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REFERENCE

Wayne Moran is a St. Paul, Minnesota, software engineer who does commercial photography on the side. Photography is my passion," he says. "As a Minnesota-based photographer and artist, I have been greatly influenced by the Upper Midwest. I focus my skills and energies on landscapes, cityscapes, architecture, fine art, and portrait work." Moran's images successfully communicate his vision and values. His photographs have been used by companies and organizations such as financial services firms, mom-and-pop ice cream shops, and local churches, most notably the Basilica of St. Mary in Minneapolis. Book, magazine, and calendar publishers have also featured Moran's work in their publications. In addition, his photos enhance the décor of many fine homes.

Born in Los Angeles, Moran lived there until he was in the fourth grade. His family then relocated to the town of Sartell in central Minnesota, to live closer to relatives. He was artistic as a child and remembers attending an interesting art class in Los Angeles, but his scientific, mathematical, and logical mind led him away from art for most of his youth. However, Moran didn't shy away from artistic pursuits entirely. "I had a camera in college—I shot photographs for recreation and events," he says. "I was also in choir in college and we had fundraisers to help pay for our trips. I would put together slide shows of choir photos as part of each event. Most of the images were mine."

Moran received a bachelor of arts degree in mathematics from the University of St. Thomas in St. Paul, and another bachelor of arts degree in meteorology from Creighton University in Omaha, Nebraska. He put his camera away after college because he was busy with his career and raising a family. About 6 or 7 years ago, Moran purchased his first digital camera and rediscovered his love for photography. He was greatly influenced by the photos posted on the Flickr.com website. To get back into photography, Moran decided to take traditional art classes to learn the basics, such as lighting, composition, color, and shapes. Next, he enrolled in an online course in photography from the New York Institute of Photography, which taught him a great deal. Moran also took a photo class at Dakota County Technical College in Rosemount, Minnesota, to hone the studio and lighting aspects of his work. Along the way, he was inspired by the photography of local and national photographers—James Neely, Sean Foreman, and Trey Ratcliff are among his favorites. Ratcliff’s StickInCustoms.com blog is the most popular travel photography blog on the Internet.

Moran says, “My best work comes from images first painted in my mind. I mull over a prospective image for weeks or months, seeing it from different angles and perspectives, then I finally decide what to capture. The resulting images deeply touch people’s emotions and evoke powerful memories and dreams.”

AMCP’s 23rd Annual Meeting & Showcase is being held from April 27–29, 2011, in Minneapolis. To coincide with the event, Moran’s Minneapolis Stone Arch Bridge photograph was chosen as AMCP’s April cover image. He used a Canon EOS Digital Rebel XT camera to capture this spectacular view of the Stone Arch Bridge, with the magnificent Minneapolis skyline in the background. “My brother actually commissioned me to shoot that image for him in July 2006,” Moran recalls. “So we went out for an enjoyable dinner at historic St. Anthony Main in Minneapolis. Afterward, we waited for the arrival of the perfect light, often known as ‘the blue hour.’ I took the picture—and the rest, as they say, is history.” He says that his Minneapolis Stone Arch Bridge photo “is a view of an era gone by, mixed with the modern.”

Spanning the Mississippi River, the Stone Arch Bridge was built in 1883 for railroad tycoon James J. Hill’s St. Paul, Minneapolis, and Manitoba Railway (later called the Great Northern Railway). For many years, trains transported wheat from the Red River Valley and Canada to the Minneapolis flour mills. The structure is now used as a pedestrian/bicycle bridge and hosts numerous festivals during the summer months.

Moran is a member of the Professional Photographers of America. Many of his striking photographs can be seen via the Flickr website on his WaynePhotoGuy.com page. There you will also find a link describing Moran’s coffee-table book, Eye of the Beholder: A Visual Journey, a creative assortment of his photos. On his own website, WayneMoran.com, the photographs are arranged by category. Most of the beautiful images on Moran’s site are available for sale in the “Galleries” section. His photos are also sold at many local frame shops and other businesses. A corporate art dealer represents him as well.

Moran is thrilled with the success that he has had thus far as a commercial photographer. He is currently working on an exciting project for a company in downtown Minneapolis. A number of his images are going to be printed on 9-foot-tall panels to create murals in the conference rooms, and various photos in other sizes will be framed and hung throughout the rest of the space.

Sheila Macho
Cover Editor

COVER CREDIT
Wayne Moran, Minneapolis Stone Arch Bridge, digital photograph.
Minneapolis, Minnesota. Copyright © 2006.

SOURCE
Interview with the artist.
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ABSTRACT

BACKGROUND: The Arkansas State Employee Benefits Division (EBD) is a self-insured program comprising public school and other state employees, their spouses, and dependents. Previous research published in JMCP (2006) showed drug cost savings of $2.20 per member per month (PMPM; 37.6%) or annualized savings of $3.4 million associated with a benefit design change and coverage of the proton pump inhibitor (PPI) omeprazole over-the-counter (OTC) beginning in March 2004. On May 1, 2005, brand esomeprazole was excluded from coverage, with current users grandfathered for 4 months until September 2005. Reference pricing for PPIs, including esomeprazole but excluding generic omeprazole, was implemented on September 1, 2005, and the beneficiary cost share for all PPIs except generic omeprazole was determined from comparison of the PPI actual price to the $0.90 omeprazole OTC reference price per unit.

OBJECTIVE: To examine PPI utilization and drug costs before and after (a) excluding esomeprazole from coverage (with grandfathering current users) and (b) implementing a therapeutic maximum allowable cost (TMAC), or reference-pricing benefit design, for the PPI class in a large state employee health plan with fairly stable enrollment of approximately 127,500 members in 2005 through 2008 and approximately 128,000 members in 2009 Q1. METHODS: The pharmacy claims database for the EBD was used to examine utilization and cost data for PPIs in a longitudinal analysis for the 61-month period from March 1, 2004, through March 31, 2009. Pharmacy claims data were compared for the period 14 months prior to esomeprazole exclusion (preperiod), 4 months during the esomeprazole exclusion (postperiod 1), and the ensuing 43 months of PPI reference pricing (postperiod 2). PPI cost and utilization data for the intervention group of approximately 127,500 beneficiaries were compared with a group of 122 self-insured employers with a total of nearly 1 million beneficiaries whose pharmacy benefits did not include reference pricing for PPIs.

RESULTS: Despite 79% of existing esomeprazole users being grandfathered during the 4-month esomeprazole-exclusion period (postperiod 1), the share of omeprazole OTC claims increased from 35.2% to 42.5% (+7.3 percentage points) of all PPI claims, and esomeprazole claims decreased from 16.7% to 12.0% (-4.7 percentage points), with little change in the use of other PPIs. The average allowed charge (price) per day of PPI drug therapy decreased in postperiod 1 by 8.9% from $2.81 to $2.56, while utilization increased by 2.2% from 1.83 days PMPM to 1.87 days PMPM; the net plan cost PMPM decreased by $0.40 PMPM from $3.78 to $3.38 (-10.6%), representing a reduction in spending of $35,664 per month while the average member copayment per claim was essentially unchanged. In the 43 months of reference pricing in postperiod 2, PPI utilization was essentially unchanged at 1.82 days PMPM compared with the preperiod (1.83 days PMPM) and 2.7% lower than the esomeprazole-exclusion period (1.87 days PMPM); however, price (charge per day) decreased by 38.4% during reference pricing to $1.73 from $2.81 in the preperiod and by 32.4% compared with $2.56 in the esomeprazole-exclusion period, despite an increase in the average pharmacy dispensing fee to $5.21 per PPI claim. Net plan cost decreased by $1.87 PMPM (49.5%) to $1.91 PMPM during reference pricing compared with the preperiod ($3.78 PMPM) and by $1.47 PMPM (43.5%) compared with the esomeprazole-exclusion period 1 ($3.38 PMPM). Beneficiary costs (copayment per claim) for PPIs decreased to $1.24 PMPM ($23.27 per claim) compared with the preperiod ($1.37 PMPM, $24.95 per claim) and compared with the esomeprazole-exclusion period 1 ($1.40 PMPM, $25.06 per claim). The reductions in net plan costs represented lower plan spending for the 43 months of reference pricing (postperiod 2) of approximately $9.4 million or an average of approximately $219,500 per month compared with the preperiod or $7.9 million (approximately $183,900 per month) compared with the esomeprazole-exclusion period. Compared with a group of self-insured health plans without pharmacy benefit reference pricing of PPIs, the cost savings over the 43-month period from September 1, 2005, through March 31, 2009, were approximately $7.2 million or $1.31 PMPM.

