>
<td>0.05 [0.50]</td>
<td>0.253</td>
</tr>
<tr>
<td>beta₂-agonist, oral‡†</td>
<td>40.0 [88.0]</td>
<td>64.6 [107.6]</td>
<td>32.5 [79.6]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inhaled corticosteroids‡§</td>
<td>28,096.5 [53,897.5]</td>
<td>44,307.7 [68,515.2]</td>
<td>23,177.1 [47,528.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Theophylline‡</td>
<td>0.30 [1.24]</td>
<td>0.46 [1.48]</td>
<td>0.26 [1.15]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cromolyn‡</td>
<td>0.07 [0.59]</td>
<td>0.08 [0.65]</td>
<td>0.06 [0.57]</td>
<td>0.213</td>
</tr>
<tr>
<td>Other factors, no. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER visits‡</td>
<td>844 [15.2%]</td>
<td>207 [16.0%]</td>
<td>637 [15.0%]</td>
<td>0.353</td>
</tr>
<tr>
<td>Hospitalizations‡</td>
<td>264 [4.8%]</td>
<td>67 [5.2%]</td>
<td>197 [4.6%]</td>
<td>0.412</td>
</tr>
<tr>
<td>Steroid bursts‡</td>
<td>320 [5.5%]</td>
<td>119 [9.2%]</td>
<td>201 [4.7%]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Leukotriene modifier users compared with leukotriene modifier nonusers; Student's t test for continuous variables, chi-square test for all other comparisons.
† Measured in dose equivalents.
‡ Measured as number of prescriptions.
§ Dose equivalents per 10,000 units.
¶ ER visits, hospitalizations, and steroid bursts that occurred during the 6-month prestudy period.
ER=emergency room; GERD=gastroesophageal reflux disease.
Analysis of the Effectiveness and Cost Benefit of Leukotriene Modifiers in Adults With Asthma in the Ohio Medicaid Population

**Table 2** Predictors of Use of Leukotriene Modifiers in the 6-Month Prestudy Period

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.00</td>
<td>1.00-1.01</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.05</td>
<td>0.90-1.24</td>
</tr>
<tr>
<td>Race, nonwhite</td>
<td>0.76</td>
<td>0.66-0.88</td>
</tr>
<tr>
<td>Comorbidities:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>1.18</td>
<td>0.94-1.47</td>
</tr>
<tr>
<td>Depression</td>
<td>1.02</td>
<td>0.80-1.17</td>
</tr>
<tr>
<td>Allergies</td>
<td>1.47</td>
<td>1.25-1.72</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1.01</td>
<td>0.87-1.19</td>
</tr>
<tr>
<td>GERD</td>
<td>0.97</td>
<td>0.80-1.18</td>
</tr>
<tr>
<td>Status asthmaticus</td>
<td>1.36</td>
<td>1.06-1.74</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.78</td>
<td>0.63-0.97</td>
</tr>
<tr>
<td>Drug utilization:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting beta₂-agonist*</td>
<td>1.01</td>
<td>1.00-1.02</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist, oral†</td>
<td>1.07</td>
<td>0.95-1.19</td>
</tr>
<tr>
<td>Long-acting beta₂-agonist, inhaler*</td>
<td>1.00</td>
<td>1.00-1.00</td>
</tr>
<tr>
<td>Long-acting beta₂-agonist, oral†</td>
<td>1.15</td>
<td>1.05-1.25</td>
</tr>
<tr>
<td>Inhaled corticosteroids§</td>
<td>1.04</td>
<td>1.03-1.05</td>
</tr>
<tr>
<td>Theophylline†</td>
<td>1.07</td>
<td>1.02-1.12</td>
</tr>
<tr>
<td>Cromolyn†</td>
<td>1.01</td>
<td>0.91-1.11</td>
</tr>
<tr>
<td>Other factors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency room visit</td>
<td></td>
<td>1.11</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td>1.07</td>
</tr>
<tr>
<td>Steroid bursts</td>
<td></td>
<td>1.67</td>
</tr>
</tbody>
</table>

* Measured in dose equivalents.
† Measured as number of prescriptions.
‡ Dose equivalents per 100 units.
§ Dose equivalents per 10,000 units.
|| ER visits, hospitalizations, and steroid bursts that occurred during the 6-month prestudy period.
CI=confidence interval; GERD=gastroesophageal reflux disease.

The final logistic regression model was created for each outcome variable. (There were a total of 399 emergency room visits, 115 hospitalizations, and 135 steroid bursts. Unadjusted for severity of illness, LM users, compared with nonusers, experienced a greater percentage of steroid bursts (3.6% vs. 2.1%, P=0.002) but not emergency room visits (7.9% vs. 7.0%, P = 0.268) or hospitalizations (2.3% vs. 2.0%, P = 0.503). Because of the small number of patients who had multiple occurrences of an outcome (e.g., more than 1 emergency room visit), each outcome was reduced to a binary variable.

The logistic regression results for emergency room visits, hospitalizations, and steroid bursts are given in Table 3. The use of LMs did not have a significant effect, positive or negative, on emergency room visits, hospitalizations, or steroid bursts.

**Cost-Benefit Analysis**

Per-patient-per-month (PPPM) provider payments during the study period and outcome period are listed in Table 4 and Table 5, respectively. Because LM use was not more effective than nonuse and LM use is more expensive than nonuse, a situation of dominance prevails in which it is not practical to calculate a cost-benefit ratio. For this reason, the net benefit was calculated.

Because most patients did not experience 1 of these 3 outcomes, the cost data are skewed. The median cost for all 3 outcomes is 0. Therefore, mean costs are displayed in Tables 4 and 5; the Mann-Whitney U test was used to compare the distributions between the 2 groups. The mean difference in the cost outcome measures was $1.63 PPPM ($34.93 vs. $33.30, P=0.019). Total direct costs during the study period were $72.06 PPPM higher in the LM user group than in the LM nonuser group ($170.60 vs. $98.54, P<0.001). Therefore, for LM users, there is an additional cost of $72.06 PPPM with no apparent cost offset. Use of LMs imposed additional costs for Ohio Medicaid.

**Discussion**

In this cohort of asthmatic patients who received at least 1 asthma prescription, 23.4% of the patients used LMs. Patients who used LMs did not have significantly different cost outcomes compared with nonusers. The net cost benefit to Medicaid favored the nonuse of LMs.

This economic evaluation had a limited perspective and did not consider any potential advantage of LMs to patients and providers, such as convenience or incidence of side effects. For example, in patients who experience difficulty manipulating an inhaler, an oral tablet may be easier to use. Compliance taking LMs may be superior compared with patients using an inhaled corticosteroid or inhaled long-acting beta₂-agonist, but other studies do not confirm these results.35 Side effects of LMs are usually mild and may include headache, dizziness, or nausea; however, there have been reports of liver failure with zafirlukast, and LMs may potentially cause Churg-Strauss syndrome.37 Side effects of inhaled corticosteroids are also usually mild and may include cough, dysphonia, or oral thrush. Since asthma is a chronic disease often requiring daily medication, the development of osteoporosis is a concern; studies, however, are inconclusive.38-41

Selection bias is always a concern in database research. It is interesting to note in the propensity score analysis that the patients using LMs had significantly higher use of all other medications except for oral short-acting beta₂-agonists and cromolyn and had higher rates of status asthmaticus. This concurs with other cost-effectiveness research using retrospective claims analysis, which found that, at baseline, the LM users were potentially more severe asthmatics although 2 studies found that the LMs were potentially used less by severe asthmatics.46,47 All of these studies did attempt to control for base-
The value of the use of LMs in allergic rhinitis, however, is controversial. Studies have shown that LMs have a protective effect on the pulmonary function and nasal anatomy induced by natural cat exposure in asthmatic patients. The value of the use of LMs in allergic rhinitis, however, is controversial. Studies have shown that LMs have a protective effect on the pulmonary function and nasal anatomy induced by natural cat exposure in asthmatic patients.50,51 However, a recent review article on the use of LMs in treating allergic rhinitis shows that LMs are sometimes more effective than placebo, more effective than low-sedating antihistamines, and less effective than inhaled nasal corticosteroids in reducing the symptoms of allergic rhinitis.52 Montelukast sodium (Singulair) was approved by the U.S. Food and Drug Administration (FDA) on December 31, 2002, for the additional indication for the relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients aged 2 years and older.53 Lakomski and Chitre found that, for the 12-month period from September 1, 2001, through August 31, 2002, the majority of LM use in a large managed care organization was initial monotherapy, contrary to national treatment guidelines for asthma, and an estimated 25% of use was not for asthma.54 Both this and the present study precede the date of FDA approval of montelukast for the indication of allergic rhinitis. Zafirlukast and zileuton, which were voluntarily withdrawn from the market by the manufacturer in 2003, do not have this indication for allergic rhinitis.

**Limitations**

Foremost among the limitations of this study was that the leukotriene users differed significantly from the leukotriene nonusers in several measures, including a higher percentage of comorbidity for allergy and status asthmaticus but a lower percentage for smoking. Leukotriene users had higher mean utilization of short-acting beta-agonists, long-acting beta2-agonists (both for the oral dose form and for inhalers), inhaled corticosteroids, and theophylline. This may suggest that LMs are used in more severe asthmatics as an add-on to other controller therapy but are not as widely used as solo therapy in patients with mild persistent asthma.

Second, we used oral steroid bursts as a proxy measure for an asthma exacerbation, a method we have used previously.55 Yet, drug use can be a proxy measure of disease. For example, the chronic disease score utilizes medication use to define line differences; however, there were fewer covariates used than used in the present propensity analysis. Perhaps because of the better ability for a propensity analysis to control for selection bias, our study does not support others that found an increase in emergency room visits and hospitalizations in patients using LMs. Indeed, a prospective, longitudinal study of 349 asthma patients showed that patients receiving LMs had more severe asthma, which suggests that great care must be taken to control for selection bias.56

It is interesting that a significant predictor of LM use was allergies (odds ratio [OR] 1.47; 95% CI, 1.26-1.73). The OR associated with allergy diagnosis may have been high because LMs are used in asthma patients with allergic rhinitis. The value of the use of LMs in allergic rhinitis, however, is controversial. Studies have shown that LMs have a protective effect on the pulmonary function and nasal anatomy induced by natural cat exposure in asthmatic patients. However, a recent review article on the use of LMs in treating allergic rhinitis shows that LMs are sometimes more effective than placebo, more effective than low-sedating antihistamines, and less effective than inhaled nasal corticosteroids in reducing the symptoms of allergic rhinitis. Montelukast sodium (Singulair) was approved by the U.S. Food and Drug Administration (FDA) on December 31, 2002, for the additional indication for the relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients aged 2 years and older. Lakomski and Chitre found that, for the 12-month period from September 1, 2001, through August 31, 2002, the majority of LM use in a large managed care organization was initial monotherapy, contrary to national treatment guidelines for asthma, and an estimated 25% of use was not for asthma. Both this and the present study precede the date of FDA approval of montelukast for the indication of allergic rhinitis. Zafirlukast and zileuton, which were voluntarily withdrawn from the market by the manufacturer in 2003, do not have this indication for allergic rhinitis.

**Limitations**

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<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any emergency room visit</td>
<td>1.09</td>
<td>0.84-1.38</td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>1.03</td>
<td>1.01-1.05</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>1.10</td>
<td>0.98-1.03</td>
</tr>
<tr>
<td>Propensity score</td>
<td>1.26</td>
<td>0.29-5.47</td>
</tr>
<tr>
<td>Any hospitalization</td>
<td>1.02</td>
<td>0.66-0.99</td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>1.02</td>
<td>0.99-1.05</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>0.94</td>
<td>0.90-0.99</td>
</tr>
<tr>
<td>Propensity score</td>
<td>45.93</td>
<td>4.70-448.57</td>
</tr>
<tr>
<td>Any steroid burst</td>
<td>1.30</td>
<td>0.89-1.90</td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>1.03</td>
<td>1.00-1.05</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>0.97</td>
<td>0.93-1.00</td>
</tr>
<tr>
<td>Propensity score</td>
<td>176.14</td>
<td>27.19-1,141.06</td>
</tr>
</tbody>
</table>

**TABLE 4** Utilization Per Patient Per Month and [SD] Costs During the 6-Month Prestudy

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>All Patients (n = 5,541)</th>
<th>LM Users (n = 1,290)</th>
<th>LM Nonusers (n = 4,251)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy claims ($)</td>
<td>47.57 [60.57]</td>
<td>101.17 [73.38]</td>
<td>31.31 [44.87]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physician visits ($)</td>
<td>13.98 [47.12]</td>
<td>18.89 [54.21]</td>
<td>12.49 [44.64]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laboratory ($)‡</td>
<td>2.77 [5.71]</td>
<td>2.96 [6.07]</td>
<td>2.71 [5.60]</td>
<td>0.273</td>
</tr>
<tr>
<td>Miscellaneous services ($)§</td>
<td>7.37 [112.31]</td>
<td>5.54 [54.77]</td>
<td>7.93 [124.63]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergency room visits ($)§</td>
<td>6.54 [29.64]</td>
<td>6.16 [23.90]</td>
<td>6.65 [31.17]</td>
<td>0.375</td>
</tr>
<tr>
<td>Hospitalizations ($)§</td>
<td>37.09 [227.09]</td>
<td>35.94 [203.19]</td>
<td>37.44 [233.88]</td>
<td>0.638</td>
</tr>
<tr>
<td>Steroid bursts ($)§</td>
<td>0.05 [0.23]</td>
<td>0.08 [0.32]</td>
<td>0.04 [0.20]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>115.32 [271.14]</td>
<td>170.60 [236.16]</td>
<td>98.54 [278.75]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test.
‡ Includes chest X-ray, 2 views; blood gases: pH, pO2, automated hemogram; prolonged postexposure evaluation of bronchoscopy; bronchoscopy evaluation; sputometry.
§ Includes nursing services, home health/waivered services, supplies, transportation, other.
TABLE 5  Utilization Per Patient Per Month and [SD] Costs for Primary Outcome Measures During the 90-Day Outcome Measurement Period

<table>
<thead>
<tr>
<th>Outcome Measure*</th>
<th>All Patients (n = 5,541)</th>
<th>Leukotriene Modifier Users (n = 1,290)</th>
<th>Leukotriene Modifier Nonusers (n = 4,251)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency room visits ($)</td>
<td>5.24 [32.49]</td>
<td>5.89 [34.77]</td>
<td>5.05 [31.77]</td>
<td>0.470</td>
</tr>
<tr>
<td>Hospitalizations ($)</td>
<td>28.39 [255.88]</td>
<td>28.98 [225.78]</td>
<td>28.21 [264.36]</td>
<td>0.089</td>
</tr>
<tr>
<td>Steroid bursts ($)</td>
<td>0.04 [0.29]</td>
<td>0.07 [0.37]</td>
<td>0.04 [0.26]</td>
<td>0.001</td>
</tr>
<tr>
<td>Total ($)</td>
<td>33.68 [259.22]</td>
<td>34.93 [228.59]</td>
<td>33.30 [267.84]</td>
<td>0.019</td>
</tr>
</tbody>
</table>

* Emergency room visits, hospitalizations, and costs associated with a diagnosis for asthma (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 493, excluding 493.2x). Steroid bursts were defined as a pharmacy claim for oral prednisone 1 day prior to an office visit to 3 days following an office visit, which has an ICD-9-CM code for asthma. Utilization was calculated during the 3-month outcome period.
† Mann-Whitney U test.

certain diseases. The key to a good drug proxy is that its therapeutic use is narrow, e.g., insulin in diabetics, thereby increasing the likelihood that the patient does, in fact, have that condition. Unfortunately, steroid bursts have many uses. To ensure that we were not overestimating the number of bursts associated with asthma disease management, we required that the burst be dispensed 1 day before to 3 days after a physician visit that had an ICD-9-CM code for asthma. However, this definition may have underestimated the occurrence of steroid bursts because pharmacy claims would not be captured for prednisone refills or new prednisone prescriptions outside this relatively narrow date range around a medical office visit with an ICD-9-CM code for asthma.

Third, this study is also limited by the factors that impact all research with administrative claims, such as upcoding for reimbursement purposes or disease misclassification. For example, 5,992 (52%) of the patients who would otherwise have been included in this study had a diagnosis of asthma but did not receive asthma medication. These may be very mild asthma patients, patients who do not actually have asthma, or asthma patients who received prescription samples from their physician. However, if their only prescription was for an LM that was being used for allergic rhinitis or off-label for urticaria, and the diagnosis was misclassified as asthma, the results would be biased to the null hypothesis, i.e., that there is no difference in utilization or costs between the LM users and nonusers. We also did not calculate an estimate of the magnitude of this potential threat by determining the number and proportion of the 5,541 asthma patients who were identified by only 1 claim with an asthma diagnosis.

Fourth, we assumed that a filled prescription is consumed. We could not determine patient compliance with a medication or whether a patient correctly used a spacer for inhaled medications.

Fifth, while propensity score analysis has been shown to be a valid method to reduce selection bias, it can only control for known variables, not unknown variables. Also, the Medicaid database does not contain any clinical variables such as changes in FEV₁ (forced expiratory volume in 1 second) values or changes in nocturnal awakenings. A major component of this study, however, examined drug utilization, which has been shown to be very reliable in a Medicaid database.

Finally, this study looked at the class of LMs and not at individual drugs. The Ohio Medicaid asthma treatment guidelines do not specify one LM over another.

**Conclusion**

In this study of adult Medicaid asthma patients, the use of LMs was not associated with clinical effectiveness in asthma control as measured by lower use of emergency room visits, hospitalizations, or steroid bursts. In this cohort of adult asthma patients with at least 1 asthma medication, there does not appear to be any cost offsets to the Ohio Medicaid program associated with the additional direct drug costs of LMs, and PPPM costs were 4.9% ($1.63) higher for the 3 primary outcome measures for users of LMs versus nonusers.

**DISCLOSURES**

This project was conducted under an interagency agreement with the University of Cincinnati and the Ohio Department of Jobs and Family Services through the Ohio Medicaid Technical Assistance Policy and Program (MEDTAPP). The results and opinions expressed do not necessarily represent the official views of the Ohio Department of Jobs and Family Services. No outside funding supported this research. All authors but Joseph A. Johnston are currently employed by the University of Cincinnati; Johnston was formerly employed at the university’s medical center. The authors disclose no potential bias or conflict of interest relating to this article.

Author Pamela C. Heaton served as principal author of the study. Study concept and design were contributed primarily by Heaton, with input from authors Jeff J. Guo, Richard W. Hornung, Joseph A. Johnston, Raymond Jang, and Robert J. Cluxton Jr. Data collection was the work of author Charles J. Moomaw, with input from Heaton and Hornung; data interpretation was primarily the work of Hornung, Heaton, and Moomaw; with input from the coauthors. Drafting of the manuscript and its revision were primarily the work of Heaton, with input from the coauthors.

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Analysis of the Effectiveness and Cost Benefit of Leukotriene Modifiers in Adults With Asthma in the Ohio Medicaid Population


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Higher Costs and Therapeutic Factors Associated With Adherence to NCQA HEDIS Antidepressant Medication Management Measures: Analysis of Administrative Claims

REBECCA L. ROBINSON, MS; STACEY R. LONG, MS; STELLA CHANG, MPH; STEPHEN ABLE, PhD; ONUR BASER, PhD; ROBERT L. OBENCHAIN, PhD; and RALPH W. SWINDLE, PhD

OBJECTIVE: To determine if the type of antidepressant drug is related to adherence to National Committee for Quality Assurance (NCQA) Antidepressant Medication Management (AMM) quality measures and to assess the 6-month health care costs among newly diagnosed depressed patients.

METHODS: The MarketScan Commercial Claims and Encounter database for medical and pharmacy claims from January 2001 to September 2004 was used to assess adherence to the 3 AMM quality-of-care measures. AMM measures include (a) adequate care: the percentage of eligible members who remained on antidepressant medication continuously for 3 months after the initial diagnosis as determined by at least 84 days supply of antidepressant drugs during the first 114 days following receipt of the index antidepressant; (b) continuation phase, the percentage of eligible members who remained on antidepressant medication continuously for the 6 months after the initial diagnosis as determined by at least 180 days supply of antidepressants during the first 214 days following receipt of the index antidepressant; and (c) practitioner contacts, the percentage of members who received at least 3 follow-up office visits or telephone contacts with health care providers, including at least 1 contact with a practitioner licensed to prescribe (may not necessarily be the prescriber of the antidepressant). A fourth measure, overall adherence, was added, if all 3 AMM measures were met. Multivariate logistic regression models determined demographic, clinical (such as receipt of mental health specialty care, the Charlson Comorbidity Index score, and co-occurring, bipolar or schizophrenia), and therapy-related factors associated with outcomes of adherence and costs (paid amounts for insurance-reimbursable health care services for inpatient admissions, emergency department services, outpatient services, and outpatient prescription drugs). Health care expenditures (both total and mental-health-specific costs) were measured for each patient for 6 months following the date of service for the index antidepressant.

RESULTS: A total of 60,386 adult patients (10.7%) of 562,898 patients with a depression diagnosis met NCQA inclusion criteria in the AMM Technical Specifications (e.g., aged 18 years or older, newly diagnosed with depression and initiating antidepressant therapy, 365 days of continuous enrollment; patients were excluded if there were missing data on dose or quantity of index drug in pharmacy claims or initiated therapy on 2 or more antidepressants as the index medication, exclusion criteria not in the AMM Technical Specifications). Only 19% of patients achieved overall adherence. Rates for the 3 AMM measures were 39% for practitioner contacts, 65% for acute phase, and 44% for continuation phase. Receipt of mental health specialty care was the only factor that was positively associated with greater adherence on all 4 measures (overall measure: odds ratio [OR] = 3.895, 95% confidence interval [CI] = 3.72-4.07; acute OR = 1.36, 95% CI = 1.33-1.40; continuation OR = 1.46, 95% CI = 1.41-1.51; contacts OR = 5.83, 95% CI = 5.62-6.06). Most patients were initiated on selective serotonin reuptake inhibitors (SSRIs, 69.5%), followed by venlafaxine (21.4%), tricyclic antidepressants (TCAs, 21.4%), bupropion (11.0%), and other antidepressants (e.g., mirtazapine, nefazodone, trazodone; 7.2%). Before adjustment for confounding factors, patients initiated on venlafaxine, TCAs, or other antidepressants had higher rates of adherence on the overall performance measure versus initiators on SSRIs, but the absolute differences were relatively small: 21.4% for venlafaxine and TCAs and 23.1% for other antidepressants versus 18.5% for SSRIs (P < .001). Patients initiated on venlafaxine, TCAs, or other antidepressants were also more likely to receive care from a mental health specialist, 16.8%, 15.0%, and 54.8%, respectively, compared with SSRIs (13.0%, all P < .001). Regressions analysis showed that only venlafaxine had a higher OR (1.13; 95% CI, 1.05-1.22) compared with SSRIs for adherence on the overall measure. Initiating dose level was in the target range for 70.0% of all patients (24.9% were below target dose and 5.2% above target dose), and adherent patients on all 3 AMM measures were less likely than nonadherent patients (70.4% vs. 68.4%, P < .001) to be initiated in the target dose range. After multivariate adjustment, the initiating dose (target vs. high) was a significant factor in explaining adherence to the overall measure (OR = 1.26; 95% CI, 1.16-1.37). Adherent patients had 6-month median unadjusted total health care expenses that were nearly 2 times higher compared with nonadherent patients ($5,169 vs. $2,734) and mental health expenditures that were nearly 3 times higher ($1,922 vs. $677). After adjustment, adherent patients compared with nonadherent patients incurred an additional $644 in mental health expenditures and $866 in overall health care expenditures in the 6 months following initiation of antidepressant therapy.

CONCLUSIONS: Only 19% of depressed patients initiated on antidepressants met all 3 criteria set forth in the NCQA Health Plan Employer Data and Information Set (HEDIS) AMM quality-of-care performance measures. Receipt of mental health specialty care was the single factor most strongly associated with quality of treatment by these measures. Type and dosage level of initial antidepressant was associated with adherence to the NCQA HEDIS AMM measures, but the absolute difference in rates of adherence were relatively small among types of antidepressants. Patients were more likely to receive care from a mental health specialist for antidepressant therapy. These analyses were limited to administrative claims that lack indicators of depression disease severity.

KEYWORDS: Depression treatment guidelines, Antidepressants, NCQA, HEDIS, Health care expenditures

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T he management of depression and associated costs of care continue to be topics for policy and health plan leaders.1 Well-established depression treatment guidelines have been created, yet inadequate use of antidepressants continues.2-4 This study examines factors associated with adherence to national treatment guidelines, including investigations of the impact of antidepressant and initial dosage level on adherence measures and costs.

An estimated 16% of the costs of antidepressant treatment were found to be associated with patients who were never adequately treated.4 Inadequate dose and duration of antidepressant treatment has been reported to directly hinder treatment outcomes.6 Nevertheless, in samples of privately insured patients, rates of inadequate antidepressant care have ranged from 35% to 51%.4,7 Across studies, patients treated in primary care reported the lowest rates of adequate care,1 whereas patients seen by both primary care physicians and psychiatrists had higher rates than patients only seen in primary care.7 Shasa et al. (1997) found that psychiatrists were more likely to prescribe antidepressants at an adequate dosage level, but nonpsychiatric physicians were more likely to attain adequate duration of treatment.8

Continuation of treatment during the acute and maintenance phases of therapy is encouraged by treatment guidelines regarding the adequate care of patients with depression. The National

Note: An editorial on the subject of this article appears on pages 78-80 of this issue.

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Committee for Quality Assurance (NCQA) standardized performance measures are based on the most commonly used guidelines, originally set forth by the Agency for Health Research and Quality (AHRQ). NCQA performance measures are voluntarily reported by health plans, from the Health Plan Employer Data and Information Set (HEDIS), and are published annually by NCQA in an effort to improve quality of care and to assist decision makers in selecting quality health care plans.

Performance among HEDIS mental health domains lags significantly below that for non-mental health domains. Reported rates of improvement for antidepressant medication management (AMM) have shown little improvement between 2001 and 2004 (see Table 1 for definitions of AMM measures). Mental health specialty care has been reported to be an important predictor of adequate treatment. Less is known about the impact of drug-related factors independent of provider type on quality of care in the treatment of depression. With the wide variety of antidepressants available, this study sought to evaluate the independent association of the type of initiating drug dose level on adherence to the 3 individual HEDIS AMM measures and on overall adherence among depressed patients after adjusting for other clinical and demographic factors. We also examined the association of overall guideline adherence, initiating antidepressant, and initiating dosage levels on 6-month health care costs.

### Methods

#### Data Source
This retrospective claims analysis utilized data from the MarketScan Commercial Claims and Encounter database for the period of January 1, 2001, through September 30, 2004. These data included health insurance claims across the continuum of care (e.g. inpatient, outpatient, outpatient pharmacy, carve-out behavioral health care) as well as enrollment data from large employers from across the United States who funded private health care coverage for more than 4 million employees and their dependents. This administrative claims database includes a variety of fee-for-service, preferred provider organization (PPO), and capitated health plans.

#### Study Population
Patients (employees and dependents) were included in this study if they met 2004 NCQA HEDIS Technical Specifications, volume 2, for the AMM measures. All patients were required to be aged 18 years or older, newly diagnosed with depression (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] = 296.2x, 296.3x, 298.0x, 300.4x, 309.1x, 311.xx or DRG = 426 for hospital inpatient claims) is on the medical claim. For optimal practitioner contacts for medical management, the HEDIS Technical Specifications include the requirement that “at least one of the three follow-up contacts must be with a prescribing practitioner (e.g., licensed physician, physician assistant or other practitioner with prescribing privileges).” The prescribing practitioner may not necessarily be the prescriber of the antidepressant for the patient.

### Table 1

<table>
<thead>
<tr>
<th>NCQA HEDIS AMM Effectiveness of Care Measures—Commercial* Plan Performance</th>
<th>2001*</th>
<th>2002*</th>
<th>2003*</th>
<th>2004*</th>
<th>Present Study†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute-phase treatment: the percentage of eligible members who remained on antidepressant medication continuously for 3 months after the initial diagnosis</td>
<td>56.9</td>
<td>59.8</td>
<td>60.7</td>
<td>60.9</td>
<td>64.8</td>
</tr>
<tr>
<td>Continuation-phase treatment: the percentage of eligible members who remained on antidepressant medication continuously for 6 months after the initial diagnosis</td>
<td>40.1</td>
<td>42.8</td>
<td>44.1</td>
<td>44.3</td>
<td>44.3</td>
</tr>
<tr>
<td>Practitioner contacts: the percentage of eligible members who received at least 3 follow-up practitioner contacts‡ in the 12-week acute-treatment phase after a new diagnosis of depression and prescription of antidepressant</td>
<td>19.8</td>
<td>19.2</td>
<td>20.3</td>
<td>20.0</td>
<td>39.0</td>
</tr>
</tbody>
</table>

† Commercially insured patients (n = 60,386) in the Medstat MarketScan database who met the inclusion/exclusion criteria for claims from January 1, 2001, through September 30, 2004; patients were also excluded if they were missing data on the dose or quantity of the index medication or were initiated on multiple antidepressants as the initial therapy (exclusion criteria not in the AMM Technical Specifications) (see Table 2).
‡ The HEDIS measure for practitioner contacts changed in 2004 to include telephone interventions (CPT 99371-99373) as one of the visits if a depression diagnosis (ICD-9-CM 296.2x, 296.3x, 298.0x, 300.4x, 309.1x, 311.xx or DRG = 426 for hospital inpatient claims) is on the medical claim. For optimal practitioner contacts for medical management, the HEDIS Technical Specifications include the requirement that “at least one of the three follow-up contacts must be with a prescribing practitioner (e.g., licensed physician, physician assistant or other practitioner with prescribing privileges).” The prescribing practitioner may not necessarily be the prescriber of the antidepressant for the patient.

AMM = Antidepressant Medication Management; CPT = current procedural terminology; DRG = diagnosis-related group; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification. NCQA = National Committee for Quality Assurance.
TABLE 2  Patient Selection and Exclusion Criteria for Present Study

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No. of Patients Lost (%)</th>
<th>No. of Patients Remaining (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression diagnosis:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| • ≥1 principal or primary diagnosis of major depression (ICD-9-CM = 296.2, 296.3, 298.0, 300.4, 309.1, 311 or DRG = 426, excluding principal diagnosis of 301.12) in any setting (e.g., outpatient, inpatient, emergency services, or partial hospitalizations) or
| • >1 secondary diagnosis of major depression on different dates of service in any outpatient setting or                                                                                                                     |
| • >1 secondary diagnosis of major depression on any inpatient discharge                                                                                                                                             |
| Exclude patients with diagnosis history:                                                                                                                                                                                  |
| • determine patients’ earliest qualifying encounter (index diagnosis date) and                                                                                                                                           |
| • exclude patients with prior depressive episodes (ICD-9-CM = 296.2-296.9, 298.0, 300.4, 309.0, 309.1, 309.28, 311 or DRG = 426, excluding principal diagnosis of 301.12) in the previous 120 days                                                                 |
| Require continuous enrollment for 120 days prior to and 245 days following index diagnosis                                                                                                                                 |
| Require antidepressant drug therapy beginning 30 days prior to and 14 days following index diagnosis                                                                                                                                 |
| Exclude patients with antidepressant drug history:                                                                                                                                                                      |
| • identify the earliest qualifying prescription (30 days prior to or 14 days on or following index diagnosis) and                                                                                                        |
| • exclude patients with antidepressant pharmacy claims during the 90 days prior to the qualifying prescription date                                                                                                      |
| Exclude patients with an acute mental health or substance abuse inpatient stay during the 245 days following index diagnosis (DRG = 424-432, except discharges with principal ICD-9-CM diagnosis of 317-319; or ICD-9-CM principal diagnosis of 290, 293-302, 306-316, or DRG = 433-437; or ICD-9-CM principal diagnosis of 291-292, 303-305, 960-979 with a secondary diagnosis of chemical dependency) |
| Additional exclusion not in the AMM Technical Specifications: Exclude patients with an invalid index drug claim (unknown dosage, unknown quantity, adjustment claim [adjudicated claims that were later found to be erroneous], or multiple antidepressant starts) |
| * 4.9% of the 11,488,791 health plan members in the available dataset as of September 30, 2004.                                                                                                                             |
| † 0.5% of the 11,488,971 health plan members in the available dataset as of September 30, 2004.                                                                                                                             |

DRG = diagnosis-related group; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

compliance, patients whose index drug claim had missing or invalid dosage or quantity and patients who started on multiple antidepressant treatments were excluded from the study (1.9% of available patients, but 14.8% of otherwise-eligible patients, Table 2). Patients who switched or added drug therapies at a later time remained in the study. Patients who had an acute mental health or substance abuse hospital stay during the 245 days following the index diagnosis date were excluded.

Study Measures

To assess factors associated with adherence to 2004 NCQA HEDIS AMM measures, 4 dichotomous variables were created (where achievement = yes, failure to achieve = no). Three measures followed the individual components of the NCQA HEDIS AMM Technical Specifications criteria. A fourth variable was created to capture an aggregate measure of overall adherence.

1. Optimal practitioner contacts. At least 3 billable claims for contacts with a primary care or mental health practitioner had to be coded with a mental health diagnosis during the 84 days following the new diagnosis of major depression. Consistent with HEDIS specifications, one of these visits may be for billable telephone interventions (current procedural terminology [CPT] 99371–99373) as long as a depression diagnosis was on that claim. The HEDIS Technical Specifications include the requirement that “at least one of the three follow-up contacts must be with a prescribing practitioner (e.g., licensed physician, physician assistant or other practitioner with prescribing privileges).” The prescribing practitioner may not necessarily be the prescriber of the antidepressant for the patient.

2. Effective acute-phase treatment. Pharmacy claims had to include at least 84 days supply of antidepressants during the first 114 days following initiation of the index medication.

3. Effective continuation-phase treatment. Pharmacy claims had to include at least 180 days supply of antidepressants during the 214 days following initiation of the index medication.

4. Overall adherence. All 3 of the above performance measures had to be met.

To measure the influence of AMM adherence on costs, overall health care expenditures and depression-related expenditures during the 6-month postperiod were calculated. Total health care expenditures included the health plan paid amounts for insurance-reimbursable health care services, stratified by inpatient admissions, emergency department services, outpatient services, outpatient prescription drugs, and overall totals incurred during the 6 months following initiation of antidepressant therapy. The mean absolute days between the index
Higher Costs and Therapeutic Factors Associated With Adherence to NCQA HEDIS Antidepressant Medication Management Measures: Analysis of Administrative Claims

TABLE 3 Dosage Range of Antidepressants*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low-Dose Range (mg)</th>
<th>Target-Dose Range (mg)</th>
<th>High-Dose Range (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>&lt;20</td>
<td>20-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>&lt;20</td>
<td>20-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>&lt;20</td>
<td>20-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Sertraline</td>
<td>&lt;50</td>
<td>50-150</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Fluvoxamine maleate</td>
<td>&lt;50</td>
<td>50-100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>SNRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine IR or XR</td>
<td>37.5-74</td>
<td>75-150</td>
<td>151+</td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion hydrochloride (Wellbutrin SR)</td>
<td>&lt;150</td>
<td>150-300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Bupropion hydrochloride (tablet)</td>
<td>&lt;200</td>
<td>200-300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>&lt;15</td>
<td>15-30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Nefazodone hydrochloride</td>
<td>&lt;200</td>
<td>200-400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Isocarboxazid</td>
<td>&lt;20</td>
<td>20-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Maprotiline hydrochloride</td>
<td>&lt;75</td>
<td>75-150</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Phelazine sulfate</td>
<td>&lt;45</td>
<td>45-60</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Tranylcypromine sulfate</td>
<td>&lt;30</td>
<td>30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Trazodone hydrochloride</td>
<td>&lt;150</td>
<td>150-400</td>
<td>&gt;400</td>
</tr>
</tbody>
</table>

TCA:
- Amintrypirine hydrochloride <75 75-150 >150
- Clomipramine hydrochloride <25 25-150 >150
- Desipramine hydrochloride <100 100-200 >200
- Doxepin hydrochloride <25 75-150 >150
- Imipramine hydrochloride <50 50-100 >100
- Imipramine pamoate <50 50-100 >100
- Nortriptyline hydrochloride <25 25-100 >100
- Protriptyline hydrochloride <45 45-100 >100
- Trimipramine maleate <75 75-150 >150


IR = immediate release; XR = extended release; SNRI = serotonin norepinephrine reuptake inhibitor; SR = sustained release; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Diagnosis and filled prescription was 7 days (median = 4 days). The subset of overall expenditures that were depression-related also was assessed.

Encounter records for patients in some plans are based on capitated payment records, and the payment field is rarely populated. To address this issue, a payment rate was assigned to each procedure code based on a regionally adjusted mean payment amount for that procedure from all Marketscan fee-for-service claims occurring in that year. All actual and proxy payments were then adjusted to 2004 dollars using the Consumer Price Index for all Urban Consumers (CPI-U).15

Measures of index antidepressant class, dosage level, patient characteristics, and clinical characteristics were used as independent variables.

Index medication. Patients initiated on any of the following agents were classified into 5 comparison groups based on the index antidepressant claim:
- TCAs (tricyclic antidepressants);
- SSRIs (selective serotonin reuptake inhibitors; fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram);
- SNRIs (serotonin norepinephrine reuptake inhibitors; venlafaxine IR, venlafaxine XR), bupropion; or
- “Other antidepressant” (i.e., mirtazapine, nefazodone, trazodone, isocarboxazid, maprotiline, phelazine sulfate, and tranylcypromine sulfate).

Medication use in this analysis was based on intent to treat. That is, if a patient initiated on an SSRI and switched or augmented using another drug class, their adherence rate and costs would be associated with the patient’s initiation on SSRIs. No minimum duration period on the initiating drug was required in order to avoid biasing the sample toward adherent patients. Overall, 12.6% of patients switched or augmented sometime during the 6-month follow-up.

Index dosage level. Daily dose was calculated for the index medication based on the number of pills, strength, and days supplied. Daily doses were then defined as low, target, or high based on the dosage ranges specified in the product insert (PI) for each drug (see Table 3). For example, “target dose” was defined as 20-40 mg per day for fluoxetine and 75-150 mg per day for venlafaxine.

Patient characteristics. Patient characteristics were based on data available at the time of the index medication claim, including age, gender, geographic region (Northeast, North Central, South, or West), insurance plan type (capitated vs. non-capitated), and a proxy for household socioeconomic status (salary vs. hourly pay). Insurance plan types defined as capitated included health maintenance organizations and point of service (POS) with capitation. Noncapitated health plans included PPOs, basic/major medical, comprehensive, and noncapitated POS.

Clinical characteristics. Comorbid anxiety and bipolar disorders were measured in the preperiods and postperiods using individual ICD-9 codes (300.0x for anxiety disorder and 296.4x, 296.5x, 296.6x, 296.8x for bipolar disorder). Chronic disease was assessed by using inpatient and outpatient diagnoses to calculate the Charlson Comorbidity Index Score (CCI).16 An indicator variable identifying patients receiving any mental health specialty care (any billed contact/encounter coded with a psychiatrist, mental health and chemical dependency treatment facility, psychologist, or psychiatric nurse) during the study period was also included.

Statistical Analysis

Univariate analyses, including t tests and chi-square tests, were used to analyze patient and clinical characteristics by initiating treatment groups. Multivariate regression models were used to evaluate differences across outcomes of interest: adherence to HEDIS guidelines and economic impact of adherence to HEDIS.
Logistic regression models were used to assess the impact of the index medication and dosage level (low, target, high) with adherence to AMM for appropriate treatment in patients with depression. A series of expenditure models were estimated to evaluate the incremental economic impact of adherence to the 3 HEDIS measures and the overall adherence measure, controlling for other observable variables of index medication, dosage level, patient demographics, and clinical characteristics.