CONCLUSIONS: For this state employee health plan, the policy change that excluded esomeprazole from coverage but grandfathered current users was associated with a relatively small reduction in PMPM spending on PPIs compared with the subsequent policy change that applied reference pricing to the PPI class based on the price (drug cost plus dispensing fee) for omeprazole OTC. Over 43 months of reference pricing, net plan costs fell dramatically by 49.5% PMPM compared with the preperiod or decreased by 43.5% compared with the esomeprazole-exclusion period. While utilization was essentially unchanged compared with the 18 months before reference pricing, the average pharmacy dispensing fee per PPI claim increased, and beneficiary costs PMPM decreased.

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What is already known about this subject

- A longitudinal analysis of 15 months pre-intervention and 15 months post-intervention for the Arkansas State Employee Benefits Division (EBD) found that the addition of omeprazole OTC to coverage and adjustment of the community pharmacy dispensing fee to account for fewer prescriptions filled (with a 42-day vs. 30-day supply) were associated with a decrease of $4,207,350 in proton pump inhibitor (PPI) drug cost or $3,365,880 over 12 months ($2.20 PMPM).
What is already known about this subject (continued)

- A therapeutic maximum allowable cost (TMAC) intervention in 2006 in 1 small U.S. employer that imposed a defined benefit amount of $0.67 per day ($20 per month) for heartburn drugs including PPIs was associated with an 81% reduction in net health plan cost per day for heartburn drug therapy (from $3.33 to $0.62), 92% reduction in PMPM heartburn drug cost (from $4.59 to $0.39), and 18% reduction in total PMPM drug benefit cost (from $29.30 to $23.91).
- A change in formulary status to tier 3 (nonpreferred) for esomeprazole in the Veterans Affairs formulary and a modest financial incentive of as little as $13 copayment for a 90-day mail-order supply, and $0 copayment at military pharmacies if esomeprazole was obtained via prior authorization (PA), was associated with 15.0% of esomeprazole users switching to other prescription PPIs, 73.3% of esomeprazole users continuing the use of esomeprazole, 0.6% of users switching to a non-PPI prescription, and 11.1% stopping all prescription acid-reducing medications.

What this study adds

- In the pre/post comparison, excluding esomeprazole from coverage was associated with a net plan cost decrease of 7.7% for PPIs (from $465,746 to $430,082 per month) or an average cost savings of $35,664 per month. Although not analyzed specifically, grandfathering exempted 79% of esomeprazole users and appeared to have limited the potential savings from this intervention.
- In the pre/post comparison, reference pricing was associated with an immediate and sustained reduction in the net EBD cost from an average $3.78 PMPM in the 14-month preperiod to $1.91 PMPM during the 43-month postperiod, savings of $1.87 PMPM (49.5%) in the pre/post comparison or drug cost savings of approximately $1.31 PMPM ($7.2 million over 43 months) versus projected costs without reference pricing in a comparison group.
- Compared with a group of health plans that did not implement PPI reference pricing, this health plan experienced a decrease in PMPM cost after subtraction of member cost share that was approximately 50% ($1.67) in the first 4 months but declined over the 43-month follow-up period to about $0.63 PMPM during the first 3 months of 2009.
- The average member cost share per PPI claim was essentially unchanged in the esomeprazole-exclusion period compared with the preperiod ($25.06 vs. $24.95, respectively) and 6.7% less in the 43-month reference-pricing period ($23.27); PPI utilization was 1.83 days PMPM in the preperiod and 1.82 days PMPM in the 43-month reference-pricing period.

Previously, we reported the cost and utilization of proton pump inhibitors (PPIs) associated with the decision by the Arkansas State Employee Benefits Division (EBD; Little Rock) to cover omeprazole over-the-counter (OTC) beginning in March 2004.1,2 Because the PPIs constituted a substantial portion of the pharmacy benefit spending, 12% ($8.9 million) of the total drug budget of $74.6 million in 2003 for approximately 127,500 beneficiaries, the PPI class was targeted for a possible cost savings measure to be implemented if the necessary access to needed therapies could be maintained.1

Based on cost considerations, the Drug Utilization and Evaluation Committee (DUEC) 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 (Prilosec OTC), there was a large cost savings opportunity. Analysis of 15 months of coverage of omeprazole OTC in this drug benefit plan showed $4.2 million in cost savings for the drug plan sponsor or approximately $2.20 PMPM.1

The specific pharmacy benefit design change that produced the PPI cost savings was implemented in March 2004, when coverage was extended for a 42-day supply of omeprazole OTC 20 mg tablets at a $5 copayment and a $13 dispensing fee for pharmacists.1,3 With the enhanced dispensing fee for community pharmacists, the market share moved quickly from prescription PPIs to omeprazole OTC. Over the first year of coverage of omeprazole OTC, its share of total PPI claims rose from 0% to 35% in the first 4 months of 2005, compared with 22% share for generic omeprazole claims. Because brand PPIs still accounted for 43% of PPI claims, there was additional cost savings opportunity if more members switched to either omeprazole OTC or generic omeprazole.

EBD is a self-insured plan that comprises Arkansas state employees and public school employees. In 2005, EBD covered approximately 127,500 beneficiaries of whom approximately 78,000 (61%) were employees, yielding a beneficiary-to-employee ratio of approximately 1.63. In 2007, EBD had an annual drug budget of $98.3 million in pharmacy and third-party administrative costs. EBD employs a pharmacy benefits management (PBM) company to administer the prescription drug benefit, including adjudicating claims, providing drug coverage strategies and consultative support regarding benefit design, reporting, and rebate support. The pharmacy benefit plan has a 3-tier copayment structure with the following copayments for up to a 31-day supply: $10 for generic, $30 for preferred brand, and $60 for nonpreferred brand.

EBD strives to keep pharmacy costs controlled while maintaining access to medications for its membership. To achieve
Five-Year Examination of Utilization and Drug Cost Outcomes Associated with Benefit Design
Changes Including Reference Pricing for Proton Pump Inhibitors in a State Employee Health Plan

The purpose of this study was 2-fold: to examine PPI utilization and drug costs before and after (a) excluding esomeprazole from coverage (with grandfathering current users) and (b) implementing a therapeutic maximum allowable cost (TMAC), or reference-pricing benefit design, for the PPI class in a large state employee health plan of approximately 127,500 members in 2005, which rose slightly to almost 130,000 members in 2008 and the first quarter of 2009.

Description of the Pharmacy Benefit and Interventions
The PPI interventions for EBD considered PPI drug cost in making coverage decisions for PPIs in the pharmacy benefit. The benefit design structure for PPIs at the beginning of the present study remained as it existed at the end of the previous evaluation that included omeprazole OTC coverage with $5 member copayment and $13 pharmacy dispensing fee; generic omeprazole with a $10 copayment; and brand esomeprazole (Nexium), rabeprazole (Aciphex), pantoprazole (Protonix), and lansoprazole (Prevacid) with nonpreferred $50 copay per prescription.1-3 The first intervention for the present study began on May 1, 2005, when brand esomeprazole was excluded from coverage, and current users were grandfathered until September 1, 2005 (Table 1). Drugs excluded from plan coverage were eligible for the PBM contractual discount (AWP minus 13% plus $2.50 dispensing fee), and the member was responsible for 100% of the allowed charge for esomeprazole unless grandfathered due to prior use.

The second intervention began on September 1, 2005, when reference pricing was adopted for the entire PPI class, including coverage for esomeprazole. The reference-pricing strategy this goal, the DUEC meets quarterly to discuss and vote on various clinical and formulary issues. The DUEC decisions are then confirmed, changed, or denied by the State and Public School Life and Health Insurance Board. Any approved changes generally take effect at the beginning of the following calendar quarter, depending on the need for member-specific communication. The DUEC is composed of 3 pharmacists, 4 physicians, 1 registered nurse, 1 state employee, and 1 public school employee.

The purpose of this study was 2-fold: to examine PPI utilization and drug costs before and after (a) excluding esomeprazole from coverage (with grandfathering current users) and (b) implementing a therapeutic maximum allowable cost (TMAC), or reference-pricing benefit design, for the PPI class in a large state employee health plan of approximately 127,500 members in 2005, which rose slightly to almost 130,000 members in 2008 and the first quarter of 2009.

Description of the Pharmacy Benefit and Interventions
The PPI interventions for EBD began with a literature search that revealed 3 systematic reviews that found the 5 available PPIs to be similar in tolerability, safety, and efficacy when dosed equipotently for use in the treatment of gastroesophageal reflux disease (GERD), the treatment and prevention of peptic ulcer disease, and for eradicating Helicobacter pylori infection.4-7 The literature review showed that the PPIs are a particularly well-tolerated class of drugs. Using this evidence, the DUEC concluded that all PPIs were therapeutically equivalent in efficacy and safety. From an evidence-based perspective, any PPI would be clinically acceptable as the preferred drug. Thus, the EBD considered PPI drug cost in making coverage decisions for PPIs in the pharmacy benefit.