After reviewing the distribution of the dependent expenditure variables, it was determined that exponential conditional mean (ECM) models were most appropriate. These models produced parameter estimates for each covariate, which were used to compute the marginal effects (MEs) of these characteristics on health care expenditures. To ensure that 2 or more variables were not measuring the same construct, variance inflation factors were examined to assess potential multicollinearity, and no interaction terms were deemed necessary. T tests and chi-square tests were conducted using SAS version 8.0 (Cary, NC), and multivariate analyses were conducted using STATA 8.0 (College Station, TX) software.

**Results**

**Descriptive Statistics**

Table 4 provides baseline characteristics for the overall study population stratified by the index therapy. The mean age in the overall study population was 43 years, and 69% of subjects were female. Most of the 60,386 individuals in the study initiated on SSRIs (69.5%), followed by bupropion (11.0%), SNRIs (venlafaxine, 8.7%), and TCAs (3.7%). Seven percent of
individuals were initiated on “other antidepressants.” The largest proportion of patients who received “other antidepressants” was 3.3% for trazodone, 1.9% for mirtazapine, 1.9% for nefazadone, and <0.1% for the remaining monoamine oxidase inhibitors and maprotiline. Aside from initiating dose levels and proportion of patients with mental health specialty care, differences in patient clinical and demographic characteristics across the comparator drug groups were minimal, although several differences between the SSRI cohort and other classes of antidepressant users were considered statistically significant. Overall, approximately 70% of patients initiated antidepressant drug therapy at target (recommended) dose ranges. The proportion of TCA (37%) and other antidepressant users (44%) initiating at target dose ranges was significantly lower, while the proportion of bupropion (82%) and venlafaxine (SNRI, 77%) users initiating at target levels was significantly higher than SSRI users (72%).
Overall, 32% of patients titrated at some point during the 6-month follow-up (data not shown). Across the entire study population, 19% of patients met all 3 HEDIS AMM measures, 39.0% met the criteria for the optimal practitioner contacts measure (the proportion of telephone contacts was not measured), 64.8% met criteria for acute-phase treatment, and 44.3% were adherent for the continuation-phase treatment measure (Table 4).

Unadjusted 6-month, postindex direct health care expenditures stratified by the overall adherent cohort versus nonadherent cohort are presented in Table 5. Individuals adherent with all 3 HEDIS AMM measures had median total costs that were nearly 2 times higher ($5,169 vs. $2,734), and approximately 37% of the total costs were for depression-related care in the adherent group ($1,922) versus 25% ($677 of $2,734) in the nonadherent group. On average, adherent individuals had depression-related outpatient service costs that were more than double those in patients who were nonadherent. Depression-related outpatient pharmaceutical costs also were 2 times higher for adherent individuals.

### Multivariate Modeling Results

Table 6 (logistic regression models) and Table 7 (exponential conditional mean regression models) report the results of the multivariate analyses, controlling for all potential patient and clinical confounding factors as specified in Table 4. Receipt of mental health specialty care was the only consistently significant association and was the largest single contributor in each model. Individuals with at least 1 encounter with a psychiatrist, psychologist, mental health treatment facility, or psychiatric nurse were 5 times more likely to meet optimal practitioner contacts (OR = 1.382; 95% CI, 1.33-1.43) and continuation-phase treatment (OR = 1.459; 95% CI, 1.41-1.51).

Results varied according to initiating antidepressant therapy and individual adherence measures. Patients initiating on venlafaxine (SNRI) were more likely than SSRI initiators to meet optimal practitioner contacts (OR = 1.382; 95% CI, 1.33-1.43) and continuation-phase treatment (OR = 1.459; 95% CI, 1.41-1.51).
Higher Costs and Therapeutic Factors Associated With Adherence to NCQA HEDIS Antidepressant Medication Management Measures: Analysis of Administrative Claims

TABLE 7 Impact of Adherence to NCQA HEDIS AMM Measures on 6-Month Overall and Depression-Related Expenditures: Results From Exponential Conditional Mean Regression Models (Marginal Effects*)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Marginal Effect on Overall Costs (P Value)</th>
<th>Marginal Effect on Depression-Related Costs (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall adherence</td>
<td>$806 (0.001)</td>
<td>$644 (0.001)</td>
</tr>
<tr>
<td>TCA†</td>
<td>$964 (0.001)</td>
<td>$692 (0.001)</td>
</tr>
<tr>
<td>SNRI (venlafaxine)†</td>
<td>$402 (0.001)</td>
<td>$304 (0.001)</td>
</tr>
<tr>
<td>Bupropion†</td>
<td>$131 (0.142)</td>
<td>$79 (0.001)</td>
</tr>
<tr>
<td>Other AD†</td>
<td>$654 (0.001)</td>
<td>$90 (0.001)</td>
</tr>
<tr>
<td>Northeast†</td>
<td>$661 (0.001)</td>
<td>$198 (0.001)</td>
</tr>
<tr>
<td>North Central†</td>
<td>$752 (0.001)</td>
<td>$149 (0.001)</td>
</tr>
<tr>
<td>South†</td>
<td>$930 (0.001)</td>
<td>$179 (0.001)</td>
</tr>
<tr>
<td>Unknown region†</td>
<td>-$631 (0.221)</td>
<td>-$142 (0.008)</td>
</tr>
<tr>
<td>Age</td>
<td>$42 (0.001)</td>
<td>$2 (0.001)</td>
</tr>
<tr>
<td>Salaried-wage household</td>
<td>$233 (0.001)</td>
<td>-$15 (0.207)</td>
</tr>
<tr>
<td>Unknown-wage-type household</td>
<td>$144 (0.080)</td>
<td>$48 (0.003)</td>
</tr>
<tr>
<td>CCI=0</td>
<td>-$62 (0.400)</td>
<td>-$42 (0.001)</td>
</tr>
<tr>
<td>Comorbid anxiety</td>
<td>$334 (0.001)</td>
<td>$25 (0.045)</td>
</tr>
<tr>
<td>Comorbid bipolar</td>
<td>$1,867 (0.001)</td>
<td>$432 (0.001)</td>
</tr>
<tr>
<td>Capitated insurance</td>
<td>-$670 (0.001)</td>
<td>-$139 (0.001)</td>
</tr>
<tr>
<td>Any MH specialty care</td>
<td>$494 (0.001)</td>
<td>$335 (0.001)</td>
</tr>
<tr>
<td>Low-dose initiator§</td>
<td>-$227 (0.001)</td>
<td>-$99 (0.001)</td>
</tr>
<tr>
<td>High-dose initiator§</td>
<td>$1,195 (0.001)</td>
<td>$360 (0.001)</td>
</tr>
</tbody>
</table>

* For optimal contacts, the HEDIS Technical Specifications include the requirement that “at least one of the three follow-up contacts must be with a prescribing practitioner (e.g., licensed physician, physician assistant or other practitioner with prescribing privileges).” The prescribing practitioner may not necessarily be the prescriber of the antidepressant for the patient.

† Relative to recommended (target) dose initiators.
‡ Relative to West.
§ Relative to SSRI.
|| Any MH specialty care = one or more contacts with psychiatrist, mental health and chemical dependency treatment facility, psychologist, or psychiatric nurse.
AD = antidepressant; AMM = antidepressant medication management; CCI = Charlson Comorbidity Index; HEDIS = Health Plan Employer Data and Information Set; MH = mental health; NCQA = National Committee for Quality Assurance; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

CI, 1.12-1.26) as well as achieving combined overall adherence (OR = 1.134; 95% CI, 1.05-1.22). Bupropion initiators were less likely to meet the criteria on these same measures relative to SSRIs (effective acute treatment [OR = 0.700; 95% CI, 0.66-0.74]; continuation-phase treatment [OR = 0.702; 95% CI, 0.67-0.74]; and overall guideline adherence [OR = 0.866; 95% CI, 0.81-0.93]). Venlafaxine and bupropion users did not differ from SSRI initiators with respect to likelihood of meeting criteria for the optimal practitioner contacts measures after controlling for confounding factors.

Other antidepressant initiators were more likely to achieve optimal contacts (OR = 1.348; 95% CI, 1.26-1.45) than SSRI initiators but were less likely to receive effective treatment in both the acute and continuation phases (OR = 0.741; 95% CI, 0.69-0.79 and OR = 0.859; 95% CI, 0.80-0.92). Other antidepressant users did not differ from SSRI users with respect to overall guideline adherence. TCA initiators were less likely than SSRI initiators to meet effective acute-phase treatment guidelines (OR = 0.766; 95% CI, 0.70-0.84) but did not differ from SSRI patients on all other measures.

Compared with patients initiating therapy at target doses, low-dose initiators were more likely to receive optimal practitioner contacts (OR = 1.099; 95% CI, 1.05-1.15) but less likely to meet effective acute- and continuation-phase treatment (OR = 0.861; 95% CI, 0.83-0.90 and OR = 0.845; 95% CI, 0.81-0.88, respectively). Low-dose initiators did not differ from target-dose initiators with respect to likelihood of overall guideline compliance. High-dose initiators, however, were more likely than target-dose initiators to meet effective acute- (OR = 1.317; 95% CI, 1.21-1.43) and continuation-phase treatment (OR = 1.583; 95% CI, 1.47-1.71) and overall adherence (OR = 1.259; 95% CI, 1.16-1.37) but did not differ on optimal practitioner contacts (OR = 0.966; 95% CI, 0.89-1.05).

Three additional factors were significantly associated with all adherence measures; however, the direction of the relationship for optimal contacts was the opposite to that of the acute- and continuation-phase treatment measures. Being male, younger, and having higher CCI scores were associated with receiving at least 3 practitioner contacts (all P < 0.01); however, these same factors were also associated with significantly less likelihood of adhering to acute- and continuation-phase treat-
Mean predicted total 6-month health care cost from the ECM models was $3,067 overall, and the ME associated with AMM measure adherence on overall health care expenditures was an additional $806. Predicted depression-related costs were $743, and the ME of overall AMM compliance was $644. The MEs of other patient characteristics on overall and depression-related costs are presented in Table 7. Figure 1 presents the ME of HEDIS AMM adherence on estimated overall and depression-related regression-adjusted health care expenditures for patients for the individual NCQA components and the overall adherence measure.

Among the subset of subjects meeting overall AMM adherence, SSRI users had significantly lower expenditures during the 6-month follow-up observation period than users of TCAs, venlafaxine, bupropion, and other antidepressants ($ < 0.030, ME for TCA=$794, venlafaxine=$853, bupropion=$364, other antidepressant = $934; data not shown) after controlling for confounding patient, clinical, and drug-related factors. With regard to depression-related expenditures, fully adherent venlafaxine (ME=$291), bupropion (ME=$184) and other antidepressant initiators (ME = $416) had significantly higher depression-related expenditures in the 6-month observation period than did adherent SSRI initiators. Depression-related expenditures in the follow-up period did not significantly differ between SSRI and TCA users. Among fully guideline-adherent individuals, those initiating antidepressant drug therapy at higher than target doses had significantly higher expenditures ($1,036 overall, $546 depression-related, $ < 0.001) than persons who initiated at target doses, while expenditures for those initiating at lower-than-target doses were significantly lower ($ < 0.001) from target-dose initiators (ME = $369; $187 for overall and depression-related expenditures, respectively).

Discussion

Consistent with previous research, we found that mental health specialty care was the largest contributor to performance on AMM adherence measures. Individuals with at least 1 encounter with a psychiatrist, psychologist, mental health treatment facility, or psychiatric nurse were 5 times more likely than those receiving fluoxetine (adequate dose: 18–22 mg) to achieve dose-related “adequate” treatment during acute and continuous treatment phases in a large managed care organization claims database. Yu-Isenberg et al. speculated that the higher remission rates with SNRIs (venlafaxine) than SSRIs in clinical trials may be reflected in their findings.

Busch et al. (2004) found that the specific antidepressant initiated relative to a TCA had little impact on adherence to the guideline for continuation-phase treatment in the Department of Veterans Affairs (VA). We, too, found no difference between TCA and SSRI initiators on effective continuation treatment, optimal number of practitioner contacts, or overall adherence measures. We did, however, find TCA initiators were less likely to achieve guideline-adherent acute-phase treatment.

Quality care in the VA as reported by Busch et al. was similar regardless of whether it was provided in a mental health clinic or other setting, whereas in the Marketscan data from January 1, 2001, to September 30, 2004, used in the present study, receipt of specialty mental health care was the largest contributing factor across all adherence measures. These differences may underscore the complexities associated with specific payer settings that are unmeasurable in retrospective administrative claims. This highlights an important limitation that these findings are not generalizable to other settings. Further work is necessary to determine if consistent patterns of associations with adherence outcomes are found in different payer settings or if quality differences are an artifact of the method of data collection.

Likewise, adherence rates in the 2001 VA data were higher, at 85% and 54% for effective acute-phase and continuation-phase treatment, in contrast to 65% and 44%, respectively, in the present study, and the ranges of 57% to 61% for acute care and 40% to 44% for continuation-phase care during the 2001-2004 reporting years for the NCQA Quality Compass reports of commercial populations.

Rates of optimal practitioner contacts reported by NCQA are considerably lower (19.2% to 20.3%) than our finding of 39%. A possible explanation may be due to differences in study
population characteristics. The database used in the present study includes claimants that have their insurance coverage through large Fortune 500 companies. These employers may offer premium coverage at rates affordable to their recipients or may encourage disease management programs to enhance quality care. Cost constraints have been reported to impact antidepressant medication adherence and threaten quality care.21 Lee and Zapert (2005) reported data from the Harris Interactive Strategic Health Perspectives Survey that found that patients enrolled in higher-deductible plans were less likely to fill antidepressant prescriptions because of costs than patients in the non-high-deductible group.22 In a recent article from The New York Times, employers, who are especially concerned about depression impacting employee productivity, have influenced insurers to pay for programs to manage depression.23

Another reason adherence to optimal contacts may be higher in the present study is that we excluded patients with incomplete index drug claims (i.e., unknown dosage, quantity) or prescription fills for multiple antidepressants on a single day following the depression diagnosis. These patients represented 1.9% of all patients prior to application of the exclusion criteria and 14.8% of otherwise-eligible patients according to the other exclusion criteria; they may have been more likely to be missing visit data as well and therefore may have reduced our rate slightly if they had remained in the study.

Another finding from the present study was that low-dose initiators were more likely to receive an optimal number of practitioner contacts than patients initiated at target doses. However, low-dose initiators were less likely to meet guideline adherence on acute- and continuation-phase treatment, whereas high-dose initiators were more likely to adhere to these measures than those initiating therapy at target doses. These findings are consistent with those reported by Katzelnick et al. (1996), who found that patients initiating at inadequate doses were less likely to receive a second antidepressant prescription, regardless of provider specialty.24 Both of these studies addressed populations of patients aged 65 years or younger. These findings may vary in study populations of older patients who may initiate anti-depressant therapies at lower doses and who may tend to have lower AMM quality scores (based on rates of adherence for Medicare patients).25

Not surprisingly, costs were higher for AMM-adherent individuals in the 6 months following initiation of treatment. This was consistent with previous research by Eaddy et al. (2005) that found that, among patients with depression and prescribed SSRIs, no medical cost offsets for higher pharmacy costs were found in patients who remained on their antidepressant for 90 days or longer;26 although research reported 9 years earlier found that adherent patients incurred lower medical-only charges.27

The present study found that the major cost drivers were outpatient contacts and depression-related pharmaceuticals, factors that determine AMM compliance. The ME associated with AMM adherence on overall 6-month health care expenditures was $806, of which $644 was attributable to depression-related services and antidepressant therapies. As expected, those with capitated insurance and low-dose initiators (compared with target-dose initiators) had significantly lower expenditures. Controlling for other factors, including overall guideline adherence, SSRI users had significantly lower overall costs than all other antidepressants with the exception of bupropion users. Depression-related costs were significantly lower among SSRI users, with the exception of TCA users (data not shown).

Limitations
Several factors should be considered when interpreting these findings. Foremost among the considerations is the large size of the groups, which allows us to detect statistically significant results for relatively small absolute differences between groups in some comparisons.

Second, a significant limitation of this study is its reliance on administrative (insurance) claims and the absence of depression severity, which may directly impact both therapy decisions and adherence measures. The findings of this study are also subject to the usual limitations of administrative datasets.26,27 For example, the treatment groups may be misclassified or there may be unobserved confounders that were not adequately controlled for in the multivariate analysis.

Third, rates of adherence to AMM quality measures may underreport actual quality of care since patients may receive treatment (e.g., advice or consult rendered by telephone) that is not submitted to their health plan for reimbursement and thus not included in the administrative claims data, or coding errors or omissions may have occurred. Kobak et al. (2002), in a separate study of those patients failing to meet one or more of the 3 AMM measures, found that the most common reason for visits failure (77% of overall failures) was that the patient restarted a previously prescribed successful antidepressant (16% of visits failure), including 12% of patients who had a visit with the prescribing provider, but mental health was not coded or documented in the case notes.28 Overall, misclassification of contacts was the most common reason for failure to meet the optimal number of practitioner contacts. On the other hand, 25% of patients had told their physician that they were taking their medication when the pharmacy claims database showed that they were not.

Fourth, generalizability is limited to the time frame assessed and to privately insured patients who may differ from the uninsured or publicly funded patients. Since the time of these analyses, the U.S. marketplace has changed, including (a) the introduction of more generic antidepressants such as paroxetine and citalopram, (b) the introduction of new products such as duloxetine, (c) the partial withdrawal of nefazadone, and (d) U.S. Food and Drug Administration warnings regarding the possibility of suicidality and other safety considerations for the
use of all antidepressants.

Fifth, this study only addresses adherence to the 3 NCQA HEDIS AMM measures. We did not assess the HEDIS measure of follow-up after hospitalization for depression. We also cannot assert that these performance measures are directly related to treatment outcomes. For example, there is no assurance that a given guidelines-adherent patient will achieve clinical response or remission of depression. Those with persistent or treatment-resistant depression may be more likely to satisfy the requirements of current measures but may still not receive adequate care.

Sixth, the expenditure assessment only focuses on costs incurred during the 180 days following initiation of antidepressant therapy; therefore, some of the cost savings due to medication adherence may not be realized for several months or possibly years following treatment. Rost et al. (2005) found that it took 2 years to realize the cost offset of enhanced care provided through successful depression management. This may be a period longer than a patient stays in a health plan.

Despite these significant limitations, this study appears to be the first to simultaneously address the impact of antidepressant class and dosage level on NCQA HEDIS AMM measures in a commercial setting. And while the study is limited by its reliance on administrative claims data, this is the same type of information that health plans are required to use when reporting NCQA AMM measures. Claims data do provide a naturalistic method for observing real-world treatment patterns that are unavailable in data collected in clinical trials.

These findings may reveal many implications for policy and health plan leaders. Although specialty care may improve rates of quality depression treatment, increasing the amount of treatment provided by psychiatrists may not be feasible because of the limited number of available psychiatrists and limitations on insurance benefits for such mental health interventions. Sherbourne et al. (2004) found that patients with depression in the United States were likely to receive treatment only from primary care providers and, half of the time, this was ineffective care. Sherbourne et al. concluded that either marked changes in the delivery infrastructure, allowing greater availability of treatments or greater integration of primary care with mental health specialty practices to facilitate combined treatments, was necessary to improve quality of care.

Thomas et al. (2002) found that quality care, as measured by response speed and rate of remission, was comparable in primary care and mental health specialty settings when an intervention was implemented to facilitate the use of AHRQ depression treatment guidelines. These are the same guidelines that are the bases for the NCQA HEDIS performance measures. Thomas et al. designed their intervention based on the research findings that showed that when primary care physicians follow practice guidelines, their use can positively influence process of care and clinical outcomes of care. Quality improvement strategies should consider targeting each performance measure separately since significant associations with therapy, patient, and clinical characteristics varied greatly between individual performance measures. Current evidence suggests that collaborative care models most strongly improve both the likelihood of quality treatment and outcome, especially in depressed patients who were prescribed adequate dosages of antidepressants.

### Conclusions

Adherence to NCQA guidelines for appropriate care for depression was highest for the measure of acute-phase treatment (65%), and lower for continuation-phase treatment (44%) and number of practitioner contacts (39%). These absolute rates are slightly higher than NCQAs reported rates for acute-phase and continuation-phase treatment and significantly higher for practitioner contacts. Contact with a mental health specialist was associated with higher adherence to NCQA guidelines. Type of antidepressant was associated with adherence to treatment guidelines—higher for venlafaxine and lower for bupropion compared with SSRIs—but the ORs were smaller than for the receipt of mental health specialty care, high initial dose of drug, and comorbid disorders (anxiety or bi-polar disease). Total pharmacy and medical costs and depression-related costs were higher for guideline-adherent individuals in the 6 months following treatment initiation with an antidepressant. Achieving guideline-adherent care appears to be related to initial treatment choices of drug, dosage level, and provider type, but it will likely increase the cost of care in the short term. These analyses were limited to administrative claims that lack indicators of depression disease severity, and the group sizes were very large.

### DISCLOSURES

Funding for this research was provided by Eli Lilly and Company and was obtained by authors Rebecca L. Robinson, Stacey R. Long, and Ralph W. Swindle. Robinson, Swindle, and authors Stephen Able and Robert L. Obenchain are employees and stockholders of Eli Lilly and Company. Long and authors Stella Chang and Onur Baser disclose no potential bias or conflict of interest relating to this article. Robinson served as principal author of the study. Concept and design were contributed by all authors. Data collection was primarily the work of Long and Chang, with input from the coauthors; data interpretation was the work of all authors. Drafting of the manuscript was primarily the work of Robinson, Long, and Basur, its revision was the work of Able, Obenchain, and Swindle.

### REFERENCES

Higher Costs and Therapeutic Factors Associated With Adherence to NCQA HEDIS Antidepressant Medication Management Measures: Analysis of Administrative Claims

A Comparison of Clinical Practice Guidelines in the Initial Pharmacological Management of New-Onset Epilepsy in Adults

NALIN PAYAKACHAT, MS; KENT H. SUMMERS, RPh, PhD; and JOHN P. BARBUTO, MD

ABSTRACT

OBJECTIVE: Clinical practice guidelines (CPGs) are intended not only to provide supportive information for health care providers but also to act as a guide for health care policy decisions. However, extant CPGs do not always reach the same conclusions. The objective of this study was to compare recommendations for initial pharmacological treatment of new-onset epilepsy in adults as stated within published CPGs.

METHODS: We performed a systematic review of CPGs, which were published by prominent national organizations between January 2000 and June 2005, regarding the initial pharmacological treatment of epilepsy in adults.

RESULTS: Five CPGs and 1 evidence report were identified that focus on pharmacological management in epilepsy. The 3 guidelines most relevant to the question of new-onset epilepsy treatment in adults were developed by the American Academy of Neurology (AAN), Scottish Intercollegiate Guidelines Network (SIGN), and the National Institute for Health and Clinical Excellence (NICE). AAN recommends the use of both recently introduced antiepileptic drugs (AEDs: gabapentin, lamotrigine, topiramate, and oxcarbazepine) and standard agents (carbamazepine, phenytoin, valproic acid/valproate, and phenobarbital) in newly diagnosed epilepsy, i.e., a nontiered approach. Alternatively, NICE recommends using newer AEDs (lamotrigine, topiramate, and oxcarbazepine) only in patients who derive no benefit from older agents—a tiered approach. SIGN notes that all AEDs licensed for monotherapy have similar efficacy in newly diagnosed epilepsy—a recommendation for a nontiered approach. The newer AEDs (lamotrigine and oxcarbazepine) are recommended as first-line initial treatment as are standard agents (carbamazepine and valproic acid/valproate). The NICE guideline includes economic and quality-of-life evidence in their recommendations while AAN and SIGN do not. In these regards, current data fails to show superiority for newer agents.

CONCLUSION: In the past 5 years, several CPGs have been published in epilepsy management. Only 3 guidelines have explicit recommendations for initial pharmacological treatment of adults with epilepsy. With some variation regarding which medications are recommended from each group, all CPGs promote standard and newer AEDs as having similar clinical efficacy. Until efficacy, quality of life, or cost data for the newer agents demonstrates a superior outcome, older AEDs remain viable options as first-line for monotherapy in newly diagnosed patients and may provide cost benefits over newer drugs.

KEYWORDS: CPGs, Systematic review, Epilepsy, Initial treatment, Policymakers, Policy

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Epilepsy is a life-altering chronic condition that affects approximately 2.3 million people in the United States, with 150,000 to 200,000 new cases diagnosed each year.¹ The annual cost of epilepsy is approximately $12.5 billion, with 85% of expenditures attributable to nonmedical costs such as lost productivity both at work and at home.² Patients with newly diagnosed epilepsy have approximately a 50% chance of seizure remission after initial treatment with moderate doses of antiepileptic drugs (AEDs).¹

The number of available AEDs has increased recently. Prior to 1990, carbamazepine, phenobarbital, phenytoin, primidone, valproic acid, and ethosuximide were used to treat all forms of epilepsy. Although these older AEDs are generally effective in newly diagnosed epilepsy and are much less expensive than newer agents, some undesirable characteristics such as complex pharmacokinetics and adverse-effect profiles make them less appealing to clinicians and patients. The newer U.S. Food and Drug Administration (FDA)-approved AEDs include felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide. It has been argued that the advantages of the newer agents compared with the older agents are fewer side effects and drug interactions. With the large number of AEDs available, physicians are presented with difficult drug selection decisions. While the most critical aspect of AED product selection is safety, tolerability, and efficacy, cost is an additional and increasingly important consideration.

Concern about health care quality has contributed to policymakers’ need for the development of uniform and systematic guidelines to aid physicians in making better-informed decisions.⁴ Clinical practice guidelines (CPGs) are systematically developed statements of clinical recommendations to assist practitioners and patient decisions regarding appropriate health care. Consistent use of CPGs promotes the concept of “best practices” in order to improve treatment outcomes.⁵ CPGs rely on 2 basic assumptions: (1) outcomes identified in clinical trials are reproducible in normal practice and (2) adoption of effective treatment guidelines leads to improved treatment for the whole population. Guidelines developed by an evidence-based approach are founded upon conclusions supported by scientific evidence as well as expert opinion. Efforts are made to link the strength of recommendations to the quality of evidence.⁶

In the past 5 years, several epilepsy management CPGs have been published that refer to efficacy and safety of both older and newer AEDs. This paper is intended to provide policymakers with a comparison of conclusions reached in the extant CPGs that deal with pharmacological choices for initial management.
of epilepsy in adults. Specifically, we sought to answer the question “How do current, prominent guidelines compare in regard to recommendations for treatment of new-onset epilepsy in adults?” Thus, it does not address AED selection when treating refractory epilepsy, management of children, or any AED treatment patterns. It is intended to facilitate the practice of pharmacy benefit managers by providing information for policy-makers and to compare clinical treatment guidelines.

## Methods

### Search Strategy

A systematic review process was applied to obtain relevant CPGs that were published by prominent national organizations between January 2000 and June 2005 in the United States and other countries (published in English only). We did not include the guidelines that were published before the year 2000 because we considered them to be outdated.6,7 The research question in this review was “What are the differences among guideline recommendations of new-onset seizure in adults?” National CPGs were identified by a computerized search from various sources, including electronic databases, (e.g., MEDLINE, PsycINFO, Cochrane Library, Current Contents, and Proquest Research Library), guideline Web sites (e.g., the U.S. National Guideline Clearinghouse [NGC], National Institute for Health and Clinical Excellence [NICE], Scottish Intercollegiate Guidelines Network [SIGN], Agency for Healthcare Research and Quality [AHRQ]), and hand searches of relevant journals. MeSH terms used were “epilepsy or seizure” with limits of “all adult: 19+ years,” “publication date from 2000/1/1 to 2005/6/31,” “English, practice guideline/ review,” “humans.” Other key search terms were “clinical practice guideline and epilepsy,” “antiepileptic drug and epilepsy,” “initial treatment and epilepsy,” “review and drug treatment of new-onset epilepsy in adult,” “monotherapy and newly diagnosed epilepsy,” “drug management and newly diagnosed epilepsy,” “first seizure,” “new-onset epilepsy,” and “first diagnosis.”

### Inclusion and Exclusion Criteria

Inclusion criteria regarding selection of CPGs were: (1) guidelines that are sponsored by governmental and prominent professional organizations, (2) publication in the English language, and (3) CPGs that address the role of AEDs in the initial management of epilepsy in adults (age > 18 years). Exclusion criteria were: (1) CPGs in refractory epilepsy only, (2) CPGs of epilepsy treatment in childhood only, (3) any other examples of complex presentations of epilepsy that may be referred for specialist care, and (4) CPG does not address the research question “How do current prominent guidelines compare in regard to recommendations for treatment of new-onset epilepsy in adults?” Searches of the reference lists and bibliographies of all papers for additional studies were performed as a part of the review.

## Comparison of Clinical Practice Guidelines

Similarities and differences of the guidelines were evaluated and addressed to provide policymakers with information to support the use of CPGs in rational policymaking in the United States, focusing on the initial pharmacological treatment of new-onset epilepsy in adults.

### Results

Five national CPGs and 1 evidence report were identified from a systematic search according to the inclusion criteria. These CPGs included 3 from the United Kingdom (NICE, National Collaborating Centre for Primary Care [NCCP], and Joint Epilepsy Council [JEC]), 1 from Scotland (SIGN) and 1 from the United States (American Academy of Neurology [AAN]).6-12 The evidence report was from AHRQ.13 Characteristics of each are summarized in Table 1.

Although some guidelines included some exclusionary criteria such as recommendations for refractory symptoms or children, they were included because they addressed the primary research question. AAN, in conjunction with the American Epilepsy Society, addressed specific initial drug agent selection in the first part of its guideline.11 SIGN provided complete recommendations for epilepsy management for both adults and children. The NICE guideline reviewed all aspects of newer drugs for epilepsy in adults. The NCCP guideline regarding newly diagnosed patients mirrors the NICE guideline; therefore, it was excluded to prevent redundancy. We also excluded the JEC guideline and AHRQ report because they do not have specific therapeutic recommendations for initial treatment of epilepsy. After excluding the guidelines from NCCP, JEC, and AHRQ according to our established criteria, the CPGs from AAN, NICE, and SIGN were included in the final comparison chart (see Table 2).

### Discussion

After comparing the guidelines, we found valid evidence that older, less-expensive AEDs still have an important role as first-line drugs of choice in adults with new-onset epilepsy; the role of newer AEDs is still controversial. SIGN and NICE guidelines contain recommendations to use AEDs as first-line treatment only under their licensed indications, while AAN recommendations include the use of AEDs that fall outside labeled FDA indications.13 AAN and SIGN also recommend the use of newer agents as first-line treatment in newly diagnosed patients. SIGN states, “Comparative, randomized, double-blind trials in patients with newly diagnosed partial and generalized tonic-clonic seizures suggest similar efficacy for phenytoin, carbamazepine, sodium valproate, lamotrigine, and oxcarbazepine” and “The newer AEDs, lamotrigine and oxcarbazepine, seem to be better tolerated and may produce fewer long-term side effects and adverse interactions.”15 These recommendations are consistent with other scientific literature.16 NICE supports the
A Comparison of Clinical Practice Guidelines in the Initial Pharmacological Management of New-Onset Epilepsy in Adults

### Table 1: Summary of National Practice Guidelines and Evidence Reports for Epilepsy Management (Published January 2000-June 2005)

<table>
<thead>
<tr>
<th>Title</th>
<th>AHRO13*</th>
<th>AAN12†</th>
<th>NICE6†</th>
<th>NCCP9*</th>
<th>JEC10*</th>
<th>SIGN11†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHRO13</strong>*</td>
<td>Management of Newly Diagnosed Patients with Epilepsy: A Systematic Review of the Literature</td>
<td>Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy</td>
<td>Newer drugs for epilepsy in adults</td>
<td>The JEC National Statement of Good Practice for the Treatment and Care of People Who Have Epilepsy</td>
<td>Diagnosis and Management of Epilepsy in Adults—A national clinical guideline</td>
<td></td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To systematically review the best available evidence in the published literature regarding health care services pertinent to the diagnosis, treatment, and monitoring of patients with a first diagnosis of epilepsy</td>
<td>To assess the evidence demonstrating efficacy, tolerability, and safety of 7 new AEDs (gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide) in the treatment of children and adults with newly diagnosed partial and generalized epilepsies</td>
<td>To examine the clinical effectiveness, tolerability, and cost-effectiveness of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and vigabatrin for epilepsy in adults</td>
<td>To offer best-practice advice on the diagnosis, treatment, and management of the epilepsies in children and adults</td>
<td>To provide a series of recommendations for attaining high-quality National Health Service care for people with epilepsy in England</td>
<td></td>
</tr>
<tr>
<td><strong>Type of document</strong></td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Clinical guideline</td>
<td>Clinical guideline</td>
<td>Clinical guideline</td>
<td>Clinical guideline</td>
</tr>
<tr>
<td><strong>Intended users</strong></td>
<td>Developers of clinical practice guidelines and other quality-enhancement tools, those involved with reimbursement and coverage policies</td>
<td>Physicians</td>
<td>Patients, physicians, health care providers, caregivers, those involved in public policy</td>
<td>Individual health care professionals, people with epilepsy and their caregivers, health care commissioning organizations, provider organizations</td>
<td>Advanced-practice nurses, nurses, occupational therapists, physician assistants, physician assistants, psychologists, nonphysician, behavioral health clinicians, social workers</td>
<td>Advanced practice nurses, patients, pharmacists, physician assistants, physicians, public health department social workers</td>
</tr>
<tr>
<td><strong>Type of patients</strong></td>
<td>Newly diagnosed (not specific in any age group)</td>
<td>Children and adults with newly diagnosed partial and generalized epilepsies</td>
<td>Adults with newly diagnosed or refractory epilepsy</td>
<td>Children, adolescents, adults, older people, women who are pregnant, women of childbearing potential, and people with learning disabilities</td>
<td>Individuals with epilepsy</td>
<td>Adult patients with epilepsy or status epilepticus</td>
</tr>
<tr>
<td><strong>Major outcomes consider</strong></td>
<td>Health outcomes: clinical, HRQoL, and cost-effectiveness</td>
<td>Efficacy, tolerability, and safety of newer AEDs</td>
<td>Clinical effectiveness, serious, rare, and long-term adverse events, cost-effectiveness</td>
<td>All issues important in the diagnosis, treatment, and management of epilepsy in children and adults</td>
<td>Rate of epilepsy misdiagnosis and efficacy of AEDs and their adverse-event profiles</td>
<td>Clinical outcomes</td>
</tr>
<tr>
<td><strong>Method used</strong></td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Systematic review</td>
</tr>
</tbody>
</table>

* CPGs that were excluded from the final comparison.
† CPGs that were included in the final comparison (See Results section in article).
AAN = American Academy of Neurology; AED = antiepileptic drug; AHRO = Agency for Healthcare Research and Quality; CPG = clinical practice guideline; HRQoL = health-related quality of life; JEC = Joint Epilepsy Council; NCCP = National Collaborating Centre for Primary Care; NICE = National Institute for Health and Clinical Excellence; SIGN = Scottish Intercollegiate Guidelines Network.
A Comparison of Clinical Practice Guidelines in the Initial Pharmacological Management of New-Onset Epilepsy in Adults

TABLE 2

| AEDs as Monotherapy of Partial/Mix Generalized Tonic-Clonic Seizure | AAN* | NICE† | SIGN‡ | Typical Dose (mg)/Day*§ | Cost/Unit, U.S.$|| (30-Day Supply) |
|---------------------------------------------------------------|------|-------|-------|-------------------------|-------------|-------------|
| Phenobarbital                                                  | 1st  | -     | -     | 100                     | 0.07 (97.2 mg) | 2           |
| Carbamazepine (generic Tegretol)                              | 1st  | 1st   | 1st   | 1,000                   | 0.18 (200 mg) | 27          |
| Valproic acid (generic Depakene)                              | 1st  | 1st   | 1st   | 1,500                   | 0.29 (250 mg cap) | 52         |
| Ethosuximide (generic Zarontin)                               | -    | -     | -     | 500                     | 0.78 (250 mg) | 47          |
| Primidone (generic Mysoline)                                  | -    | -     | -     | 1,000                   | 0.45 (250 mg) | 54          |
| Gabapentin (generic Neurontin)                                | 1st  | -     | -     | 1,200                   | 0.85 (300 mg tab) | 102        |
| Divalproex (Depakote)                                          | 1st  | 1st   | 1st   | 1,500                   | 2.00 (500 mg tab) | 180        |
| Divalproex (Depakote ER)                                       | 1st  | 1st   | 1st   | 1,500                   | 2.07 (500 mg ER tab) | 187       |
| Zonisamide (Zonegran)                                          | -    | -     | -     | 200                     | 2.06 (100 mg) | 123         |
| Tiagabine (Gabitril)                                           | -    | -     | -     | 300                     | 3.47 (16 mg) | 208         |
| Oxbcarbazepine (T rileptal)                                    | 1st  | 2nd†  | 1st   | 1,200                   | 3.80 (600 mg) | 228         |
| Topiramate (Topamax)                                           | 1st  | 2nd   | -     | 300                     | 5.24 (200 mg) | 236         |
| Levetiracetam (Keppra)                                         | -    | -     | -     | 2,000                   | 2.09 (500 mg) | 250         |
| Lamotrigine (Lamictal)                                         | 1st  | 2nd   | 1st   | 500                     | 3.82 (200 mg) | 287         |

* AAN: Patients with newly diagnosed epilepsy who require treatment can be initiated on standard AEDs such as carbamazepine, phenytoin, valproic acid, phenobarbital or on the new AEDs: lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice of AED will depend on individual patient characteristics. Both new and old drugs are generally equally effective in new-onset epilepsy. The newer drugs tend to have fewer side effects. 12 (p.1258)
† NICE: First-line monotherapy should be initiated with one of the older antiepileptic drugs such as carbamazepine or sodium valproate unless these drugs are not suitable because there are contraindications or the potential for interactions with other drugs the person is taking, because they have been poorly tolerated by the person in the past, or because the person is a woman of childbearing potential.8 (section 4.3.2, p.22) The newer antiepileptic drugs—gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and vigabatrin—with their licensed indications, are recommended for the management of epilepsy in people who have not benefited from treatment with the older antiepileptic drugs. 12 (section 1.1, p.6)
‡ SIGN: Carbamazepine, sodium valproate, lamotrigine, and oxcarbazepine can all be regarded as first-line treatments for partial and secondary generalized seizures. Sodium valproate and lamotrigine are drugs of choice for primary generalized seizures and should also be prescribed if there is any doubt about the seizure types and/or syndrome classification. The side-effect and interaction profiles should direct the choice of drug for the individual patient. All AEDs licensed for monotherapy have similar efficacy in newly diagnosed epilepsy. Note: Formulations of AEDs are not interchangeable and generic substitution should not be employed. All antiepileptic drugs licensed for monotherapy have similar efficacy in newly diagnosed epilepsy.11 (section 3.2, p.9)
§ Typical doses that were used in this table: (1) were the average typical full daily dose (neither starting nor maximum dose), (2) if used in combination with other AEDs, patient may require a different dose, and (3) are for comparison purpose only, not for specific treatment recommendation.14
|| Prices were obtained from www.drugstore.com (accessed December 6, 2005). 14
† 1st = first-line drug; 2nd = second-line drug.
AAN = American Academy of Neurology; AED = antiepileptic drug; ER = extended release; NICE = National Institute for Health and Clinical Excellence; SIGN = Scottish Intercollegiate Guidelines Network; XR = extended release.

Use of the older AEDs and clearly states that newer AEDs should be second-line in initial treatment, based upon a lack of good-quality evidence from clinical trials to support the preferential use of newer AED monotherapy over the older drugs. They state, “Almost all studies comparing newer drugs with older drugs have found no statistically significant differences in terms of seizure-related outcomes…. However, it cannot be concluded that the drugs have been shown to be equivalent in terms of efficacy…." “One important clinical question for the treatment of newly diagnosed patients is whether lamotrigine, oxcarbazepine, and topiramate are more effective than older AEDs. This review found insufficient evidence from good-quality clinical trials to answer this question.”13 NICE suggests that a review of the adverse events and tolerability from clinical trials does not provide sufficiently consistent results necessary to draw conclusions to support a preference for the newer AEDs compared with the older ones.