The benefit design structure for PPIs at the beginning of the present study remained as it existed at the end of the previous evaluation that included omeprazole OTC coverage with $5 member copayment and $13 pharmacy dispensing fee; generic omeprazole with a $10 copayment; and brand esomeprazole (Nexium), rabeprazole (Aciphex), pantoprazole (Protonix), and lansoprazole (Prevacid) with nonpreferred $50 copay per prescription.1-3 The first intervention for the present study began on May 1, 2005, when brand esomeprazole was excluded from coverage, and current users were grandfathered until September 1, 2005 (Table 1). Drugs excluded from plan coverage were eligible for the PBM contractual discount (AWP minus 13% plus $2.50 dispensing fee), and the member was responsible for 100% of the allowed charge for esomeprazole unless grandfathered due to prior use.

The second intervention began on September 1, 2005, when reference pricing was adopted for the entire PPI class, including coverage for esomeprazole. The reference-pricing strategy
Five-Year Examination of Utilization and Drug Cost Outcomes Associated with Benefit Design
Changes Including Reference Pricing for Proton Pump Inhibitors in a State Employee Health Plan

### TABLE 2
Summary of Cost and Utilization of PPI Drugs Before and After Implementation of Reference Pricing

<table>
<thead>
<tr>
<th>Evaluated Monthsa</th>
<th>Member Months</th>
<th>Claims</th>
<th>Days Supply</th>
<th>Days Per Claim</th>
<th>Ingredient Cost ($)b</th>
<th>Dispensing Fee ($)c</th>
<th>Allowed Charge ($)d</th>
<th>Copayment ($)</th>
<th>Net EBD Cost ($)e</th>
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<tbody>
<tr>
<td><strong>Preperiod—coverage of omeprazole OTC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
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<td>8,457,304</td>
<td>432,373</td>
<td>8,889,677</td>
<td>2,374,730</td>
<td>6,520,449</td>
</tr>
<tr>
<td>Average per month</td>
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<td>6,918</td>
<td>231,824</td>
<td>33.51</td>
<td>604,093</td>
<td>30,884</td>
<td>634,977</td>
<td>169,624</td>
<td>465,746</td>
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<td><strong>Postperiod 1—exclusion of esomeprazole from coverage</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Totals</td>
<td>508,565</td>
<td>28,288</td>
<td>951,665</td>
<td>33.64</td>
<td>2,328,213</td>
<td>100,723</td>
<td>2,428,936</td>
<td>708,608</td>
<td>1,720,328</td>
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<tr>
<td>Average per month</td>
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<td>7,072</td>
<td>237,916</td>
<td>33.64</td>
<td>582,053</td>
<td>25,181</td>
<td>607,234</td>
<td>177,152</td>
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<tr>
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<td>154</td>
<td>6,093</td>
<td>0.13</td>
<td>-22,040</td>
<td>-5,703</td>
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<td>-35,664</td>
</tr>
<tr>
<td>% change</td>
<td>-0.2%</td>
<td>2.2%</td>
<td>2.6%</td>
<td>0.4%</td>
<td>-3.6%</td>
<td>-18.5%</td>
<td>-4.4%</td>
<td>4.44%</td>
<td>-7.7%</td>
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<tr>
<td><strong>Postperiod 2—reference pricing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>5,489,404</td>
<td>293,536</td>
<td>10,028,631</td>
<td>34.16</td>
<td>15,813,967</td>
<td>1,530,515</td>
<td>17,344,482</td>
<td>6,757,383</td>
<td>10,587,099</td>
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<tr>
<td>Average per month</td>
<td>127,661</td>
<td>6,826</td>
<td>233,224</td>
<td>34.16</td>
<td>367,767</td>
<td>35,593</td>
<td>403,360</td>
<td>157,148</td>
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<tr>
<td>Change from preperiod</td>
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<td>-1,400</td>
<td>0.5</td>
<td>-237,326</td>
<td>4,710</td>
<td>-231,617</td>
<td>-12,475</td>
<td>-219,534</td>
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<tr>
<td>% change from preperiod</td>
<td>-0.2%</td>
<td>-2.3%</td>
<td>-0.6%</td>
<td>1.9%</td>
<td>-39.1%</td>
<td>15.3%</td>
<td>-36.5%</td>
<td>-7.4%</td>
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</tr>
<tr>
<td>Change from postperiod 1</td>
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<td>-246</td>
<td>-6,093</td>
<td>0.3</td>
<td>-214,287</td>
<td>10,413</td>
<td>-203,874</td>
<td>-20,004</td>
<td>-183,870</td>
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<tr>
<td>% change from postperiod 1</td>
<td>-0.4%</td>
<td>-3.5%</td>
<td>-2.0%</td>
<td>1.6%</td>
<td>-36.8%</td>
<td>41.4%</td>
<td>-33.6%</td>
<td>-11.3%</td>
<td>-42.8%</td>
</tr>
</tbody>
</table>

aBecause of the timing of interventions, not all time periods are the same.
bAllowed drug ingredient cost reimbursement to pharmacies is average wholesale price minus 13%.
cDispensing fee may be greater than $2.50 because of generic incentive programs that pay a higher dispensing fee. The dispensing fee for omeprazole OTC is $13.00.
dAllowed charge is the sum of the dispensing fee plus the drug ingredient cost.
eNet EBD costs are slightly higher than the allowed charge minus copayment because the net cost includes the administrative fee paid to the pharmacy benefits manager for processing the pharmacy claims.

Generic prescription omeprazole was not reference priced and remained available at the $10 generic-tier copayment throughout the study period (Table 1). Generic omeprazole was excluded from reference pricing because the plan wanted to ensure members would have access to a less costly PPI, and there was a shortage of omeprazole OTC during 2004. Later, generic omeprazole was excluded from reference pricing because the market price for generic omeprazole was expected to fall substantially. However, by 2007 the price per unit for generic omeprazole was not considerably different from the allowed cost per unit established by the reference price.

The pharmacy benefit design for all covered drugs included copayment tiers $10/$25/$50 per prescription. PPIs were the only therapeutic category for which there was a $5 copayment option (for omeprazole OTC). The $5 PPI option began in March 2004 and remained unchanged throughout the 61-month evaluation period. Beginning in 2007 Q1, copayments for all non-PPI drug categories increased to $10/$30/$60 and remained constant through the end of the evaluation period (March 2009). Members receiving omeprazole OTC paid a $5 copayment. Although the increase in copayments for tier 2 and tier 3 non-PPI drugs may have affected some beneficiaries’ abilities to afford other medications, the effect on the ability to afford PPIs was not explored.

The EBD health plan offers a mail-order pharmacy option, but it is used by a small proportion (approximately 0.1%) of the members. Thirty-day and 90-day fills are available to members by mail order or a community pharmacy.

## Methods
PPI claims were extracted from the EBD pharmacy claims database using Medi-Span (Wolters Kluwer Health, Indianapolis, IN) Generic Product Identifier (GPI) codes beginning with 4,927 for claims with dates of service from March 1, 2004, through March 31, 2009. This time period encompasses the 14 months prior to implementation of the 2 policy changes (preperiod), 4 months of the esomeprazole exclusion from coverage intervention (postperiod 1), and 43 months following the reference-pricing intervention (postperiod 2). Member-months and the PPI cost and utilization data were aggregated by calendar periods to permit pre/post analyses of changes in PPI market.
Five-Year Examination of Utilization and Drug Cost Outcomes Associated with Benefit Design
Changes Including Reference Pricing for Proton Pump Inhibitors in a State Employee Health Plan

Table 3
Derived Measures for Cost and Utilization of PPI Drugs Before and After Implementation of Reference Pricing

<table>
<thead>
<tr>
<th>Derived Measures for Evaluation Periods</th>
<th>Claims PMPM</th>
<th>Days PMPM</th>
<th>Allowed Charge PMPM ($)</th>
<th>Allowed Charge Per Claim ($)</th>
<th>Allowed Charge Per Day ($)</th>
<th>Copayment Per Claim ($)</th>
<th>Net Per Claim ($)</th>
<th>Net Per Day ($)</th>
<th>Net PMPM ($)</th>
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</thead>
<tbody>
<tr>
<td>Preperiod—coverage of omeprazole OTCc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mar–May 04</td>
<td>0.053</td>
<td>1.82</td>
<td>4.23</td>
<td>80.25</td>
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<td>21.77</td>
<td>58.59</td>
<td>1.69</td>
<td>3.09</td>
</tr>
<tr>
<td>Jun–Aug 04</td>
<td>0.052</td>
<td>1.77</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>
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<td>Sept–Nov 04</td>
<td>0.055</td>
<td>1.81</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>3.91</td>
</tr>
<tr>
<td>Dec 04–Feb 05</td>
<td>0.057</td>
<td>1.88</td>
<td>5.57</td>
<td>97.01</td>
<td>2.96</td>
<td>25.82</td>
<td>71.22</td>
<td>2.17</td>
<td>4.09</td>
</tr>
<tr>
<td>Mar–Apr 05</td>
<td>0.056</td>
<td>1.87</td>
<td>5.45</td>
<td>97.30</td>
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<td>25.64</td>
<td>71.65</td>
<td>2.14</td>
<td>4.01</td>
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<tr>
<td>Preperiod average</td>
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<td>1.83</td>
<td>5.15</td>
<td>93.71</td>
<td>2.81</td>
<td>24.95</td>
<td>67.77</td>
<td>2.06</td>
<td>3.78</td>
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<td>Postperiod 1—exclusion of esomeprazole from coverage</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>May–Jun 05</td>
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<td>1.84</td>
<td>4.82</td>
<td>87.76</td>
<td>2.62</td>
<td>25.66</td>
<td>62.10</td>
<td>1.86</td>
<td>3.41</td>
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<td>Jul–Aug 05</td>
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<td>4.73</td>
<td>84.00</td>
<td>2.48</td>
<td>24.45</td>
<td>59.55</td>
<td>1.76</td>
<td>3.36</td>
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<td>Postperiod 1 average</td>
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<td>1.87</td>
<td>4.78</td>
<td>85.90</td>
<td>2.56</td>
<td>25.06</td>
<td>60.84</td>
<td>1.81</td>
<td>3.38</td>
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<td>-7.80</td>
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<td>-12.3%</td>
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<td>Postperiod 2—reference pricing</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sep–Dec 05</td>
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<td>2.92</td>
<td>56.52</td>
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<td>24.74</td>
<td>32.40</td>
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<td>24.64</td>
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<td>1.67</td>
<td>23.16</td>
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<td>Jul–Sep 06</td>
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<td>1.74</td>
<td>2.92</td>
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<td>22.16</td>
<td>36.85</td>
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<td>3.50</td>
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<td>22.43</td>
<td>37.38</td>
<td>1.09</td>
<td>2.19</td>
</tr>
<tr>
<td>Postperiod 2 average</td>
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<td>59.02</td>
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<td>-0.009</td>
<td>-2.00</td>
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<td>-1.08</td>
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<td>% change from preperiod</td>
<td>-3.6%</td>
<td>-0.5%</td>
<td>-38.8%</td>
<td>-37.0%</td>
<td>-38.4%</td>
<td>-6.7%</td>
<td>-47.2%</td>
<td>-49.0%</td>
<td>-49.5%</td>
</tr>
<tr>
<td>Change from postperiod 1</td>
<td>-0.002</td>
<td>-0.049</td>
<td>-1.62</td>
<td>-26.88</td>
<td>-0.83</td>
<td>-1.80</td>
<td>-25.08</td>
<td>-0.76</td>
<td>-1.47</td>
</tr>
<tr>
<td>% change from postperiod 1</td>
<td>-4.0%</td>
<td>-2.7%</td>
<td>-34.0%</td>
<td>-31.3%</td>
<td>-32.4%</td>
<td>-7.2%</td>
<td>-41.2%</td>
<td>-42.1%</td>
<td>-43.5%</td>
</tr>
</tbody>
</table>

aBecause of the timing of the interventions, the time periods do not all have the same number of months.

bAverages were used to report the numbers and may not be exactly equal to the results from calculation using the raw numbers.

cCoverage of omeprazole OTC was continuous throughout the study period, through March 31, 2009.

OTC = over-the-counter; PMPM = per member per month; PPI = proton pump inhibitor.

share, beneficiary cost (copayment), ingredient cost, dispensing fees, allowed charge (ingredient cost plus dispensing fee), and net plan (EBD) cost after subtraction of beneficiary cost share. Derived measures included utilization and cost per claim, per day of therapy, and per member per month (PMPM).

Due to the differences in the number of months in pre/post periods, monthly averages were also calculated for the 3 principal time periods (14 months for the preperiod, 4 months for postperiod 1, and 43 months for postperiod 2). The PPI cost and utilization data were also aggregated by calendar quarter to permit long-term trend analysis. A comparison group was created by the EBD’s PBM from 122 self-insured employer health plans and 50 union trust funds. These individual health plans had the ability to implement plan-specific pharmacy benefit designs but none implemented PPI reference pricing during the study period. The health plans in this comparison group were managed by the PBM for the entire study period, and the average eligible membership was 984,731.

Results
The member-month counts and PPI utilization and cost data are aggregated by calendar period in Table 2, and the derived measures per claim, per day, and PMPM are shown in Table 3. Cost and utilization trend data by calendar quarter are shown.
was $24.95 (or $1.33 PMPM, data not shown). Omeprazole OTC accounted for 35.2% of the PPI pharmacy claims in the 4 months immediately before the first intervention (January-April 2005; Figure 3).

The 14-Month Preperiod
During the 14 months of the preperiod, the average member enrollment was 127,451 per month (Table 2). The total number of prescriptions was 96,851, or an average of 6,918 per month. The average net cost per claim was $67.77 (Table 3). The average allowed charge per day was $2.81, and the net plan (EBD) cost per day was $2.06. The net plan (EBD) cost PMPM was $3.78. Utilization, measured by the number of claims PMPM, was 0.055 or 1.83 days PMPM. The average copayment per claim

in figures 1 and 2. PPI market shares by prescription claims are shown in Figure 3 for time periods associated with the PPI benefit design changes. Cost and utilization data for EBD versus the comparison group are shown in tables 4 and 5 and in Figure 4. All cost data are unadjusted for inflation.

The 4-Month Postperiod 1—Esomeprazole Exclusion
Of the total of 1,448 members who received esomeprazole during the exclusion period, 1,145 (79%) were continuing users and were grandfathered; 303 (21%) were not grandfathered and paid 100% of the cost. During the 4-month esomeprazole-exclusion period (postperiod 1), the omeprazole OTC market share as measured by the number of claims increased from 35.2% to 42.5% (+7.3 percentage points; Figure 3). Esomeprazole market share in claims decreased from 16.7% to 12.0% (-4.7 percentage points) with little change in the other

---

*The downward trend that started prior to 2004 Q1 included data from implementation of the $5 omeprazole OTC when the 47% of the PPI claim share shifted to omeprazole OTC.

*Allowed charge is the sum of the dispensing fee plus the ingredient cost.

*Net EBD costs are slightly higher than the allowed charge minus copayment because the net cost includes the administrative fee paid to the pharmacy benefits manager for processing the pharmacy claims.

EBD = Arkansas Employee Benefits Division; OTC = over-the-counter; PPI = proton pump inhibitor; Q = quarter.
and Figure 2). Assessed by the less precise measure of claims in August 2005 before reference pricing began, PPI utilization was 5.80 claims per 100 members per month (Figure 2 inset shows monthly utilization). After 2 months of reference pricing, PPI utilization fell to the low point of 4.96 claims per 100 members per month. However, by December 31, 2005, utilization rebounded and gradually increased so that by the end of the evaluation period in 2009 Q1 (Figure 2), utilization had increased to 5.86 claims per 100 members per month.

Compared with the preperiod average of 0.055 claims PMPM, utilization decreased 3.6% to an average of 0.053 claims PMPM for the entire postperiod 2. By the more precise measure of days PMPM, PPI utilization was unchanged at an average 1.82 days PMPM in postperiod 2 during reference pricing, compared with 1.83 days PMPM in the preperiod (Table 3). The average copayment per claim decreased by 6.7% from $24.95 in the preperiod to $23.27 during the 43 months of reference pricing.