Important information uniquely found in NICE is the health-related quality-of-life (HrQoL) evidence review. Quality of life is an important advantage proposed for the newer AEDs.
NICE states, “However, only nine of the 19 studies comparing monotherapy using newer drugs versus older drugs assessed quality-of-life” and “These studies do not provide strong evidence of improved quality of life with the newer drugs.” Based on a broader review of the literature, NICE concludes that there is insufficient evidence to confirm an advantage for the newer AEDs over the older agents related to their ability to improve patients’ HrQoL. AAN did mention in its guideline that “… the burden is on the treating physician to select the AED that is the most tolerable, has the lowest potential for harm, and has the least likelihood of negatively impacting quality of life”; however, AAN did not include this parameter in its review.

The NICE guideline declares that the evidence on cost-effectiveness considered by the reviewing committee indicates that none of the published economic evaluations satisfied the criteria for a robust economic evaluation, but monotherapy with the older AEDs is considerably less expensive, considering only drug cost." They state, “Even when the most optimistic treatment scenario for the newer drugs was compared with the worst-case treatment scenario for the older drugs, monotherapy with the older drugs was considerably less costly.” Finally, they conclude that “the older monotherapies appeared to be cost effective when compared to newer AEDs for the treatment of newly diagnosed patients experiencing generalised seizures.” When comparing U.S. and European studies, a limiting factor is the insufficient cost-effectiveness and HrQoL information for AEDs used as initial treatment of epilepsy in the United States. AAN states, “The older AEDs have an advantage of broad familiarity, lower cost, known efficacy, wide availability via coverage by third-party payers, and long-term experience” and “The new drugs are all substantially more expensive than the old. There is no literature that addresses the cost-benefit related to these issues.” In the United Kingdom, NICE asks pharmaceutical companies to submit both published and unpublished information to incorporate into the CPG. This provides a broader foundation for the examination of cost-effectiveness and HrQoL assessments. Although the AHRQ guideline includes costs and HrQoL in its review, it does not have recommendations regarding these issues for newer AEDs.

The AAN guideline recommends 4 newer AEDs (oxcarbazepine, gabapentin, lamotrigine, and topiramate) as first-line drugs along with the older agents. Notable is that 3 of these AEDs (except for oxcarbazepine) are not approved in the United States for monotherapy of newly diagnosed patients. AAN states, “The FDA does not accept such a finding as proof of efficacy, due to the possibility that two ineffective drugs might also exhibit no difference in effect when compared against one another. For the purpose of this parameter, we accepted the demonstration of equivalence between an established AED such as carbamazepine or phenytoin and a new drug as confirmation of effectiveness.” The FDA uses placebo-controlled clinical trials to evaluate the use of new AEDs as monotherapy in initial treatment of newly diagnosed epilepsy. This type of trial can present an ethical dilemma to investigators who must randomize newly diagnosed patients to the placebo arm. In the recommendation for future research, AAN states “There is no doubt that the ideal methodology for detecting drug effect in most cases is to use a placebo/control comparison. However, because trials in patients with newly diagnosed epilepsy must be performed, by definition, in the monotherapy condition, there are ethical concerns regarding a placebo or substandard control in this population. Therefore, comparative trials remain the preferred tactic. Clinicians favor these trial designs” and “…these trials are not acceptable for registration purposes in the United States, as the FDA has required demonstration of superiority.… Discussion is ongoing as to how to resolve this conflict between the needs of the clinician and the needs of regulatory bodies.”

Beghi, in 2004, published a comparison of AAN and NICE guidelines. His review included the use of newer AEDs in the treatment of epilepsy for both adults and children as well as in special populations (children and patients with learning disabilities and intellectual deficits, women of childbearing age, the elderly). Yet, the paper mainly focused on the place in therapy of newer agents according to these recent guidelines. He concluded that “Both guidelines offer a clear picture of the efficacy, safety, and tolerability of the new antiepileptic drugs and agree on their use as add-on treatment in patients who do not respond to conventional drugs. The guidelines differ in the type and strength of recommendation.” And “The U.K. guidelines are more conservative when compared to the U.S. guidelines.”

When evaluating specific recommendations from CPGs, it is crucial to understand the rationale for excluding CPGs whose recommendations are not considered. This permits a more transparent understanding of the potential for bias in the recommendations used in managed care. In this paper, we attempted to model this as a practice that should be employed when using CPG recommendations to inform drug policy decisions. Policymakers tend to utilize the findings or recommendations from research evidence sources that are clear in content, valid, and up-to-date. The differences among CPGs recommendations present a dilemma to those trying to make drug policy decisions with an evidence-based approach and limit utilization of newer AEDs for maximum patient benefit. The variation among these CPGs might be a result of the process of guideline development. An evidence review to assess the treatment pattern of epilepsy management might be of interest, but it is beyond the scope of this paper. However, we could find no literature review regarding managed care in the U.S. practice. Since pharmacoeconomics and HrQoL are obvious
concerns of policymakers, future research should evaluate the cost-effectiveness and HrQoL of the initial AEDs treatment in adult patients with new-onset epilepsy in the United States to support drug policy decisions.

**Conclusion**

From our review of current CPGs for AEDs in the initial pharmacological management of epilepsy in adults published in the past 5 years, we found that the older AEDs, including carbamazepine, phenytoin, and valproic acid, still play an important role as first-line monotherapy for management of new-onset epilepsy in adults. Until cost-effectiveness data or quality-of-life studies show a convincing benefit for newer agents, they should remain second-line.

**DISCLOSURES**

No outside funding supported this study. The authors disclose no potential bias or conflict of interest relating to this article. Author Nalin Payakachat served as principal author of the study. Study concept and design were contributed by Payakachat and authors Kent H. Summers and John P. Barbuto. Data collection was the work of Payakachat; data interpretation was primarily the work of Payakachat, with input from Summers and Barbuto. Drafting of the manuscript and its revision was primarily the work of Payakachat, with input from Summers and Barbuto.

**REFERENCES**


CONTEMPORARY SUBJECT

Impact of a Clinical Pharmacy Consult Service on Guideline Adherence and Management of Gabapentin for Neuropathic Pain

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ABSTRACT

OBJECTIVE: Our objectives were to (1) determine whether a computerized clinical pharmacy approval and follow-up consult process for ordering new prescriptions for gabapentin for the treatment of neuropathic pain decreased the number of patients without documented treatment benefit while increasing follow-up and documentation of effectiveness, and (2) describe gabapentin use patterns prior to gabapentin therapy for neuropathic pain.

METHODS: The clinical pharmacy intervention included review of (1) the indication for gabapentin; (2) the required use and failure or contraindication of 3 first-line therapies: nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (TCAs), and capsaicin cream; (3) the initial pain assessment; and (4) patient follow-up in 4 to 6 weeks, with repeat pain assessment. A retrospective chart review was performed for all patients who received a new prescription for gabapentin from October 2002 to April 2003 at the Portland VA Medical Center (PVAMC). The outcomes of interest for the provider group versus the clinical pharmacy managed group included follow-up at 6 weeks or less versus follow-up at more than 6 weeks, documentation of treatment benefit, how many of the 3 first-line therapies were tried before gabapentin, and whether the gabapentin therapy was discontinued.

RESULTS: There were 237 patients who received a new prescription for gabapentin between October 2002 and April 2003. Of these gabapentin prescriptions, 61% (n = 144) were prescribed for neuropathic pain. Of the new gabapentin prescriptions for neuropathic pain, 61% (n = 88) were made from approved clinical pharmacy consults, 38% (n = 54) were ordered without a clinical pharmacy consult, and 1% (n = 2) were not included because the patient received the drug despite denial by the clinical pharmacy consult. The rate of follow-up to assess documentation of benefit of therapy with gabapentin was 87% (n = 62) in the clinical pharmacy consult group compared with 51% (n = 27) in the provider-managed group (χ² = 18.07, P < 0.001). Of the patients who were assessed by follow-up, 89% (n = 55) of the clinical pharmacy consult group received follow-up within 6 weeks versus 52% (n = 14) of the provider-managed group (χ² = 12.63, P < 0.001). Compared with the patients managed by clinical pharmacists, 43% (n = 23) of the gabapentin patients in the provider-managed group had no evidence of prior use of any of the 3 agents required by the gabapentin neuropathic pain guideline, 55% (n = 29) had evidence of prior use of 1 or 2 first-line agents, and only 2% (n = 1) had evidence of prior use of all 3 required first-line agents, versus 100% (n = 71) of the patients managed by clinical pharmacy consult. There was no difference in the rate of continuation of gabapentin therapy in the group of patients who received clinical pharmacy consults (65%) compared with the provider-managed group (68%, χ² = 0.11, P = 0.718). Of the 148 pharmacy consults for new gabapentin prescriptions that were completed during the 7-month period from October 2002 through April 2003, 60 (40%) were denied, which resulted in the lack of gabapentin use in these 60 patients.

CONCLUSIONS: A clinical pharmacy intervention as part of the management of a treatment guideline for appropriate gabapentin use promotes documentation of drug therapy effectiveness in neuropathic pain and prevention of gabapentin use prior to a trial with alternative first-line therapies.

KEYWORDS: Gabapentin, Neuropathic pain, Clinical pharmacy, Formulary management

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When gabapentin (Neurontin) was introduced to the market in December 1993, its only approved indication was the adjunctive treatment of partial seizure disorders.1 The only other indication for gabapentin is for postherpetic neuralgia, which was approved by the U.S. Food and Drug Administration (FDA) in May 2002. Since market introduction, gabapentin has been used to treat a number of other conditions not approved by the FDA, including neuropathic pain. This outcome is not a new phenomenon since other antiepileptics have also been used to treat neuropathic pain.2-4

Gabapentin use continues to increase nationwide. In 2001, it was the 31st most prescribed drug, and in 2002, the 25th most prescribed drug.5 In May 2002, the manufacturer of gabapentin was accused of promoting non-FDA-approved uses of gabapentin.6,7 In June 2004, Pfizer, on behalf of the acquired company Warner-Lambert, pleaded guilty to criminal marketing of Neurontin. Pfizer agreed to pay $430 million in fines, including a criminal fine of $240 million and $190 million in economic damages to settle civil liability suits brought by 50 state attorney generals.8 The off-label uses promoted for gabapentin included bipolar mental disorder, various pain disorders, amyotrophic lateral sclerosis (ALS or Lou Gehrig’s disease), attention-deficit disorder, migraine, drug and alcohol withdrawal seizures, restless leg syndrome, and first-line monotherapy for epilepsy. It is not known how these marketing strategies may have affected the quality of patient care or the potential overutilization of gabapentin, but off-label use of gabapentin has been the subject of other evaluations.9,12

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Pain with abnormal sensations, i.e., paresthesias (uncomfortable

Consider trial of different agents:

Peripheral neuropathy, radicular pain (not low back pain), postherpetic neuralgia, peripheral nerve injury, central (poststroke syndrome), etc. Remember to evaluate for etiology of concomitant pain prior to selection of pain therapy.

Carefully designed treatment trials for neuropathic pain are few. Current medication regimens are based on a combination of observations from clinical studies, clinical anecdotes, and experimental findings. Treatment strategy is "trial and error" and yields clear improvement in only a minority of patients.

**First-Line Therapy:** (must be used on a scheduled basis for 1 month before failure is established)

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs):** Patient must have failed therapy with at least 1 NSAID. Consider trial of different agents:
   - Ibuprofen 600 mg QID
   - Naproxen 500 mg BID
   - Comments: Use with caution in patients with GI disease, cardiovascular disease, renal or hepatic impairment, and patients receiving anticoagulants

2. **Tricyclic antidepressants (TCAs):** Patient must have failed therapy with at least 1 TCA. Consider trial of 2 different agents:
   - Nortriptyline 10-75 mg QHS
   - Amitriptyline 10-100 mg QHS
   - Imipramine 25-200 mg QHS
   - Desipramine 10-100 mg QHS
   - Doxepin 10-100 mg QHS
   - Comments: Nortriptyline and desipramine have fewer incidences of anticholinergic side effects, sedation, and orthostatic hypotension than amitriptyline. Use with caution in those patients with cardiac conduction disturbances. An EKG prior to initiation of therapy is recommended. May titrate up to full antidepressant doses.

3. **Capsaicin cream 0.025% or 0.075% QID scheduled:** Patient must have failed capsaicin cream.
   - In normal renal function, dose should be started at 300 mg QHS for 1 week, 300 mg BID for 1 week, then 300 mg TID for 1 month to increase tolerability. Initial prescriptions will be filled with 120 capsules with no refills. At 4 weeks, efficacy and tolerability will be evaluated by clinical pharmacist or designee and dose will be titrated to 3,200 mg per day if appropriate.
   - In impaired renal function (serum Cr > 1.3 mg/dL), dose should be started at 100 mg QHS for 1 week, 200 mg QHS for 1 week, then 300 mg QHS for 1 week. Titrate as above to maximum of 300 mg QHS if CrCl 15-30 mL/min, 300 mg BID if CrCl 30-60 mL/min, or 400 mg TID if CrCl > 60 mL/min.
   - Patient will be telephoned and evaluated by clinical pharmacist or other designee at 4 weeks.
   - If gabapentin is ineffective or not tolerated, taper over 1 week and reassess pain level.

*Patient must have failed all 3 prerequisite therapies to receive approval of use of gabapentin by clinical pharmacy consult.

**TABLE 1** Gabapentin Neuropathic Pain Guideline—VA Medical Center*

**Definition:** Pain with abnormal sensations, i.e., paresthesias (uncomfortable tingling) or dysesthesias (aching, burning, pricking, or shooting pain, either spontaneous or in response to normally painless stimuli like pulling sheets over feet)

**Diagnosis:** Peripheral neuropathy, radicular pain (not low back pain), postherpetic neuralgia, peripheral nerve injury, central (poststroke syndrome), etc. Remember to evaluate for etiology of concomitant pain prior to selection of pain therapy.

At the Portland Veterans Affairs Medical Center (PVAMC), the use of gabapentin for non-FDA-approved indications increased from the time the drug appeared on the formulary, raising concerns regarding the ability to assess the effectiveness of gabapentin when used for neuropathic pain syndromes and the cost of the drug. In 1998, gabapentin appeared on the PVAMC list of highest expenditure drugs. Between 1999 and 2002, PVAMC experienced a 37% increase in the number of gabapentin prescriptions. In October 1999, there were 268 prescriptions of gabapentin and 1.6 fills per 100 primary care patients. In October 2002, there were 367 prescriptions of gabapentin and 1.3 fills per 100 primary care patients. While the proportion of primary care patients who received gabapentin did not increase between October 1999 and October 2002, the drug accounted for one third of the yearly financial allotment for care for the average VA patient.

Local prescribers participated in the development of the guideline for appropriate use of gabapentin. A literature review was conducted to assess the value of the evidence, including searches of PubMed and the Cochrane Collaboration. Search terms included neuropathic pain, nonsteroidal anti-inflammatory drugs (NSAIDs), diabetic neuropathy, postherpetic neuralgia, and anti-inflammatory drugs; combinations of the terms were also used in the search. Emphasis was placed on the results of randomized controlled trials (RCT) and meta-analyses of RCTs.

The results of RCTs published since 1999 supported the use of gabapentin for painful diabetic neuropathy and Herpes Zoster. However, a search of the Cochrane Collaboration found gabapentin no better than older antiepileptics or tricyclic antidepressants (TCAs) for treatment of chronic pain, including neuropathic pain, and no benefit for treatment of acute pain. This latter finding stands today. The causes of neuropathic pain are many, yet the treatment with gabapentin is supported in the literature with the results of RCTs only for the 2 etiologies: diabetic neuropathy and Herpes Zoster. For the remainder of neuropathic pain patients, there is little published evidence of effectiveness of gabapentin compared with other therapies. In such cases, providers have a choice to use drugs for non-FDA-approved indications or use older medications, often with less evidence of effectiveness.

The PVAMC developed a guideline in 2000 for appropriate use of gabapentin for neuropathic pain. This was done to control costs of this expensive medication when its effectiveness could not be determined. The guideline defines neuropathic pain and diagnoses where neuropathic pain can exist. Prior to use of gabapentin, the guideline required that patients must have tried and failed, or have contraindications to, 3 first-line treatments: (1) an NSAID, (2) a TCA, and (3) capsaicin cream, prior to using gabapentin (Table 1). The NSAIDs and capsaicin cream of this protocol are not first-line treatment for neuropathic pain today. However, when this guideline was developed in 2000, the data were insufficient to support use of gabapentin in chronic neuropathic pain.
Impact of a Clinical Pharmacy Consult Service on Guideline Adherence and Management of Gabapentin for Neuropathic Pain

pain of nerve origin that was not diabetic neuropathic pain or postherpetic neuralgia. NSAIDs and capsaicin cream are recommended in guidelines for malignant pain, and nonmalignant chronic pain may be considered for individual neuropathic pain cases.17-20

The drug choices of the PVAMC guideline for treating neuropathic pain (Table 1) reflect the standard of practice in the treatment for chronic nerve pain at the time of the review, excluding painful diabetic neuropathy or postherpetic neuralgia. Trials of these drug choices were required prior to use of gabapentin. There is ample evidence supporting TCA use for neuropathic pain. Capsaicin is FDA-approved for postherpetic neuralgia, diabetic neuropathy, and arthritis pain. While NSAIDs have not been shown consistently to treat neuropathic pain effectively, they are frequently used for chronic pain, pain of nerve entrapments, and pain with an inflammatory component. In 2002, neuropathic pain was treated by the medical community with therapies that worked on other forms of neuropathy and chronic pain.

Clinical assessment of gabapentin therapy was proposed to detect drug side effects and instances of ineffective use, and hence, to increase the safe use of gabapentin. In the fall of 2002, the PVAMC developed an electronic consult for gabapentin. Providers wishing to prescribe gabapentin for neuropathic pain, in accordance with the definition in the guideline, submitted a consult request to the clinical pharmacy department for assessment of adherence to the guideline, evaluation of treatment effect, and recommendation of titration or discontinuation of gabapentin when appropriate. Providers were educated about the process through conferences and e-mails. The objectives of the present study were, through the conduct of a retrospective chart review of all new gabapentin prescriptions, to (1) evaluate the effectiveness of a computerized clinical pharmacy process to review gabapentin prescriptions for neuropathic pain and (2) describe the current pattern of use of gabapentin at the PVAMC.

Methods

Clinical Pharmacy Intervention

The consult requests that the clinical pharmacy department received for gabapentin were reviewed in accordance with the existing guideline for gabapentin use at the facility (Table 1). Patients had to have tried and failed, or have contraindications to, all 3 first-line agents of the guideline prior to consideration of gabapentin. Treatment failure with a first-line agent was defined as no treatment benefit or an adverse drug reaction. Providers at our institution include physicians, nurse practitioners, and physician assistants. On the consult, the prescribing provider was required to indicate (1) the patient's diagnosis of neuropathic pain in accordance with the definition in the treatment guideline, (2) the trial and failure of the 3 first-line therapies (or contraindications), and (3) the patient's current pain score. The pain score was based upon the patient's subjective assessment of pain on a scale from 0 (no pain) to 10 (the most excruciating pain). Pain is routinely assessed using this scale for all patients at PVAMC. If information was missing or unclear, the provider and patient were contacted for further information. Although consults were required for neuropathic pain, gabapentin prescriptions could be ordered without a consult. Those prescriptions were filled solely at the PVAMC outpatient pharmacist's discretion and did not require the treatment indication or the value from the pain scale.

Consult requests for use of gabapentin were managed by 3 clinical pharmacists. This became part of their regular formulary management duties, and no additional staff members were hired. One of the pharmacists reviewed each consult for appropriateness and either approved or denied gabapentin (Figure 1). The consult was denied and the prescription for gabapentin was not issued if the patient did not have a diagnosis of neuropathic pain or had not completed the appropriate trials of all 3 first-line therapies.