During the first 4 months of reference pricing, omeprazole OTC accounted for 77.1% of all PPI pharmacy claims, up from...
42.5% in the preceding 4 months during the esomeprazole-exclusion period (Figure 3). The generic omeprazole market share in claims decreased from 18.5% to 3.5% over that time. Esomeprazole accounted for 16.7% of claims in the 14 months prior to its exclusion period, 12.0% of claims during the exclusion period, 6.4% and 5.4% of PPI claims in the first 4 months and last 3 months of reference pricing, respectively. Most of the other PPIs accounted for lower market share during reference pricing compared with postperiod 1. At the end of the evaluation period in 2009 Q1, omeprazole OTC market share had decreased to 53.7% and generic omeprazole market share had increased to 32.1%, for a combined 85.8% share of all PPI claims. The average enrollment was 127,661 during 43 months of reference pricing, a slight increase of 0.2% compared with the preperiod (Table 2). The average number of PPI claims decreased by 1.3% during reference pricing compared with the preperiod.
Five-Year Examination of Utilization and Drug Cost Outcomes Associated with Benefit Design Changes Including Reference Pricing for Proton Pump Inhibitors in a State Employee Health Plan

<table>
<thead>
<tr>
<th>Table 5</th>
<th>PPI Cost Savings Estimates Based on PMPM Net Cost for EBD and Comparison Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Period</td>
<td>EBD Member Months</td>
</tr>
<tr>
<td>Jan-Apr 2005</td>
<td>513,826</td>
</tr>
<tr>
<td>May-Aug 2005</td>
<td>508,565</td>
</tr>
<tr>
<td>Sept-Dec 2005</td>
<td>501,529</td>
</tr>
<tr>
<td>2006</td>
<td>1,514,661</td>
</tr>
<tr>
<td>2007</td>
<td>1,542,348</td>
</tr>
<tr>
<td>2008</td>
<td>1,545,183</td>
</tr>
<tr>
<td>2009 Q1</td>
<td>385,683</td>
</tr>
<tr>
<td>Total</td>
<td>5,489,404</td>
</tr>
</tbody>
</table>

with the preperiod, but utilization adjusted for enrollment was unchanged at 1.82 days PMPM compared with 1.83 days PMPM during the 14-month preperiod (Table 3). The net cost per claim decreased by $32.01 (47.2%) from an average of $67.77 in the preperiod to $35.76 in postperiod 2.

Price, as measured by the average allowed charge (drug cost plus pharmacy dispensing fee) per PPI claim, dropped by 37.0% ($34.69), from an average $93.71 during the preperiod to $59.02 in the 43-month reference-pricing period. Adjusted for days supply per claim, the price per PPI day of therapy dropped accordingly by 38.4% ($1.08), from $2.81 in the preperiod to $1.73 in 43 months of reference pricing. After considering the average decrease of $1.68 per PPI claim in member cost share (copayment), the net plan cost per day of PPI drug therapy dropped by $1.01 (49.0%), from $2.06 to $1.05 during 43 months of reference pricing. Adjusted for membership, the net plan PMPM decreased by $1.87 (49.5%) from $3.78 in the 14-month preperiod to $1.91 PMPM during 43 months of reference pricing (Table 3). The reductions in PMPM costs represented lower plan spending for the 43 months of reference pricing of approximately $9.4 million or an average of $219,534 per month compared with the preperiod, or $7.9 million ($183,870 per month) compared with theesomeprazole-exclusion period (preperiod 1).

Comparison Group

The key measures of PMPM cost, average charge per claim, utilization rate, and cost share were compared with comparison data obtained from the same PBM in an attempt to better isolate the effects on PPI cost and utilization of the 2 plan design changes. The comparison data were composed of a mix of 122 self-insured employer groups and 50 union trust funds that used the PBM during the entire study period. Although these 122 pharmacy benefit plans had the flexibility to implement pharmacy benefit design changes, none adopted reference pricing of PPIs during the period of the present study. Specific information was unavailable regarding the mail-order options in the 122 plans in the comparison group, but the cost and utilization data suggest common use of mail service and/or quantities greater than 30-day supply for PPI claims (Table 4). Days supply was not provided for the comparison group, preventing calculation of the average days supply per PPI claim to contrast with the approximate average 34 days supply for the EBD group (Table 2). However, the data in Table 4 show an average allowed charge per claim for the comparison group that was nearly twice that for the EBD group in calendar year 2005, and utilization in PPI claims per 100 members per month was about one-half that of the EBD group. The combination of utilization and price (i.e., allowed charge per claim) was $288.37 per 100 member-months for EBD in calendar year 2006 versus $396.23 for the comparison group (Table 4), but the gap narrowed to only an approximate 8% advantage for EBD in calendar year 2008 ($337.16 vs. $365.71).

EBD Versus Comparison Group

Net plan cost was nearly identical for EBD ($3.38) and the comparison group during the esomeprazole-exclusion period, but the EBD costs for the calendar year were composed of $3.93 PMPM during the first 4 months of 2005, $3.38 during 4 months of esomeprazole exclusion, and $1.66 during...
reference pricing in the last 4 months of the year (Table 5). The cost difference between the 2 groups was large during the first full year of reference pricing; $1.74 PMPM in the EBD group versus $3.39 in the comparison group, a PMPM cost ratio of 1.95 with estimated cost savings of approximately $2.5 million in calendar year 2006.

Using this method of comparing net plan cost PMPM for EBD and the comparison group, the estimated cost savings declined to an estimated $2.0 million in calendar year 2007, $1.6 million in calendar year 2008, and approximately $245,000 in 2009 Q1 (Table 5). Total estimated PPI drug cost savings for EBD were $7,205,031 over the 43 months of reference pricing from September 1, 2005, through March 31, 2009, or an average $1.31 PMPM.

Discussion

Many different strategies exist to control costs of pharmacy benefits. An evaluation of a small U.S. employer described a 92% reduction in PMPM cost for heartburn drugs when a TMAC strategy was applied to all agents used to treat heartburn.8 Although cost reduction for the TMAC intervention was dramatic, a drop in utilization of more than 50% factored significantly in the cost reduction for the plan sponsor. In another study, a Canadian TMAC intervention for PPIs was associated with an 11.7% reduction in average cost per day and an 11.9% decrease in utilization for PPI users in an employer-based plan, but this intervention did not include an OTC product.9 Both of these interventions were associated with reduced plan costs, but the evaluations showed decreases in utilization by the members or increased member cost share.

The present study of this large state-employee health plan describes the relatively unsuccessful attempt at cost savings with the exclusion of a single product, esomeprazole, followed by successful reference pricing of the entire class. The reference-pricing strategy was associated with no reduction in PPI utilization, a small but favorable 6.7% reduction in the average member copayment per PPI claim, and a large effect on the average PPI price associated with an increase in the share of PPIs attributable to generic omeprazole and omeprazole OTC from approximately 61% in the 4 months immediately preceding reference pricing (i.e., the esomeprazole-exclusion period) to 86% in 2009 Q1. In the pre/post comparison, net plan cost savings PMPM were approximately 50% for reference pricing compared with the 14-month period before the benefit design changes or 44% for comparison of 43 months of reference pricing versus the 4-month period of esomeprazole exclusion that immediately preceded reference pricing.

Utilization, as measured by claims PMPM, decreased to a low point of 0.047 in 2006 Q1 but rebounded quickly and steadily increased to 0.059 claims PMPM in 2009 Q1, which exceeded the utilization of 0.055 claims PMPM in the 14-month baseline period. The initial decrease was not unexpected because some member disruption was anticipated with the 2 benefit design changes as members transitioned to alternate therapies or forewent filling a prescription in anticipation of increased out-of-pocket expense for high-cost brand PPIs. However, overall PPI utilization was not adversely affected by reference pricing. Our finding of no effect of reference pricing on PPI utilization may contrast with the TMAC studies because our follow-up period was much longer.8,9

Redistribution of plan cost onto members via higher copayments was avoided in this intervention as evidenced by a 6.7% decrease in average copayment per claim from $24.95 for the preperiod to $23.27 during 43 months of reference pricing. The average copayment per claim was essentially unchanged during the esomeprazole-exclusion period compared with the preperiod and decreased by approximately 7% during reference pricing compared with the 4-month period of esomeprazole exclusion. Beginning January 1, 2007, the EBD plan increased copayments from $5/$10/$25/$50 to $5/$10/$30/$60 per prescription; for omeprazole OTC; and for tier 1, 2, and 3 drugs, respectively. The reference-pricing strategy effectively capped what the plan would pay for any PPI prescription with the exception of generic omeprazole and was not based on the copayment tier placement. The plan's increase in copayments for all nonreference-priced drugs in tiers 2 or 3 did not directly affect costs for this class of drugs because the copayment for omeprazole OTC and generic omeprazole remained the same; members who received omeprazole OTC or generic omeprazole continued to pay $5 or $10 copayments, respectively. Members who received any other PPI continued to pay a copayment calculated by the difference in the price of the PPI compared with the reference price as measured by the price per unit instead of a dollar copayment. It is unknown to what degree the increase in the dollar copayments for tier 2 and tier 3 drugs affected the utilization of PPIs, but overall utilization of PPIs did not change over the 61 months in the present study, and average member cost share as a percentage of the allowed charge per claim declined slightly in 2007 through 2009 Q1 compared with 2006.

The short-lived esomeprazole-exclusion period (postperiod 1) was associated with a small change in the combined omeprazole OTC and generic omeprazole share from approximately 57% in the preceding 14-month period to approximately 61%. Although the precise effect of grandfathering current esomeprazole users could not be determined, a total of 1,448 utilizing members continued esomeprazole, 1,145 (79%) were grandfathered, and 303 (21%) were not grandfathered and paid 100% of the cost. Other branded PPI market shares remained essentially unchanged during esomeprazole exclusion. In the pre/post comparison, net plan costs decreased by –10.6% from $3.78 PMPM to $3.38 PMPM, and the allowed charge decreased by –7.3% from $5.15 PMPM to $4.78 PMPM.