FIGURE 1 Clinical Pharmacy Intervention—Consult Review and Follow-up Process

<table>
<thead>
<tr>
<th>Consult Submission</th>
<th>Requested Information: 1. Diagnosis of Neuropathic Pain 2. Documented trial of 3 first-line therapies 3. Pain Score (0-10 pain scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical Pharmacist’s Review</td>
</tr>
<tr>
<td></td>
<td>Was consult documentation completed?</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Consult approved</td>
</tr>
<tr>
<td></td>
<td>Gabapentin initiated and patient counseling provided by pharmacist</td>
</tr>
<tr>
<td></td>
<td>Patient contacted by clinical pharmacist within 5-6 weeks to assess treatment effectiveness and tolerability</td>
</tr>
<tr>
<td></td>
<td>Irritative side effects? Yes</td>
</tr>
<tr>
<td></td>
<td>Treatment discontinued</td>
</tr>
<tr>
<td></td>
<td>Outcomes of assessment</td>
</tr>
<tr>
<td></td>
<td>Yes / No</td>
</tr>
<tr>
<td></td>
<td>Treatment continued</td>
</tr>
<tr>
<td></td>
<td>No / No</td>
</tr>
<tr>
<td></td>
<td>Intervention complete</td>
</tr>
<tr>
<td></td>
<td>Intervention complete</td>
</tr>
<tr>
<td></td>
<td>Dose increased</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Alternative therapy recommended to physician</td>
</tr>
<tr>
<td></td>
<td>Intervention complete</td>
</tr>
</tbody>
</table>

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medications (Table 1). If approved, the patient was contacted by phone for counseling and the prescription was mailed. Patients with normal renal function were started on a standard titration of 300 mg at bedtime for 7 days, followed by 300 mg twice a day for 7 days, then 300 mg 3 times a day, in accordance with the prescribing information for gabapentin. Otherwise, dosing based on renal function was used.

A clinical pharmacist contacted the patient again after 4 to 6 weeks to evaluate the treatment effectiveness and tolerability. Pain was reassessed at the time of follow-up using the same 0 to 10 pain scale. The prescription for gabapentin was continued if there was improvement in the pain score, self-defined improvement in pain, or improvement in other signs or symptoms of neuropathy. The prescription was discontinued if the patient experienced self-defined side effects warranting discontinuation of the drug or had no improvement in pain. In some cases where treatment effect was unclear at the time of follow-up based on the patient's impression or conflicting pain scale scores, the prescription was continued or the dose increased by the clinical pharmacist, and additional follow-up was scheduled.

Efficacy already established

Patient Selection

Impact of a Clinical Pharmacy Consult Service on Guideline Adherence and Management of Gabapentin for Neuropathic Pain

Results

The consultants in the clinical pharmacy group that resulted in a prescription for gabapentin were examined. There were consultations that were denied by a clinical pharmacist because of lack of first-line drug trials. There were also 2 patients who received the gabapentin from staff pharmacists even though the consultants had been refused by a clinical pharmacy specialist. In the provider-managed group, no clinical pharmacy consultations occurred.

Patient Selection

Figure 2 illustrates the method of patient selection for this study. Two hundred and thirty-seven patients had a new prescription for gabapentin initiated within the study period. Of the 144 prescriptions (61%) for neuropathic pain, 88 had clinical-pharmacy-approved consultations, and these constitute the clinical-pharmacy-managed group. Unexpectedly, 54 patients had prescriptions resulting from the provider-prescriber's bypassing the consult and ordering the drug directly. This finding led us to compare these 2 groups to help determine the effectiveness of the consult process. Two patients with denied consultations received a gabapentin prescription through dispensing by staff pharmacists outside of the consult protocol, and these two patients were excluded. An additional 18 patients were excluded who had previous prescriptions of gabapentin for neuropathic pain prior to receiving care at the PVAMC and that were documented in the PVAMC Veterans Health Information System and Technology Architecture (VistA) database. A new prescription was defined as a prescription filled between October 2002 and April 2003 for a patient who had not had a prior prescription for gabapentin filled since May 1997, when gabapentin first appeared in pharmacy records. The pharmacy data were extracted from VistA using VA Filemanager and then uploaded into Microsoft Excel. Data collected during the VA electronic medical chart review included (1) indication for the prescription, (2) whether a consult to the clinical pharmacy department was submitted, (3) the prescriber's specialty, (4) whether and when treatment follow-up occurred, (5) documentation of treatment effectiveness, (6) continuation of the gabapentin prescription, and (7) whether the gabapentin prescription was initiated by a previous provider outside of the PVAMC. Information was also gathered on side effects and reasons for discontinuation. Prescriptions for neuropathic pain were then selected for further analysis. The number and status of all consults submitted were also collected for the same time frame using the VistA consult tracking reports. Data were analyzed using descriptive and chi-square statistics in Microsoft Excel and Vassar Stats statistical software. Prescription data for TCAs, NSAIDS, and capsaicin were gathered for all patients on gabapentin to assess compliance with the gabapentin treatment guideline.
already had demonstrated benefit with the drug (i.e., the efficacy of gabapentin had already been established in these patients).

Ninety-three patients (39%) had indications other than neuropathic pain for gabapentin and were therefore excluded from further analysis (Figure 2): 42 (18%) for migraine headaches; 18 (8%) for other pain syndromes; 15 (6%) for mental health usages; 15 (6%) for unknown indications; and 3 (1%) for seizure.

For the final analysis, 124 patients were included in the study: 71 (57%) of these patients received gabapentin prescriptions through the consult process (clinical-pharmacy-managed) and 53 (43%) received gabapentin prescriptions without a consult (provider-managed).

Denied Consults

A total of 148 consults were submitted to clinical pharmacy, and 60 (40%) of these were denied. The reasons for the 60 denials included the following: 2 (3%) patients chose not to start gabapentin; creatinine was elevated in 1 patient (2%); 9 (15%) consultations had indications other than neuropathic pain (e.g., trigeminal neuralgia, nonanginal chest pain, restless leg syndrome, and chronic pain); and 48 (80%) consults did not document a trial of first-line medications as per protocol.

Overall, 61% (54) of the prescribers used the clinical pharmacy consult service. Surgical subspecialties used the clinical pharmacy consult according to the gabapentin treatment guideline 29% of the time, neurology 35% of the time, and medicine subspecialties 50% of the time. VA primary care providers and community (fee-based) providers used the clinical pharmacy consult according to the treatment guideline more often when ordering gabapentin than did other categories of prescribers, 76% and 82%, respectively. Fee-based providers are VA-authorized and are reimbursed as community providers; they are used by some patients who live a great distance from VA outpatient care. The pharmacy service department submitted consult requests to clinical pharmacists on behalf of the fee-based providers, which likely accounts for the high compliance rate with the gabapentin treatment guideline that was seen with this category of provider.

Table 2 summarizes the follow-up of all patients, the timing of follow-up, the documentation of treatment benefit in the time frame of the study, the number of required therapies tried according to the treatment guideline, and whether the gabapentin therapy was continued or not. Of the 124 patients eligible for follow-up, 89 (72%) patients had documentation in the medical record of follow-up. Patients in the clinical-
pharmacy-managed group were more likely to receive documented follow-up after starting gabapentin than patients managed by the provider (usual care) group, 87% (n = 62) of patients compared with 51% (n = 27) of patients, respectively ($\chi^2 = 18.07, P \leq 0.001$). Of the patients who received follow-up, a greater percentage of clinical-pharmacy-managed patients received follow-up within 6 weeks compared with the provider-managed group.

Of the 89 patients with follow-up in the 2 groups, 64% (n = 57) experienced clinical improvement, and 24% (n = 21) had no improvement. Of the 21 patients with follow-up who had no improvement, 15 (71%) were in the clinical pharmacy group (1 patient died and 14 patients had their gabapentin therapy discontinued), and 6 (29%) were in the provider-managed group (1 patient died and 5 patients had their gabapentin therapy discontinued). The outcomes were unknown for 12% (n=11) of the patients who received follow-up. This occurred if documentation could not be found or if the treatment benefit was unclear at the time of the first follow-up. For several of the patients followed up by clinical pharmacy, their date of evaluation had not yet come due at the time of data collection for the present study.

Forty-two (68%) of 62 patients managed by the clinical pharmacy group experienced benefits with the use of gabapentin versus 15 (56%) of 27 patients managed by providers (68% vs. 56%, $\chi^2 = 0.74, P = 0.390$). The effect of treatment was unknown for 6 (22%) of the 27 patients followed up by providers versus 5 (8%) of the 62 patients followed up on by clinical pharmacists ($\chi^2 = 2.3, P=0.129$).

Similar percentages of prescriptions for gabapentin were continued and discontinued by the clinical pharmacists and providers. However, of the 53 patients followed by providers, 29 (55%) had tried 1 or 2 of the first-line therapies prior to the gabapentin trial. Only 1 patient (2%) had tried all 3 therapies, and 23 (43%) had no record of trying any of the 3 first-line therapies. Gabapentin prescriptions were continued in 46 (65%) of the 71 patients in the clinical pharmacy group versus 36 (68%) of the 53 patients in the provider group ($\chi^2 = 0.11, P=0.718$). There were 5 deaths in the group followed by clinical pharmacy and 1 death in the group followed by providers. The cause of death for the 6 patients was reviewed by a physician, and the deaths were determined to be related to comorbid conditions and not attributable to the use of gabapentin.

## Discussion

Through participation of stakeholders, a clinical pharmacy consult process was developed at the PVAMC to review and follow up on gabapentin efficacy for neuropathic pain. The goals of this project were (1) to evaluate the effectiveness of this process and (2) to describe the current pattern of use of gabapentin at our institution. Patients with a provider-given diagnosis of neuropathic pain were referred to clinical pharmacists for assessment, titration, and evaluation of treatment effect. The use of gabapentin by providers who bypassed this process and their assessment and management of neuropathic pain were compared with the use of gabapentin by the clinical pharmacy group and their assessment and management of neuropathic pain.

Of the 124 patients who received gabapentin prescriptions for the indication of neuropathic pain included in our review during the 7-month period, 57% of the patients went through the consult process and 43% did not. Although a similar percentage of patients in both groups ultimately continued gabapentin (65% and 68%), patients who did not have clinical pharmacy consults were less likely to receive follow-up within 6 weeks. A more coordinated pharmacy review process could have redirected some of this usage to the consult process.

The consult process allowed for a monitored trial of gabapentin, documentation of its efficacy, and denial of the prescription if guidelines for trial of other medications had not been followed or if the indication was inappropriate. In this study, 40% of consults were denied and thus 60 unnecessary prescriptions were avoided. This process contributed to increased documented effectiveness and quality for patients, education of providers on treatment criteria prior to use of gabapentin for neuropathic pain, and assistance with the management of neuropathic pain for providers and patients. The prompt assessment of efficacy and discontinuation and trial of other medications prior to trial of gabapentin promote efficient use of resources.

In theory, patients who had failed trials of NSAIDs, capsaicin, and TCAs and who had then received titrated gabapentin trials might be more refractory to treatment or more difficult to treat. However, when compared with the patients receiving gabapentin initially for neuropathic pain, a similar percentage of gabapentin prescriptions were continued for the groups of patients managed by providers versus clinical pharmacists. This suggests that the response to gabapentin is independent of response to trials of alternate, first-line therapies for neuropathic pain. Since nearly the same percentage of patients in the clinical-pharmacy-managed and provider-managed groups discontinued gabapentin therapy, 30% and 28%, respectively, a tiered trial of lower-cost therapeutic options seems particularly reasonable.

The pattern of gabapentin use at PVAMC showed that 39% of patients received the drug for non-FDA indications. Very few patients were on the drug for seizure or herpetic neuralgia. The primary care providers of the VA were most likely to use the consult process for the use of gabapentin for neuropathic pain. They had a formal training on the consult that was well attended. The pharmacy had a clinical pharmacist reviewing fee-basis prescriptions for formulary adherence, and thus the consult was completed for these patients.

Our attempt at standardizing the use of gabapentin for
neuropathic pain was based on the studies available in 2002 with the thought that this process would save this resource for patients failing the other standard therapies at the time. Unfortunately, some providers did not follow the procedure for neuropathic pain consults, resulting in 53 gabapentin prescriptions outside the consultation process. Had these prescriptions gone through the consult process, some would have received a trial of other therapies and most would have received more prompt follow-up and discontinuation if the drug was not effective. Provider desire for autonomy and the desire to please patients may have contributed to disregard of the clinical pharmacy consult protocol for gabapentin prescription. However, lack of knowledge of the process was another possible factor.

At PVAMC, consult in-services and discussions about needed documentation of efficacy and cost information occurred for several drug classes, and providers have begun to change prescribing behavior. Educational processes have been changed to identify target opportunities (e.g., rotating resident provider-prescribers) and respond with more in-service presentations.

The PVAMC has found the clinical pharmacy consult process helpful in documenting and assessing the effectiveness of expensive therapies and has adapted this model for other treatments. The success of this process depends on support of leadership; buy-in of providers, pharmacists, patients, and informatics staff; and reassessment of work required versus savings as prices change. Since patient follow-up occurs outside of a provider visit and is handled by a pharmacist, it does not increase the need for additional clinic appointments with the patient’s provider.

In addition, the evaluation process in the present study brought attention to the documentation of clinical benefit and trial of other medications prior to use of an expensive drug for a non-FDA-approved indication. As providers become more familiar with the protocol, the need for consults might decline. On the other hand, when another new, expensive agent for neuropathic pain is placed on formulary, this approach could be adapted to require step therapy trials with first-line agents.

At the time our guideline was created, there were few RCTs of gabapentin use for neuropathic pain syndromes other than nonherpetic neuralgia or diabetic neuropathy. Since that time, RCTs have been conducted, resulting in the recommendation of gabapentin as a first-line agent by the Agency for Healthcare Research and Quality’s National Guideline Clearinghouse on the topic. This guideline is for neuropathic pain, including peripheral neuropathic pain and central neuropathic pain of many etiologies. We have found patient literature of one other large managed care system that discusses similar therapies during 2002.

In 2003, Dworkin et al. published a review of the literature that is commonly cited as a reference for the treatment of neuropathic pain and is the basis for the guideline for the diagnosis and treatment of neuropathic pain from the National Guideline Clearinghouse; it was first released in November 2003. The section recommending use of gabapentin for neuropathic pain is based on 8 double-blind, placebo-controlled, randomized clinical trials. Three of these studies looked at the treatment of postherpetic neuralgia, 2 studies looked at diabetic neuropathy, 1 study looked at phantom limb pain, 1 study looked at Guillain Barre, and 1 study looked at spinal cord injury. These studies might be used to support treatment of these conditions compared with placebo.

Neuropathic pain is the end stage of many disease states, most of which are not well studied. The drugs recommended as first-line agents by Dworkin et al. in their review published in 2003 included 5% lidocaine patch, opioid analgesics, tramadol, and TCAs. The second-line agents listed are lamotrigine, carbamazepine, paroxetine, citalopram, sustained-release bupropion hydrochloride, venlafaxine, and imipramine hydrochloride. Treatments beyond second-line medications included capsaicin, clonidine, dextromethorphan, and mexiletine. Most of the cited studies are placebo-controlled without comparison of therapies. Dworkin et al. acknowledged variable responses to drugs within a class and hypothesized that variable pain mechanisms are responsible. The review states that there are empiric and theoretical reasons for trying different agents in a class and in various classes for a patient not finding relief of neuropathic pain.

One appealing aspect of the use of gabapentin is its relatively benign side effects compared with other therapies such as TCAs. The side-effect profile of gabapentin is thought to be less severe, including dizziness, somnolence, gastrointestinal symptoms, ataxia, fatigue, nystagmus, viral infection, and mild peripheral edema. These are the side effects occurring in more than 8% of users as listed in Lexi-Comp for gabapentin. Gabapentin can cause gait, balance, and cognitive problems in the elderly but is thought to have excellent tolerability and safety.

The factors that are evaluated for use in a tiered approach to the use of medications include effectiveness, effectiveness over other therapies, costs, safety, and availability. While gabapentin appears to be relatively safe, available, and effective in many patients, it is expensive in the customary dose range of 900 mg to 1800 mg, yielding a price range of $117 to $219 per month according to data from drugstore.com as of December 2005. In 2002, with no generic gabapentin available, these prices were higher. Dworkin et al. also considered the cost to patients when they selected the first-line agents for neuropathic pain.

There is a large body of literature on the subject of physician adherence to medical practice and drug therapy guidelines. An algorithm designed to encourage physicians in an integrated health system to use over-the-counter NSAIDs as first-line therapy in musculoskeletal pain and arthritis was associated with a decrease in the number of prescription NSAID claims per member per month (PMPM). Use of a risk-scoring tool in a large group-model HMO was associated with a more-than-5-fold lower ratio
of the use of COX-2 selective NSAIDs for arthritis patients in the lowest decile of risk (1.5% of these patients) compared with patients in the highest decile of risk for serious gastrointestinal complications (8.3%). However, poor prescriber adherence to FDA-approved guidelines for drug therapy has emphasized the need for managed care interventions. The lack of complete documentation in the electronic medical record was also evident in the fact that, among the patients who received follow-up contact, 5 patients (8%) in the clinical-pharmacy-managed group and 6 patients (22%) of the provider-managed group had unknown treatment benefit at follow-up.

Interventions such as physician profiles used in conjunction with academic (prescriber) detailing have been associated with savings in PMPM spending on antidepressants despite increased utilization due to use of lower-cost therapeutic alternatives. Use of electronic clinical decision support systems based upon evidence from the medical literature has similarly been associated with drug cost savings from the use of lower-cost therapeutic alternatives despite increased drug utilization in primary care medical groups. Previous research in the VA health system found that simple dissemination of national criteria for the appropriate use of tamsulosin had no measurable effects on prescribing and that a formal education process was probably necessary to reduce inappropriate prescribing of the nonformulary drug.

The PVAMC receives funding per patient, and there is no incentive pay for PVAMC providers to either conserve or use resources. In 2002, if a patient was on gabapentin, more than one third of their allotment for care was spent on this drug therapy alone. To place this in context, most VA patients receive an average of 7 drugs. Gabapentin is not approved by the FDA for neuropathic pain. The benefits of managing PVAMC resources allows for more services per patient and more care for more patients.

Limitations

There were several methodological limitations in the present study, including the retrospective evaluation of a clinical process. When the process started, some prescriptions for gabapentin were being written and accepted that did not go through the protocol of the clinical pharmacy consult. This loop has since been closed by eliminating all other computer ordering routes of gabapentin except through the clinical pharmacy consult.

We did not investigate the potential bias that might have been introduced had more difficult pain cases been referred to the clinical pharmacist since consults were only approved when the provider-managed group to determine how many had received one or more of the first-line therapies in the gabapentin treatment protocol.

Finally, this evaluation study depended on chart documentation of the effectiveness of gabapentin treatment for patients’ neuropathic pain. Providers may have assessed the effect of gabapentin but did not document it, which may have resulted in an underestimate of the actual rate of follow-up assessment of treatment effect; other research has shown that providers tend to do more than they document in the medical chart. The lack of complete documentation in the electronic medical record was also evident in the fact that, among the patients who received follow-up contact, 5 patients (8%) in the clinical-pharmacy-managed group and 6 patients (22%) of the provider-managed group had unknown treatment benefit at follow-up.

This study also did not measure service outcomes, such as patient dissatisfaction with care, or cost outcomes, including the administrative costs of this intervention or the possible offsetting cost reduction in expenditure for gabapentin. The follow-up period for a patient in this study could have been as short as 6 months.

Conclusions

Implementation of a clinical pharmacy consult for neuropathic pain resulted in 100% of patients using 3 first-line therapies prior to gabapentin compared with 2% for physician-managed patients. The clinical-pharmacy-managed patients also had a higher rate of follow-up to document response to gabapentin therapy and had more timely follow-up compared with physician-managed patients.

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ABSTRACT

OBJECTIVE: To evaluate patient satisfaction, effectiveness, and safety of at-home treatment of acute deep vein thrombosis (DVT) with subcutaneous enoxaparin dosed at 1.5 mg/kg once daily plus oral warfarin.