Reference pricing, by contrast, was associated with a quick
The combined market share of OTC and generic omeprazole of 86% of all PPI claims was associated with an average charge of $3.50 PMPM in 2009 Q1. Directly comparable national data are not available, but one source reported PPI spending of $45.76 per member per year (PMPY) in 2009 or $3.81 PMPM including a 40% PPI market share. How these national data compare with EBD net plan cost of $2.19 PMPM in 2009 Q1 is not known. PPI net price and net cost per day are unfortunately not available from national data sources. The ratios of generic omeprazole and omeprazole OTC in the EBD plan in the most recent period (2009 Q1) were 32.1% and 53.7%, respectively. Some of the generic omeprazole utilization with a $10 copayment per claim versus $5 copayment for omeprazole OTC may be explained by the small difference in the copayment amounts because generic omeprazole was not subject to reference pricing. Some of generic omeprazole utilization might also be explained by some patients using a higher dose of 1 generic omeprazole 40 mg tablet rather than two 20 mg tablets of omeprazole OTC. A small amount of generic omeprazole versus omeprazole OTC use might be explained by new members or new PPI users who may not be fully aware of the benefit design features and therapeutic alternatives. The influence of patient or prescriber perception of lower efficacy with OTC products is also unknown.

Savings in this pharmacy benefit plan could have been larger if generic omeprazole had been subject to reference pricing (Figure 5). In the first 4 months of reference pricing, generic omeprazole accounted for 3.5% of all PPI claims, but the proportion increased to 32.1% in the last 3 months of the

![Figure 5](https://example.com/figure5.png)

*The average EBD (plan) paid cost is calculated from allowed charge (ingredient cost plus dispensing fee) minus member copayment.

EBD = Arkansas Employee Benefits Division; OTC = over-the-counter; Q = quarter.

and dramatic change in PPI market shares (Figure 3). Upon the implementation of reference pricing, all brand products were limited to the maximum plan paid price per unit of $0.90. During the first 4 months of reference pricing, the omeprazole OTC market share increased from 42.5% to 77.1%, and the combined share of omeprazole OTC and generic omeprazole was over 80%. In the pre/post comparison, net plan costs decreased by almost 50% during 43 months of reference pricing, associated with an increase in the proportion of generic omeprazole and omeprazole OTC to approximately 86% of all PPI claims.

![Figure 6](https://example.com/figure6.png)

*Market share represents the percentage of claims within the PPI class.

OTC = over-the-counter; PPI = proton pump inhibitor; Q = quarter; Rx = pharmacy claim.
study period in 2009 Q1 (Figure 6). By 2009 Q1, the unit cost of omeprazole OTC averaged $0.68 while generic prescription omeprazole had edged back up to an average cost of $0.85 per unit. Excluding generic omeprazole from reference pricing was important during 2005 when there were shortages of omeprazole OTC, but this decision might have been revisited in subsequent periods when the supply of omeprazole OTC stabilized and the acquisition price of generic omeprazole changed. Generic pantoprazole also became available during the study period, and because its cost exceeded the PPI reference price, the cost was capped by the reference price. Cost savings from new generic PPIs are automatic because all PPIs are subject to the reference price. Accordingly, the initially higher costs of single-source generic products are also not paid by the plan sponsor because all products are capped at the reference price.

Limitations
This study assessed drug cost and utilization outcomes and did not consider other clinical or service outcomes. Second, the study did not account for administrative costs associated with implementing the policy, although the increase in dispensing fees to $13 per omeprazole OTC claim for pharmacy dispensing costs was included in the evaluation. Third, the absence of actual claims data for the comparison group precluded a more definitive difference-in-difference analysis. We also could not determine the mix of benefit designs in the comparison group other than the absence of reference pricing for PPIs, and we were not able to compare the 2 groups by demographic characteristics.

Conclusions
Whereas previous studies of managed care interventions have achieved savings by excluding coverage of nonpreferred PPIs or applied a type of reference pricing to PPIs (e.g., TMAC), the reported savings were associated with increased member cost share and reduction in PPI utilization. The present study shows that PPI drug cost savings for the plan sponsor were attained with rapid and sustained reduction in plan cost as well as reduction in the average price per day of PPI therapy, both with negligible effects on utilization and member cost share. The present study found reductions in PMPM costs representing reduced plan spending of approximately $9.4 million over 43 months of reference pricing compared with the preperiod. When compared with a group of health plans not utilizing PPI reference pricing, the net plan (EBD) estimated PPI cost savings were $7.2 million over 43 months or an average of $1.31 PMPM. These savings were associated with essentially unchanged PPI utilization in days of therapy PMPM, a 6.7% reduction in member copayment per PPI claim, and an increase in the average pharmacy dispensing fee per PPI claim. Cost savings may have been larger if the exclusion of generic omeprazole from reference pricing had been rescinded and the reference price per unit had been reset to adjust for changes in the PPI market over time.

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Johnson and Neill designed the study, collected and interpreted the data, and wrote the manuscript, with the assistance of Davis. Johnson revised the manuscript with the assistance of Neill and Davis.

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REFERENCES
Five-Year Examination of Utilization and Drug Cost Outcomes Associated with Benefit Design Changes Including Reference Pricing for Proton Pump Inhibitors in a State Employee Health Plan


Antiretroviral Therapy Adherence, Medication Use, and Health Care Costs During 3 Years of a Community Pharmacy Medication Therapy Management Program for Medi-Cal Beneficiaries with HIV/AIDS

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

ABSTRACT
BACKGROUND: The types of pharmacist-provided medication therapy management (MTM) services provided to patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and the effects of MTM on medication adherence and patient outcomes have only recently begun to be studied. Although available studies suggest that patients receiving MTM services have better antiretroviral therapy (ART) adherence and outcomes, only 1 study has examined a large group of patients with HIV/AIDS, and none has examined adherence or outcomes for more than 1 year. A pilot program conducted by the California Department of Health Care Services (DHCS) and Medi-Cal (California’s Medicaid program) provided an opportunity to examine ART adherence and outcomes in a large patient population receiving MTM services in community pharmacies over 3 years.

OBJECTIVES: To examine an HIV/AIDS pharmacy MTM compensation pilot program over a 3-year period (2005–2007) in a sample of Medi-Cal beneficiaries by describing the associations between use of pilot pharmacies and (a) adherence to ART regimens; (b) medication utilization, including number and type of ART medication regimens and use of contraindicated ART regimens; (c) occurrence of opportunistic infections; and (d) all-cause pharmacy and medical costs.

METHODS: This was a cohort study examining Medi-Cal pharmacy and medical claims data (2005–2007) for patients with HIV/AIDS who were served by pilot pharmacies versus other (nonpilot) pharmacies. The study groups, pilot and nonpilot pharmacy patients with HIV/AIDS, consisted of Medi-Cal beneficiaries aged 18 years or older as of January 1, 2005, who were continuously enrolled from January 1, 2004, through December 31, 2007, and who received both a diagnosis of HIV/AIDS and at least 1 ART pharmacy claim during both the index period (2004) and the study period (January 1, 2005, through December 31, 2007). Pilot pharmacy patients were identified as having filled 50% or more of their ART prescriptions each year at 1 of the 10 pilot pharmacies. Patients for whom comprehensive medication data were not available, including those enrolled in managed care plans and/or Medicare, were excluded. Adherence was defined as a medication possession ratio (MPR) of 80%-120% and excess medication fills as MPR greater than 120%. Logistic regression was used to investigate the factors associated with adherence. Comparisons were made between groups using bivariate statistics and t-tests for continuous variables. For comparisons of costs, generalized linear models were used including predictor variables for age, gender, and race/ethnicity.

RESULTS: The study sample consisted of 2,234 patients meeting the study inclusion criteria. The proportion of study patients receiving the majority of their prescription medications (ART plus non-ART) at pilot pharmacies was 19.7% in 2005 and increased to 27.6% in 2006 and 28.1% in 2007. The demographic profile of pilot pharmacy patients was similar to that of patients receiving medications at nonpilot pharmacies, except that pilot pharmacies had a higher proportion of Latino patients (e.g., 19.7% vs. 14.9% in 2007, respectively). A greater percentage of pilot than nonpilot pharmacy patients were adherent to their ART medication regimens (e.g., 2007: 69.4% vs. 47.3%, respectively). After controlling for age, gender, and ethnicity/race in logistic regression analysis, use of a pilot pharmacy (odds ratio [OR] = 2.74, 95% CI = 2.44-3.10) was the most important factor associated with likelihood of adherence. Each year, pilot pharmacy patients were more likely than nonpilot pharmacy patients to remain on a single type of ART regimen (e.g., 2007: 71.7% vs. 49.1%, respectively). Payment from the DHCS Medi-Cal program for MTM services was approximately $1,000 per pilot pharmacy patient per year.