METHODS: Patients with acute DVT and no more than 1 previous episode of DVT received enoxaparin plus oral warfarin until their international normalized ratio (INR) was >2 on 2 consecutive days. Patients were recruited between November 2000 and June 2003, and a home-care nurse visited the patient daily to administer the enoxaparin and to perform a fingerstick INR test. Patients received warfarin at doses adjusted to maintain an INR in the range of 2 to 3. Efficacy and safety were assessed daily by a home-care nurse and then by telephone interview conducted by a pharmacist at 14, 30, and 90 days during follow-up. Patient satisfaction with treatment was assessed by a verbal questionnaire.

RESULTS: There were 52 patients enrolled. The mean duration of enoxaparin home treatment was 4.5 days, and the mean INR on discontinuation of enoxaparin was 2.73. Most patients (84.6%) had INRs within the desired therapeutic range (INR value 2-3); no patient had a subtherapeutic INR. There were no symptoms derived from the substitution of inpatient care with home care.

CONCLUSION: The results of this pilot study suggest that home treatment with initial once-daily enoxaparin in conjunction with long-term oral warfarin is a safe and effective alternative to inpatient therapy with once-daily enoxaparin or unfractionated heparin for select patients with acute DVT. Cost savings are derived from the substitution of inpatient care with home care.

KEYWORDS: Outpatients, Home treatment, Enoxaparin, Deep vein thrombosis, Thromboembolism

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Deep vein thrombosis (DVT) affects approximately 1 of every 2,000 people in the general population each year in the United States and is a major cause of mortality and morbidity because of the risk of complications such as pulmonary embolism (PE) and postthrombotic syndrome. The economic costs and the inconvenience to the patient of in-hospital treatment of DVT create a strong rationale for safe and effective home anticoagulant therapy in eligible patients.

Traditionally, the treatment of DVT involved unfractionated heparin (UFH) administered intravenously in a hospital setting for 5 to 7 days. However, the use of UFH requires hospitalization for close monitoring because of the narrow therapeutic index and a nonlinear dose-response relationship that shows marked variation between individuals. By contrast, low-molecular-weight heparins (LMWHs) offer a more predictable pharmacokinetic profile and anticoagulant effect and can be administered by subcutaneous injection without routine anticoagulation monitoring. Several studies have shown that LMWHs are at least as effective as intravenous (IV) UFH in the in-hospital treatment of DVT. Furthermore, the ability to administer LMWHs subcutaneously makes it feasible to treat patients in their home, rather than in the hospital. Although treatment in an outpatient setting offers the benefits of convenience for the patient and the potential to reduce hospital costs, many physicians may be reluctant to use this approach, possibly because of a belief that the controlled conditions of clinical trials are not representative of the real-world clinical situation. While large randomized trials have shown that twice-daily LMWH treatment at home is effective and well tolerated compared with UFH treatment in the hospital, less data are available to support once-daily dosage of enoxaparin on an outpatient basis.

We carried out a pilot study in patients with acute DVT to evaluate the convenience, efficacy, and safety of the LMWH enoxaparin, 1.5 mg/kg, given once daily in a real-world U.S. patient population eligible for home treatment.

Methods

The study was a prospective, nonrandomized, open-label study performed at a single center in the United States enrolling patients eligible for home care with LMWH. William Beaumont Hospital is a 1,085-bed community, nonprofit, teaching hospital located in Royal Oak, Michigan. The study was conducted according to the Declaration of Helsinki and approved by the hospital’s Institutional Review Board. Written informed consent was obtained from all patients before inclusion in the study.
Patients were enrolled between November 2000 and June 2003. Adult patients with acute proximal DVT confirmed by Doppler ultrasound were eligible for the study if they met the eligibility criteria for home therapy summarized in Table 1. Patients were recruited from the emergency room, a short-stay ambulatory unit, and inpatient areas of the hospital. Baseline laboratory assessment included serum creatinine, hemoglobin, platelets, and prothrombin time. On the day of hospital discharge, all patients were administered a single subcutaneous (SC, 1.5 mg/kg) dose of enoxaparin (Lovenox). Prior to discharge, patients were provided with a 7-day supply of enoxaparin and 25 tablets of 2.5 mg warfarin (Coumadin). Patients or their caregivers were educated by a pharmacist prior to discharge and by the home care nurse at the first visit. Education included the purpose of anticoagulant therapy, anticoagulant monitoring, and signs and symptoms of adverse events, with a signed educational checklist added to the inclusion criteria to ensure that each patient was fully informed.

Initially, patients received enoxaparin 1.5 mg/kg SC once daily, administered by a home-care nurse, and daily oral warfarin dosage titrated by a pharmacist. The international normalized ratio (INR) was monitored by fingerstick testing (CoaguChek, Roche Diagnostics), and the warfarin dose was adjusted until the target range (2-3) was recorded for 2 consecutive days. Daily nursing visits ceased when a second INR was verified to be in the therapeutic range (with no enoxaparin administered on the final day of home nursing visits). Warfarin treatment was then continued with INR monitoring done by venous draw (not fingerstick) and dose adjustment was at the discretion of the patient’s private physician and not recorded for the study. Adherence to warfarin therapy was confirmed by telephone follow-up at 14, 30, and 90 days. To document cases of readmission, hospital computer records were checked and patients were questioned at the follow-up intervals to ensure that readmission to another institution would be reported.

Efficacy and safety were assessed daily during enoxaparin treatment and at 14, 30, and 90 days follow-up after warfarin therapy. Assessments were made by telephone interviews using a questionnaire to confirm the absence of signs or symptoms of thromboembolism (PE or DVT), bleeding, or other adverse events. Efficacy outcome was the absence of repeat thromboembolic symptoms. For example, patients were asked whether the lower limb pain or swelling had changed (which could indicate worsening of the DVT) or if they had experienced any shortness of breath or chest pain (which could indicate progression of DVT to PE). Safety outcomes were signs or symptoms of any adverse events, including bleeding, allergy, or death. For example, patients were asked whether they had any nosebleeds, bruising, rashes, or blood in stools, urine, or the mouth. A major bleed was defined as a drop in hemoglobin of >2 g/dL or evidence of any intracranial bleed or retroperitoneal bleed.

A secondary outcome was the number of days required to reach the INR target.

Patient satisfaction with treatment was assessed during follow-up by means of a questionnaire consisting of 3 questions:
1. Were you satisfied with the pain control?
2. Were you satisfied with the nursing visits?
3. Were you satisfied with the fingerstick INR blood test method?
Results

Of 233 patients screened for enrollment, 53 declined participation (through either the patient or primary care physician), and 128 were excluded by the exclusion criteria (Table 1). The reason(s) for ineligibility were: low hemoglobin or platelet count (44), creatinine clearance <30 mL/min (32), ≥2 DVT by history (22), recent surgery (13), PE or clot with ileo-caval involvement (9), total body weight greater than 150% of lean body weight (5), pregnancy (2), and spinal epidural (1). Patient demographics are shown in Table 2. A total of 52 patients were recruited, of whom 32 were inpatients started on UFH (average UFH treatment duration 3.25 ± 1.93 days), and 20 (38%) presented to the emergency room but were not subsequently admitted for inpatient care. Of the recruited patients, 51 completed the study; 1 patient was removed on physician advice due to hemorrhage at a uterine tumor site that resulted in surgery prior to further DVT treatment. For those patients receiving concomitant therapy with aspirin, clopidogrel, ibuprofen or allopurinol (n = 13), none noted bleeding.

Efficacy and safety outcomes are summarized in Table 3. The mean duration of enoxaparin treatment was 4.5 days, equating to 4.5 doses of enoxaparin when allowing for the dose on discharge from hospital and no dose given on the final day of home-care visits. The mean INR at the time of enoxaparin discontinuation was 2.73; a total of 44 patients (84.6%) had INRs within the therapeutic range, and, of the remaining patients, all had supratherapeutic INRs (>3).

There were no reports of symptoms that could indicate recurrent DVT or PE during the study. Major bleeding, resulting in a 3.6-g/dL decrease in hemoglobin concentration, occurred in one patient (1.9%) who subsequently underwent removal of a uterine tumor on day 13 of warfarin treatment (7 days after discontinuation of enoxaparin). This patient was withdrawn from the study due to impending surgery. This patient was the only readmission to the hospital identified in the study. There were 2 (3.8%) cases of minor bleeding: at the injection site in one patient and scleral hemorrhage in the other patient.

The 3-item patient satisfaction questionnaire, for which there was a 100% response rate, revealed that patients considered home treatment to be convenient. All 52 patients reported that they were satisfied with their pain control and understood the methods to reduce leg pain (i.e., they verbalized that raising the leg or taking acetaminophen were sufficient measures for relief). The fingerstick method of blood monitoring (compared with conventional venous blood sampling) was satisfactory to all patients, and 22 patients (42%) expressed an interest in continuing this method, had it been made available, after the home-care nurse was discontinued because it was “less painful” and “less invasive” than the venous method. Forty-seven patients (90.4%) were satisfied with the home-care nursing visits.

Only descriptive statistics were used in this study.

For the same study period, billing and payment data for daily home nursing visits were recorded for enrolled patients. The patient or third-party payer was billed for the number of visits, and the payment was recorded.
visits at a billed charge per visit of $118 ± 9.7. The overall cost for home-care treatment was compared with the cost for typical inpatient UFH treatment over the same study period. The average savings were $2,925 per patient despite higher pharmacy costs (Table 4). Average reimbursement for home nursing visits was 90% of billed charges ($457 ± 187).

### Discussion

The results of this pilot study suggest that once-daily treatment with enoxaparin at a dose of 1.5 mg/kg, delivered at home in conjunction with long-term therapy with warfarin, is convenient, effective, and safe for the treatment of eligible patients with DVT. Patients considered at high risk were excluded from the present study. Compared with previous practice in this medical center, inpatient hospital days were either decreased or avoided. In the present study, there were no episodes of recurrent DVT symptoms, no symptoms of PE, and no serious adverse events related to enoxaparin. The one case of major bleeding occurred in a patient with a uterine tumor with impending surgery for its removal, and the bleeding was not considered related to enoxaparin.

These results are consistent with those of recent randomized comparative trials (Table 5) in which outpatient treatment with SC enoxaparin, either once or twice daily, was as effective as in-hospital treatment with IV UFH.14,17,18 This observational study adds to the accumulating evidence to support the use of outpatient enoxaparin once daily and is in accord with a recent position statement encouraging the development and documentation of outpatient DVT treatment programs.13

Once-daily administration offers obvious advantages over twice-daily treatment in terms of greater convenience for both patients and nursing staff. This greater convenience was reflected in the high levels of patient satisfaction reported in this study. Moreover, the reduced number of hospital visits required with once-daily treatment at home offers potential savings in the costs of nursing staff, drugs, and consumables.9-11 Such savings are due largely to reductions in costs associated with hospitalization. In the present study, outpatient treatment of DVT with enoxaparin once daily provided 74% lower costs when compared retrospectively with typical inpatient UFH therapy for the same treatment duration (Table 4). The average saving of $2,925 per patient was realized despite higher pharmacy costs.

A prior retrospective analysis of average length of stay in those patients receiving UFH at our hospital found that, for the period 1998-2000, 165 patients were hospitalized for an average 5.5 days (range, 3-9). Therefore, the savings in actual practice may be larger and will certainly be different in other medical centers. In addition, the actual payer costs may be higher or lower than our findings since reimbursement for home nursing visits in the present analysis was approximately 90% of billed charges.

Thus, the data suggest that at-home treatment in select patients is a cost-effective alternative to hospitalization. This is supported by a previous study in which outpatient treatment with LMWH reduced the number of hospital days by 40% (7.2 vs. 12.1 days for UFH) and total treatment costs by 64% compared with UFH.9 Compared with UFH, LMWH treatment has been shown to produce cost savings when as few as 8% of patients with DVT were treated as outpatients.10 Moreover, studies comparing outpatient and inpatient treatment with LMWHs have shown that outpatient treatment can result in cost savings of up to 82%.11,12 Lee et al. reported in 1996 that the outpatient treatment of DVT with LMWH reduced the mean patient treatment cost from $3,266 to $584, a cost that included medications.
laboratory analyses, and home visits or hospital days as appropriate. Tillman et al. found that an outpatient program carried out in a health maintenance organization, enrolling 391 patients treated with initial enoxaparin and warfarin to 90 days, realized total cost savings of $1,108,587 over the 2-year evaluation period.

For patients with acute DVT, the American College of Chest Physicians (ACCP) recommends initial treatment with SC LMWH once or twice daily over UFH, as an outpatient if possible, or as an inpatient if necessary. Yet, despite the accumulating evidence for the safety and cost-effectiveness of at-home treatment with LMWHs, there appears to be some reluctance among physicians to use such therapy. More than 80% of patients with DVT have been shown to be eligible for outpatient treatment, yet one recent study reported that only 20% of the patients diagnosed with DVT received treatment with LMWH in an outpatient setting. This may reflect physician concerns over the patient’s ability to learn a new therapy (for self-administration) or the perceived lack of direct supervision by health care professionals. It may also reflect a view that findings from clinical trials, conducted under controlled conditions with multiple inclusion/exclusion criteria, are not necessarily applicable to the real-world patient population found in clinical practice. Thus real-world studies, such as the one presented here, can provide important insights into the potential benefits of once-daily at-home treatment with LMWH for eligible patients.

Physician acceptance of at-home treatment appeared to improve during the course of this pilot study. Physicians began to contact the investigator to enroll patients and, in some cases, sent patients to the emergency room for consideration for home care as a substitute for hospital admission. This has particular significance given that DVT has traditionally been perceived by physicians as a serious condition requiring hospitalization. Furthermore, in the early stages of this pilot study, the daily patient assessments by the home-care nurse helped convince the physicians of the safety of home treatment, such that toward the end of patient enrollment, physicians were suggesting that patients be taught to self-inject enoxaparin to avoid the need for nursing visits. This could be explored further in future studies. While the home-care nurse confirmed compliance with the medications, it may be beneficial to study daily compliance in patients trained to self-inject enoxaparin.

Limitations

Foremost among the limitations of this study is the lack of a UFH comparison arm with patients matched for disease severity. This limits clinical interpretation of our data and more robust cost-savings analysis. Second, the relatively small sample size and exclusion of high-risk patients limit the generalization of these results to all patients with DVT. Third, assessment of DVT recurrence was based on patient self-assessment and was not subject to objective screening. Fourth, the questionnaire used in this study was intended as an indicator of patient satisfaction and did not provide a validated quality-of-life assessment or quantita-tive measure of patient satisfaction. Further studies examining the service/humanistic outcomes of care for DVT would be of value in supporting once-daily home management of DVT.

Conclusion

Initial once-daily enoxaparin administered in the home with concurrent warfarin appears to provide efficacious and safe care in eligible patients with acute DVT. Home treatment with enoxaparin offers the opportunity to reduce the cost of treating DVT, without compromising clinical outcomes, and may be associated with patient satisfaction with care. This was a pilot study, and the favorable clinical and service/humanistic outcomes observed should be assessed with more quantitative measures by other researchers.

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REFERENCES


Referral Bias and Other Perspectives on the HEDIS Measuring Stick for Quality of Care in Depression Treatment

The National Committee for Quality Assurance (NCQA) is an independent not-for-profit organization based in Washington, DC, whose vision is to “to transform health care quality through measurement, transparency and accountability.”¹ Using the Health Plan Employer Data and Information Set (HEDIS), NCQA has determined how “more than 90 percent of the nation’s managed care organizations” will collect, audit, and report their performance on a range of standardized quality measures. Many of the HEDIS measures are undisputedly useful in promoting population health, such as rate of beta-blocker use after myocardial infarctions or rate of cervical cancer screening. Other measures, such as antidepressant medication management (AMM), have less evidence supporting the goals promoted by NCQA.

Although the latest report on the State of Health Care Quality 2005 from NCQA appropriately describes and cites support for the need to treat depression, it does not cite supporting trials that validate the definitions chosen for their AMM measures. Specifically, the following definitions are used by HEDIS:

1. **Effective Acute-Phase Treatment:** the percentage of eligible members who were diagnosed with a new episode of depression, treated with antidepressant medication, and remained on antidepressant medication during the entire 12-week acute phase.

2. **Effective Continuation-Phase Treatment:** the percentage of eligible members who were treated with antidepressant medication and remained on antidepressant medication for 6 months after diagnosis of a new episode of depression.

3. **Optimal Practitioner Contacts for Medication Management:** the percentage of eligible members who received at least 3 follow-up office visits with a primary care physician or mental health provider in the 12-week acute-treatment phase after a new diagnosis of depression and prescription of antidepressant medication.

Why is it that NCQA can arbitrarily (as the self-appointed information source for managed care performance) define performance measures without citing studies showing improved outcomes when adhering to AMM recommendations? Yes, the current AMM measures sound reasonable; however, once incorporated into HEDIS, they become the performance standard, validated or not. AMM performance also becomes a ripe target for researchers and quality improvement initiatives.

In this issue of *JMCP*, Robinson et al. report on the percentage of 60,386 adult patients in the Marketscan (administrative claims database who adhered to the AMM measures from January 2001 to September 2004.¹ The primary outcomes were: 19% of patients achieved overall adherence to all 3 measures, while adherence rates for the 3 individual measures were 39% for 3 or more practitioner contacts, 65% for acute-phase medication compliance, and 44% for continuation-phase compliance. Except for the optimal practitioner contact rate being higher than the national average (39% vs. 19%), rates were very similar to the U.S. overall rates.² Of note, when comparing the total health care costs with the payer, patients who had overall adherence to all 3 HEDIS measures had median total costs that were nearly 2 times higher over the 6-month follow-up period ($5,169 vs. $2,734).³ What was the return on investment for the payer? Total costs for depression-related care in the adherent group were $1,922 versus $677 in the nonadherent group.³ If employers want to spend money wisely, what concrete patient-oriented outcomes are being shaped by using the HEDIS AMM definitions? Until stronger linkage is established that shows that HEDIS depression management markers truly impact outcomes, the stream of studies joined by Robinson et al. should be redirected toward authenticating the AMM measuring stick, and not simply using it because it bears the HEDIS stamp of approval.

Besides AMM adherence rate determination from this administrative claims database, Robinson et al. also found that receipt of mental health specialty care was the only factor that was positively associated with greater adherence on all 4 measures (overall measure: odds ratio [OR] = 3.895; 95% confidence interval [CI], 3.72-4.07).¹ This take-home point was highlighted in the abstract, “(R)eceipt of mental health specialty care was the single factor most strongly associated with quality treatment by these measures.”³ Taken at face value, this statement implies that patients are adversely affected if they do not receive care by mental health providers. The convenient AMM tool makes this claim possible, but was it applied appropriately?

An important confounder that affects database mining is referral bias to other specialties, such as mental health. Patients who are referred for mental health care are typically more difficult to treat, require greater attention, have more severe symptoms, and need greater duration treatment. In a study by Simon et al., managed care patients in Washington state who were started on new antidepressant medication were compared by treating specialty provider.⁴ They found, at baseline, that psychiatrists’ patients reported slightly higher levels of functional impairment and greater prior use of specialty mental health care. During follow-up, psychiatrists’ patients made more frequent follow-up visits, and the proportion making 3 or more visits in 90 days was 57% versus 26% for primary care physicians’ patients; yet, despite these differences, the 2 groups showed similar rates of improvement in all measures of symptom severity and functioning.⁴

Another managed care study looking at outcomes for 358 patients receiving recommended depression treatment over 6 months showed that patients receiving less-than-recommended levels of antidepressant therapy for 90 days showed improvement in depression severity and health-related quality of life comparable with patients receiving minimum recommended
treatment. In contrast to Robinson et al., the group receiving minimum recommended treatment had lower mean total medical costs over 6 months ($1,872 ± $140) compared with patients receiving less-than-recommended treatment ($2,622 ± $413, P = 0.032). 5

To appreciate the differences in depression populations between mental health and primary care, and to begin reflecting on the notion that universal application of the HEDIS AMM measures may not always be appropriate, consider a 12-month randomized controlled trial reported by Katon et al. of intensive follow-up versus usual care in 217 primary care patients. 6 After stratifying into major and minor depression groups, they found that, for major depression (more likely to be referred for mental health care), the intervention group had greater adherence than the usual care controls to adequate dosage of antidepressant medication for 90 days or more (75.5% vs. 50.0%, P < 0.01), were more likely to rate the quality of the care they received for depression as good to excellent (93.0% vs. 75.0%, P < 0.03) and were more likely to rate antidepressant medications as helping somewhat to helping a great deal (88.1% vs. 63.3%, P < 0.01). Seventy-four percent of intervention patients with major depression showed 50% or more improvement on the Symptom Checklist-90 Depressive Symptom Scale compared with 43.8% of controls (P < 0.01), and the intervention patients also demonstrated a significantly greater decrease in depression severity over time compared with controls (P < 0.004).