CONCLUSIONS: Over a 3-year period, patients at pilot pharmacies consistently had higher medication adherence rates, were more likely to remain on a single type of ART regimen throughout the year, had fewer excess fills, and used fewer contraindicated regimens than nonpilot pharmacy patients. There were no significant differences in mean total cost per patient per year, and the additional MTM services payment added less than 3% to the total cost.

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A significant correlation between improved antiretroviral therapy (ART) adherence and reduced viral load has been demonstrated for patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) in several studies. For example, a study in a Veterans Affairs Medical Center found that each adherence rate increase of 10% was associated with a viral load decrease of $0.12 \log_{10} (95\% \text{ CI}=0.01 \log_{10}-0.23 \log_{10})$ copies per milliliter (mL).

Two published studies suggest that HIV/AIDS patients receiving pharmacist-provided medication therapy management (MTM) services have better ART adherence and outcomes; however, these studies used small sample sizes and were conducted in specialized clinics, not community pharmacies.

A study of the first year (2005) of a Medi-Cal pilot program that provided compensation for pharmacist-provided MTM services for Medi-Cal beneficiaries, including Medicare dual-eligibles, found that pilot community pharmacy patients were more likely to be adherent to ART medications (56.3% vs. 38.1%, P < 0.001); to use protease inhibitor-based ART medication regimens (63.8% vs. 54.8%, P < 0.001); and to remain on a single type of ART regimen throughout the study year (56.8% vs. 34.2%, P < 0.001) and were less likely to use contraindicated regimens (11.6% vs. 16.6%, P < 0.001) compared with nonpilot pharmacy patients.

The present study examined the second and third year of the Medi-Cal MTM services pilot program excluding Medicare dual-eligibles, finding that the results observed in the first evaluation year (2005) were sustained in the group of Medi-Cal patients who continued to receive care at pilot pharmacies from 2005 through 2007.

Compared with nonpilot pharmacy patients, pilot pharmacy patients were (a) more adherent to their ART medication regimens, (b) more likely to remain on a single type of ART regimen, (c) less likely to have excess fills, and (d) less likely to use contraindicated regimens; however, there was no difference in the proportion of patients experiencing opportunistic infections (about 35% in both groups).

Non-ART medication costs were approximately 30%-40% greater in the pilot pharmacy group each year, and the difference was primarily and consistently attributable to greater use of gastrointestinal agents, analgesics, and psychotherapeutic medications; however, expenditures for inpatient services were significantly lower for pilot pharmacy than nonpilot pharmacy patients each year (e.g., 2007: mean [standard error, SE] $3,083 [$293] vs. $5,186 [$300], respectively, P < 0.001).

The total mean [SE] annual cost per patient was not significantly different for pilot versus other pharmacy patients in any year (e.g., 2007: $38,983 [$1,023] vs. $38,856 [$633], respectively, P = 0.915); and the additional MTM services payment of approximately $1,000 per patient added less than 3% to the total cost per patient per year.

Achieving optimal therapeutic outcomes, such as reduced viral load, reduction of drug resistance, and improved survival, requires strict adherence to ART regimens. A significant correlation between better medication adherence and reduced viral load has been demonstrated in several studies using pharmacy claims data. For example, a study using pharmacy dispensing records in a free HIV clinic found that when adherence levels were below 95%, the percentage of patients with viral loads consistently below 400 copies per milliliter (mL) fell below 60%. A study in a Veterans Affairs Medical Center found that each adherence rate increase of 10% was associated with a viral load decrease of 0.12 $\log_{10}$ (95% confidence interval [CI] = 0.01 $\log_{10}$-0.23 $\log_{10}$) copies per mL.

The types of pharmacist-provided medication therapy management (MTM) services provided to patients with HIV/AIDS and the effects of MTM on medication adherence and patient outcomes have only recently begun to be studied. Two small studies conducted in HIV outpatient clinics reported positive outcomes associated with patient attendance at pharmacist-led clinics. The first reported that patients attending a pharmacist-led medication adherence clinic and at least 1 educational session from the clinical pharmacist (n = 80) experienced a significantly greater reduction in viral load at 6 and 12 months (P < 0.05) and improved medication adherence (refilling prescriptions on average every 31 vs. 50 days, P < 0.05) compared with those not attending. The second study, without a comparison group, reported that patients attending a pharmacist-managed drug optimization clinic (n = 34) experienced...
significant improvement from baseline in CD4+ T-lymphocyte counts ($P<0.001$) and viral loads ($P=0.004$), and a significant decrease in the severity of ART-related toxicity ($P<0.001$) over the study period (mean [standard deviation, SD] = 4 [2] months). 8

The largest published study of MTM services for patients with HIV/AIDS suggested improved patient adherence and medication usage patterns for patients using HIV/AIDS intensive community pharmacies participating in a special California Department of Health Care Services (DHCS) Medi-Cal (California’s Medicaid program) pilot program that provided compensation to community pharmacists for MTM services. 9 Pharmacists practicing in participating pharmacies had continuing and/or advanced training in HIV/AIDS patient care and offered a range of MTM services. 10 The most common MTM services were evaluation of patients’ ability to adhere to medications, identifying and managing adverse drug reactions, tailoring ART regimens to meet special lifestyle needs, counseling when medication underuse or overuse was detected, refill reminder services, and referral to other medical services as needed. Results of the first year of the pilot program (2005) indicated that more pilot pharmacy patients were classified as adherent with their medication regimens compared with patients receiving care at other (nonpilot) pharmacies. 10 In addition, fewer pilot pharmacy patients used contraindicated regimens, and pilot pharmacy patients were more likely to use PI-based ART medication regimens and to remain on a single type of ART therapy over the 1-year period. However, medical care utilization that may reflect differences in clinical outcomes (i.e., outpatient and hospitalization costs) and the rate of opportunistic infections were not significantly different between groups during the 1-year study period.

Although these studies suggest that HIV/AIDS patients receiving pharmacist-provided MTM services have better medication usage patterns (e.g., ART adherence) and clinical markers (e.g., viral load), only 1 study has examined a large group of HIV/AIDS patients, and none has examined adherence or outcomes for more than a single year. Follow-up for more than 1 year is important to determine if improved short-term behaviors and medication therapy result in fewer adverse events and better clinical outcomes that may lead to reduced medical resource utilization. Evaluation of data from the second and third year of the Medi-Cal MTM services pilot program provided an opportunity to examine ART adherence and outcomes in a patient population using MTM services provided in community pharmacies over multiple years.

**Study Objectives**

The primary purpose of this study was to examine the association between use of pharmacies participating in a California DHCS Medi-Cal MTM pilot program and adherence to ART regimens in a sample of Medi-Cal beneficiaries with HIV/AIDS during a 3-year period (2005–2007). In addition, the study used pharmacy and medical claims data for patients of pilot and nonpilot pharmacies to describe and compare (a) medication utilization, including number and type of ART medication regimens and use of contraindicated ART regimens; (b) occurrence of opportunistic infections; and (c) all-cause pharmacy and medical costs in each year.

**Methods**

**Description of the Intervention**

The intervention in this study was participation in the pilot Medi-Cal compensation program for MTM services for patients with HIV/AIDS. Participating pilot pharmacies were HIV/AIDS-intensive community pharmacies offering a wide range of MTM services of their own choosing (i.e., not determined by the Medi-Cal pilot program). The program has been described elsewhere in detail, including results from the first year of the program. 10,11 MTM services were self-reported by pharmacists, with each pilot pharmacy offering services beyond standard counseling, such as “evaluation of patients’ ability to adhere to medications, in consultation with doctors and case managers;” “identifying and managing adverse drug reactions;” and “tailoring drug regimens to fit patient lifestyle or special needs.” 11 In addition, the majority of pilot pharmacies also offered “individual appointments with pharmacists to discuss medication therapy;” “adherence packaging beyond any provided by manufacturer” (e.g., personalized blister packs for all ART medications); “identification of peer advocate to assist in medication adherence;” and “weekly telephone call or home visit after initiation of therapy.”  11 Although many types of MTM services were offered, the proportion of patients utilizing each service varied. For example, “adherence packaging beyond any provided by the manufacturer” was offered by 4 of 7 pilot pharmacies responding to a survey by the authors of the present study, but the proportion of patients utilizing the service was estimated to be between 1% and 50%. 11

**Outcome Measures and Hypotheses**

We hypothesized that use of pilot pharmacies would be a significant predictor of greater ART adherence during the 3-year study period. To measure adherence for each year, MPR was calculated as the sum of days supply of ART divided by 365.26 days (Table 1). Adherence was defined as a medication possession ratio (MPR) of 80%-120%. Three additional MPR categories were defined: nonadherent (MPR less than 50%), partially adherent (MPR 50%-79%), and excess fills (MPR more than 120%). A grouping for partially adherent was included due to its clinical significance; partial adherence can cause drug resistance, thus limiting the availability of future effective drug regimens. In addition, compared with patients using nonpilot pharmacies, we expected patients using pilot pharmacies to have (a) more rational ART medication strategies (i.e., greater
use of PI-based ART regimens, fewer medication changes, fewer contraindicated regimens); (b) fewer opportunistic infections in each study year; and (c) lower total costs by study year 3. Specific outcome measures are presented in Table 1.