In contrast, for patients with minor depression (more likely to stay in primary care), Katon et al. found no significant differences between the intervention and control groups in the percentage of patients who were satisfied with the care they received for depression (94.4% vs. 89.3%), in the percentage who experienced a 50% or more decrease in depressive symptoms, or in the decrease of depressive symptoms over time.

Since database claims typically pull International Classification of Diseases, Ninth Revision (ICD-9) codes, appreciation for the variety and spectrum of depression severity is missing. Brief depressive symptoms or adjustment disorders with high rates of spontaneous resolution are commonly coded as depression not otherwise specified, (ICD-9 code 311) and do not require the intervention patients also demonstrated a significantly greater decrease in depression severity over time compared with controls (P < 0.01).

The roadmap for how depression treatment in primary care can improve further using a systematic chronic care model and primary care nurse managers has been thoughtfully illustrated by Solberg et al. and is worth reading by all those interested in quality improvement. 7

Caution should be exercised with future application of HEDIS measures to ensure that outcomes are truly improved with NCQA definitions and that confounders such as referral bias are minimized when applying HEDIS to research efforts.

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DISCLOSURE
The author is a board-certified family physician assigned to Eglin AFB Florida, where he serves as Family Medicine Residency program director, HQ Air Armament Center. The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of any organization, including the U.S. Air Force medical department or the U.S. Air Force. He discloses no potential bias or conflict of interest relating to this editorial.

REFERENCES
Chasing Quality—Clinical Practice Guidelines and HEDIS Measures of Asthma and Depression Therapy Management

In this issue of JMCP are 4 articles that examine aspects of evidence-based medicine (EBM) in 4 different clinical pathways. Payackat, Summers, and Barbuto compare the evidence and 6 clinical practice guidelines for the treatment of epilepsy published between 2000 and 2005. Heaton et al. challenge the value of leukotriene modifiers, currently recommended as second-line therapy in the treatment of asthma. Robinson et al. found an above-average rate of adherence to one of the quality measures in the Health Plan Employer Data and Information Set (HEDIS) in the treatment of depression. Winterbottom et al. found a low rate of adherence to a clinical practice guideline for the use of gabapentin for neuropathic pain in usual care versus a clinical pharmacy consult.

In the treatment of depression, drug therapy is about as effective as psychotherapy, but patients with major depression can be stratified to predict better response to psychotherapy versus drug therapy or the combined therapy. In one of the few studies that directly compared cognitive-behavioral therapy (CBT) with drug therapy, the Treatment for Adolescents with Depression Study (TADS) team found placebo effective in about 35% of patients with major depressive disorder compared with about a 43% response to CBT, 61% response to the selective serotonin reuptake inhibitor (SSRI) fluoxetine, and 71% response to combined CBT and fluoxetine. In this randomized controlled trial (RCT) of a volunteer sample of 439 patients between the ages of 12 to 17 years with a primary Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), diagnosis of major depressive disorder, 12 weeks of fluoxetine alone (10-40 mg per day) was compared with CBT alone, CBT with fluoxetine (10-40 mg per day, and placebo). The combined treatment of CBT and fluoxetine was superior to fluoxetine alone (P = 0.02) and to CBT alone (P = 0.01).

Drug therapy alone for the treatment of major depression is not much more effective than placebo, but the magnitude of the difference varies among clinical trials. For fluoxetine, the only antidepressant with evidence of effectiveness and favorable benefit-risk ratio in children and adolescents, Emslie et al. found a 56% response rate in depressed children and adolescents versus a 33% response rate for placebo, response rates similar to TADS (above). This study by Emslie et al. was an RCT funded by the National Institute of Mental Health and published in 1997. In research in a similar population of patients funded by the manufacturer of fluoxetine and published 5 years later, Emslie et al. found a 65% response to fluoxetine versus 53% for placebo. Remission of symptoms occurred in 31% of fluoxetine patients versus 23% for placebo in the earlier study and in 41% of fluoxetine patients versus 20% of placebo patients in the later study. In other words, the placebo response ranged from 33% to 53% in these 2 clinical trials in children and adolescents and in the TADS study in adults, and complete remission of symptoms with placebo ranged from 20% to 23% of children and adolescents patients in the latter 2 clinical trials of fluoxetine.

In a meta-analysis of original data from 7 RCTs, Thase et al. found that 51% of outpatients with major depressive disorder responded to placebo and 36% of the patients randomized to placebo experienced remission during follow-up. Hjalmarsson et al. concluded that RCT studies in depressed patients show placebo response rates in the range of 30% to 50%, active drug response in the range of 45% to 50%, and the difference between active drug and placebo response rates in the range of 18% to 25%. Other researchers have suggested that the high placebo response rates in the latter (2002) study by Emslie et al. may be associated with the relatively low depression scores for the patients involved in that study, and Khan et al. found that patients with more-severe depression respond better to antidepressant therapy. Separately, Khan et al. found, from their review of 15 RCTs, that women exhibit greater response to SSRI antidepressants than men.

In the ARTIST (A Randomized Trial Investigating SSRI Treatment) study, 46% of patients (n = 256) with major depressive disorder treated with an SSRI were nonresponders at 6 months, and 53% of the patients (n = 222) who received SSRI therapy for at least 6 months did not achieve remission. The results of this prospective naturalistic trial suggest that effective treatment of depression involves more than adherence (continuation) of drug therapy. For cost outcomes, Eaddy et al. found, from administrative claims data, that total medical costs were not lower for patients who take SSRIs or other antidepressants for 90 days or longer compared with persons who take antidepressants for fewer than 90 days.

So, the accumulated evidence suggests that antidepressants are little more effective than placebo (although antidepressants appear to be more effective than placebo in patients with more-severe depression), are generally no more effective than psychotherapy, at least one half of depressed patients who take SSRIs for at least 6 months will not achieve remission, and taking antidepressants for 90 days or longer is not associated with savings in total medical costs. In light of this evidence and the absence of a measure of disease severity, the HEDIS measures of clinical quality for the treatment of depression may require further revision.

There is evidence that interventions as limited as telephone talk therapy can improve clinical outcomes in depression disease management. In a study of 600 patients beginning antidepressant treatment for depression in 7 group-model primary care clinics, a structured 8-session talk therapy program delivered by telephone was superior to usual care as measured by Hopkins Symptom Checklist Depression Scale depression scores (P = 0.02), the proportion of patients reporting that depression was “much improved” (80% vs. 55%, P = 0.001), and in the proportion of patients “very satisfied” with depression treatment (59% vs.
Quality of care for the treatment of depression involves more than antidepressant medication management (AMM).

What can the research performed with administrative claims data such as that reported by Robinson et al. in this issue of JMCP add to the clinical trial data? As pointed out by a clinical psychologist in a recent editorial, clinical trial results are not easily translated into reliable guidance for clinical practice in which patients present commonly with multiple problems versus the strict inclusion criteria of clinical trials in which the enrolled patients have isolated conditions. Yet, research with administrative claims data is dependent upon the accuracy of coding in the medical claims, and incentives exist for the convenient or purposeful miscoding of medical claims. For depression in particular, patient medical records and medical claims are not congruent. In a previous issue of JMCP, Theobald et al. found that 40% of the medical charts evaluated for patients who were prescribed an antidepressant in primary care did not document a single symptom necessary to make a diagnosis of major depression as defined by DSM-IV; another 30% of the medical charts for patients who were prescribed antidepressants had only 1 symptom of major depression recorded. Only 7% of the charts had 5 of the 9 symptoms required to make a diagnosis of major depression. This study suggests that either the medical records match poorly the medical claims for the diagnosis of major depression or patients prescribed antidepressants may not have major depression as defined by DSM-IV criteria.

The data presented by Robinson et al. should also give the reader pause, particularly the finding that the percentage of patients with a diagnosis of depression and a pharmacy claim for an antidepressant who received at least 3 follow-up provider contacts in the 12-week acute treatment phase was 39.0%, about twice the rate of 19.2% to 20.3% reported by commercial health plans in 4 consecutive measurement periods in 2001, 2002, 2003, and 2004. The significance of this finding is not immediately clear, but it is evident that either this study population received truly different care than other commercial health plans or this study population is different from the health plan members represented in 4 years of HEDIS reporting. One wonders how these factors might explain the finding by Robinson et al. that receipt of mental health specialty care was the only variable that was positively associated with greater adherence on all 4 quality measures.

Despite their finding of an above-average rate of provider contacts, Robinson et al. lament the poor performance of managed care plans in adequate medical management of depression as defined by the AMM criteria in the HEDIS quality-of-care measures. As Crownover observes in an accompanying editorial, where is the evidence to support these alleged measures of quality of care in the treatment of depression? Is it even advisable to continue pharmacotherapy for longer than necessary to relieve symptoms of depression, particularly in persons aged 60 years or older when long-term efficacy has been demonstrated only for nortriptyline and citalopram, all antidepressants carry a black-box warning in labeling regarding the increased risk of suicidality in children and adolescents, and there is evidence of increased risk of gastrointestinal (GI) bleeding with the SSRIs? Van Walraven et al. found that the use of SSRIs increased the risk of bleeding by 10.7% for octogenarians and 9.8% for those with a history of GI bleeding. Low inhibition of serotonin reuptake (bupropion and most of the tricylics) in patients with a history of GI bleeding was associated with 28.6 bleeds per 1,000 person years versus 40.3 bleeds per 1,000 per year for high inhibition of serotonin reuptake (e.g., clomipramine, fluoxetine, paroxetine, and sertraline); the number needed to harm was 85. Other research has found an association between the use of SSRIs and increased risk of GI bleeding, leading to more widespread recognition that the SSRIs, particularly the ones with more potent inhibition of serotonin reuptake, are not as safe as placebo.

The commercial (nongovernment) health plan scores for the AMM measures in HEDIS may suggest good or even optimum performance in the context of the evidence regarding patient response to antidepressant therapy and EBM. Mann suggests that the approach to therapy should include evaluation of the patient response to low-dose pharmacotherapy weekly or twice monthly for the acute treatment phase (6-10 weeks), with gradual dose increases depending on the clinical response and side effects and a minimum of 6 to 8 weeks to determine if antidepressant therapy will be effective. However, 30% to 50% of patients will have substantial residual symptoms after adequate first-line treatment. Third, absence of improvement after 4 weeks of treatment with an adequate dose of a given antidepressant medication predicts an ultimate inadequate response.

The HEDIS measures, like all performance measures, require continuous quality improvement, and some health plans have withdrawn from HEDIS reporting. Kobak et al. found in their review of medical charts that reasons for failure to meet the optimal number of provider contacts in the HEDIS measure could be explained, in part, by the patient restarting a previously prescribed successful antidepressant (16%) or a patient visit with the prescribing provider but mental health was not coded or documented in the case notes (12%). Researchers at the Foundation for Accountability (FAcct) developed alternative quality and performance measures and standards in the mid-1990s to focus more closely on patient outcomes rather than processes. For example, 5-year survival rates were measured for breast cancer patients, and the outcomes from depressed patients included assessment of patient response to survey questions regarding how well they “cope,” socially and emotionally, after treatment. The patient survey data for major depression in FAcct reporting are collected at 2 points, when the patient is diagnosed and 6 months later.
For HEDIS quality measures in asthma management, the emphasis is placed on "the use of appropriate medication for people with asthma." The actual measure is the percentage of patients with a definition of persistent asthma who receive controller medication (methylxanthine, cromolyn sodium, leukotriene modifier, nedocromil or inhaled corticosteroid) when asthma control would be better measured by the incidence of ER visits with a primary diagnosis of asthma as a ratio of total health plan membership in person-years or as a ratio of all asthmatics as defined by International Classification of Diseases, Ninth Revision (ICD-9) codes and asthma medications. As asthma control has many dimensions, which include inhaler technique, adherence to prescribed regimens, patient knowledge of asthma triggers and asthma disease management, and completion of structured asthma education programs for high-risk patients. The prescription of a “controller” medication may or may not be the best asthma care for a particular patient. So, the validity of the HEDIS measure, developed in 2000 for asthma, may not measure what it purports to measure—asthma control. As for other threats to validity, the numerator of the measure (health plan members with one or more controller medications dispensed in the measurement year) does not have the same time frame as the denominator (those persons identified as “persistent” asthmatics in the year before the measurement year). Noteworthy in the HEDIS 2006 Technical Update is the instruction for health plans to “allocate the dispensing events to the appropriate year based on the date the prescription is filled,” presumably because some plans were measuring the date-written field on the pharmacy claim rather than the date dispensed.

Aside from these issues regarding the assessment of the numerator in the quality measure, changes appear to be necessary for measurement of the denominator. Evaluation of information from 132,414 Kaiser Permanente health program patients nationwide who were included in one or more HEDIS persistent asthma study groups between 1999 and 2002 found significant error in the identification of patients with persistent asthma. Evaluation of electronic claims and pharmacy information revealed that 47.9% of these patients identified with persistent asthma actually had evidence of persistent asthma in only 1 of the 4 years of continuous insurance and pharmacy benefit coverage and only 28.2% had at least 3 consecutive years of evidence of persistent asthma. The results of this extensive study suggest that the current 1-year qualification period for identification of persistent asthma is inadequate and results in at least 30% false-positive cases.

HEDIS measures emphasize underuse of health care services and ignore overuse and misuse of services. This emphasis on the underuse of services, when corrected, increases health system costs. Measuring quality is important, but we need to be mindful that (a) measurement of quality should not impede quality improvement, (b) interpretation of quality scores is far from simple or even straightforward, (c) resource dollars spent in amassing data for quality measures necessarily makes fewer resources available for delivering care, and (d) quality performance measures must undergo continuous quality improvement.

Asthma Disease Management—Evidence-Based Medicine Must Be Dynamic

It seems reasonable for physicians and clinical pharmacists to protest, at least quietly, evidence-based medicine (EBM) for its potential to become cookbook medicine. At another level, EBM cannot be cookbook medicine because unlike recipes for cooking, the evidence in EBM is constantly changing. Perhaps, therein lies the critical distinction and the absolute need to view EBM as dynamic and continually changing as new evidence becomes available, is challenged, and survives scrutiny.

In this issue of JMCP, Heaton et al. challenge the value of leukotriene modifiers (LM) in disease management of asthma. Based upon the 3 clinical outcomes of emergency room visits, hospitalizations for asthma, and the use of oral prednisone (“steroid burst”) to indicate exacerbation of asthma, these authors concluded that LM use was not more effective than nonuse. Worse than no improvement in these 3 clinical outcomes, LM users appeared to have more ER visits, a higher rate of hospitalization, and a higher rate of use of oral prednisone bursts. Heaton et al. calculated that LM use added $1.63 per patient per month (PPPM) in costs (in 2002 dollars) for these 3 clinical outcomes compared with LM nonusers diagnosed with asthma.

This is no small matter for payers. The leading LM in the United States is montelukast (Singulair), which had community pharmacy sales of $1.85 billion in 2004, placing it at rank number 14 by expenditure among all brand-name drugs. The manufacturer reported that U.S. sales of montelukast increased by 10% in the third quarter of 2005 compared with the year-earlier period. In the last quarter of 2005, montelukast was the number 6 drug by expenditure for a leading pharmacy benefit manager, accounting for 1.6% of total drug benefit spending among 3,010 distinct brand and generic drugs. Monelukast was used by 50 times more patients than zafirlukast (Accolate), the other LM, and had a discounted allowed charge per day of about $3.00 before copayment. Some of this spending on montelukast is for allergic rhinitis—Lakomski and Chitre found that 25% of LM utilization in 2001-2002 was not for asthma. Even at 75% of current spending on montelukast, the drug ranks in the top 20 drugs in the United States, second only to combination fluticasone-salmeterol (Advair, rank number 6) among the high-expenditure drugs used in treating asthma.

Heaton et al. refer to the role of montelukast in step therapy for asthma as updated by the National Asthma Education and Prevention Program (NAEPP) in 2002. These 2002 asthma treatment guidelines included the recommendation of daily use of low-dose inhaled corticosteroids for mild persistent asthma as well as “low-to-medium-dose inhaled corticosteroids and...
either leukotriene modifier or theophylline” as one “alternative treatment” to the “preferred treatment” with low-to-medium-dose inhaled corticosteroids and long-acting beta2-agonists for moderate persistent asthma.

New evidence in 2005 calls these guidelines for mild persistent asthma into question. Boushey et al. found that the group of patients with mild persistent asthma randomized to no controller (inhaled corticosteroid) therapy did not have significantly poorer lung function and experienced no greater frequency of asthma exacerbation than those who received regular treatment.44 Daily budesonide (inhaled corticosteroid) was superior to intermittent budesonide therapy and to daily zafirlukast (LM) therapy in most clinical measures, including asthma control and symptom-free days in patients with mild persistent asthma, but daily zafirlukast therapy was not superior to intermittent zafirlukast therapy in any outcome. Based on these and other findings, Boushey et al. estimated that patients with mild persistent asthma may require, on average, as little as 1 course of inhaled budesonide every 2 years or oral corticosteroids once every 8 years. This symptom-driven treatment of mild-to-moderate exacerbations is a radical departure from current guidelines for treatment of mild persistent asthma.45 The cost savings from a change in treatment of mild persistent asthma from daily medication use to symptom-driven corticosteroid therapy could be large since up to 75% of asthma is mild disease.46

To put the analysis performed by Heaton et al. into additional perspective, the original drug application for montelukast provides some useful information on the clinical value of the drug. For Chronic Asthma Protocol 049, there was 4.65% improvement in FEV1 (forced expiratory volume in 1 second); 8.73% for montelukast vs. 4.16% for placebo) over 8 weeks of treatment with montelukast in 198 patients versus 133 patients who received placebo.47 A more interesting finding was that the patients who received placebo experienced an average of 25.7% of days with an asthma exacerbation over the 8 weeks versus 20.5% for montelukast (P = 0.049). Headache determined to be drug related occurred more often in the montelukast group, 3.5% vs. 0.7% for placebo.

A meta-analysis of 1 pediatric and 12 adult clinical trials for the primary outcome of the number of exacerbations requiring systemic glucocorticoids found that patients treated with LMs were 60% more likely to require systemic glucocorticoid as a result of exacerbation of asthma symptoms compared with patients on monotherapy with an inhaled corticosteroid.48 LMs were also more likely to be withdrawn as a result of inadequate asthma control (relative risk 2.5). The study concluded that 400 mcg of beclomethasone or 200 mcg of fluticasone is more effective than 10 mg per day of montelukast or 20 mg of zafirlukast twice daily.

Since montelukast is approved by the U.S. Food and Drug Administration for use in allergic rhinitis and asthma, the value of montelukast in a subset of asthma patients with allergic rhinitis is of interest. In a review of the medical literature, The Medical Letter consultants concluded in October 2005 that comparative studies with oral antihistamines and intransal steroids are necessary, particularly since these 2 categories of therapeutic alternatives cost less than montelukast.49 The evidence of the value of montelukast in patients with a history of both allergic rhinitis and asthma is confined to a single randomized, crossover, placebo-controlled study in 52 patients with symptoms provoked by exposure to cats.50

Nathan et al. randomized 863 adult and adolescent patients who received combination fluticasone propionate salmeterol (FSC) to receive either blinded fluticasone propionate aqueous nasal spray (FPANS) 200 mcg per day or montelukast 10 mg per day or placebo.51 Montelukast was found to be inferior to FPANS in control of allergic rhinitis in these patients with persistent asthma treated with FSC, and the addition of either montelukast or FPANS resulted in no additional improvements in overall asthma control compared with FSC alone. These clinical data from the RCT performed by Nathan et al. in a large sample of patients with persistent asthma appear to add support to the challenge to the economic value of montelukast brought by Heaton et al. in this issue of JMCP. The evidence continues to evolve.

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REFERENCES
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