**Study Design and Patient Selection**
This was a cohort study examining Medi-Cal pharmacy and medical claims data for patients with HIV/AIDS served by pilot versus nonpilot pharmacies in the state of California during the calendar years 2005–2007. The University of California San Diego and the California Health and Human Services Agency Committee for the Protection of Human Subjects approved all study procedures.

The study sample consisted of Medi-Cal beneficiaries aged 18 years or older as of January 1, 2005, who were continuously enrolled from January 1, 2004, through December 31, 2007, and diagnosed with HIV/AIDS, identified by receipt of at least 1 prescription for ART and at least 1 medical claim with a primary or secondary HIV/AIDS-related diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification).

### TABLE 1 Outcome Measures (2005-2007)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pharmacy visits</td>
<td>Number of days on which the patient visited the pharmacy to fill ART prescription or prescriptions</td>
</tr>
<tr>
<td>ART adherence level (MPR)</td>
<td>MPR = Σ number days supply ART for year</td>
</tr>
<tr>
<td></td>
<td>365.25 days</td>
</tr>
<tr>
<td></td>
<td>Nonadherent: MPR less than 50%</td>
</tr>
<tr>
<td></td>
<td>Partially adherent: MPR 50%-79%</td>
</tr>
<tr>
<td></td>
<td>Adherent: MPR 80%-120%</td>
</tr>
<tr>
<td></td>
<td>Excess fills: MPR more than 120%</td>
</tr>
<tr>
<td></td>
<td>Calculated using medication with highest days supply on day when multiple prescriptions were filled to avoid double counting of days</td>
</tr>
<tr>
<td>ART medication regimen strategy</td>
<td>Categories are mutually exclusive and are assigned the therapy with the greatest number of days supplied during the year</td>
</tr>
<tr>
<td></td>
<td>• Only 1 NRTI</td>
</tr>
<tr>
<td></td>
<td>• Multiple NRTI</td>
</tr>
<tr>
<td></td>
<td>• NRTI + NNRTI</td>
</tr>
<tr>
<td></td>
<td>• NRTI + PI, with or without NRTI</td>
</tr>
<tr>
<td>Contraindicated ART regimen <strong>a</strong></td>
<td>• amprenavir + fosamprenavir</td>
</tr>
<tr>
<td></td>
<td>• atazanavir + indinavir</td>
</tr>
<tr>
<td></td>
<td>• zalcitabine in regimen</td>
</tr>
<tr>
<td></td>
<td>• emtricitabine + lamivudine</td>
</tr>
<tr>
<td></td>
<td>• stavudine + zidovudine</td>
</tr>
<tr>
<td></td>
<td>• didanosine + stavudine</td>
</tr>
<tr>
<td></td>
<td>• saquinavir alone</td>
</tr>
<tr>
<td></td>
<td>• only a single-class NRTI regimen</td>
</tr>
<tr>
<td></td>
<td>• only mono or dual therapy with NRTI</td>
</tr>
<tr>
<td></td>
<td>• only triple therapy NRTI—except if abacavir + zidovudine + lamivudine or tenofovir + zidovudine + lamivudine</td>
</tr>
<tr>
<td>Number of ART medication regimen strategies</td>
<td>Number ART regimen strategies = Σ regimen strategies</td>
</tr>
<tr>
<td></td>
<td>• Regimen strategies: each prescription fill categorized as a single ART, multiple ART, NNRTI, or PI regimen strategy</td>
</tr>
<tr>
<td></td>
<td>• Regimen strategies counted only once: (e.g., if patient switched from single ART to NNRTI and back to ART, number of regimen strategies = 2)</td>
</tr>
<tr>
<td>Opportunistic infection <strong>a,b</strong></td>
<td>See list in previously published study</td>
</tr>
<tr>
<td>Total medication cost</td>
<td>Paid claims amount for all prescription medications</td>
</tr>
<tr>
<td>ART medication cost</td>
<td>Paid claims amount for ART medications (single agent or in combination)</td>
</tr>
<tr>
<td>Non-ART medication cost</td>
<td>Total medication cost minus ART medication cost</td>
</tr>
<tr>
<td>Medical costs <strong>a</strong></td>
<td>Paid claims amounts for:</td>
</tr>
<tr>
<td></td>
<td>Inpatient</td>
</tr>
<tr>
<td></td>
<td>Hospital outpatient (includes emergency department)</td>
</tr>
<tr>
<td></td>
<td>Outpatient</td>
</tr>
<tr>
<td></td>
<td>Mental health</td>
</tr>
<tr>
<td></td>
<td>Lab/x-ray</td>
</tr>
<tr>
<td></td>
<td>AIDS Waiver Program <strong>c</strong></td>
</tr>
</tbody>
</table>

**a**U.S. Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents, Table 8, page 65. **b**Note: didanosine + tenofovir, which is on the current list of contraindicated regimens, was not included in the present study because it was not listed in the 2006 guidelines relevant to the study period. **c**Medical costs were assigned to service categories using codes indicating type of service (i.e., Medi-Cal vendor codes). **Under contract with the Department of Health Services agencies to provide home and community-based services as an alternative to nursing facility care or hospitalization. AIDS = acquired immune deficiency syndrome; ART = antiretroviral therapy; MPR = medication possession ratio; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor; PI = protease inhibitor.
code [ICD-9-CM] = 042.0) during both the index period (from January through December 2004) and the study period years (from January 2005 through December 2007). The ART medications included in this cohort included all those that were approved by the U.S. Food and Drug Administration at any time during the study period (Appendix). Two medications (maraviroc and raltegravir) that were approved in the last half of 2007 were not included because the opportunity to utilize these agents was minimal. In each study year, patients were identified as pilot pharmacy patients if they filled 50% or more of their ART prescriptions at 1 of the 10 pilot pharmacies. Comparison group patients met the same inclusion and exclusion criteria as study patients except that they filled less than 50% of their ART prescriptions at 1 of the 10 pilot pharmacies. Individuals enrolled in managed care plans were excluded because comprehensive information on paid claims was not available for Medi-Cal participants enrolled in managed care. Notably, dual-eligible Medicare patients were excluded because they had been automatically switched to Medicare Part D for the majority of their prescription drugs as of January 1, 2006, and as a result, their medication claims data were not available for follow-up in the Medi-Cal database. Patients who died at any time from 2004 through 2007 did not meet the continuous eligibility requirement for sample inclusion and were therefore not represented in the sample.

Data Analysis

Descriptive statistics were calculated for all variables. Categorical variables were described with frequency distributions and continuous variables by means, medians, SDs, and ranges. Differences in categorical variables (gender, race/ethnicity, ART adherence, and ART medication category) between groups (pilot vs. other pharmacy patients) were assessed using the Pearson chi-square test. Differences in continuous variables (age and number of pharmacy visits to fill ART prescriptions) were compared between groups using t-tests. Binomial logistic regression with the patient-year as the unit of analysis (i.e., each patient contributed 3 observations) was used to investigate the factors associated with adherence (MPR of 80%-120%) versus any other MPR (i.e., combining patients who were nonadherent, partially adherent, or had excess fills into a single category). Independent variables included pilot pharmacy usage (yes vs. no), patient age, gender, and race/ethnicity. Differences in costs were analyzed using generalized linear models assuming a gamma distribution and log link function; predictor variables for the models included age, gender, and race/ethnicity. Standardized estimates of mean annual costs were calculated for pilot and nonpilot pharmacies. Costs for the $9.50 payment per prescription dispensed (for any medication, not just ART) paid to pilot pharmacies by DHCS were calculated separately. Statistical significance was set at P < 0.05. All statistical analyses were performed using SAS version 9.13 (SAS Institute, Inc., Cary, NC).
### Results

The study sample consisted of 2,234 patients meeting the study inclusion criteria (Figure 1). The present study cohort (continuous eligibility for 4 years from January 1, 2004, through December 31, 2007), compared with the original cohort identified for the previously published 2005 analyses (continuous eligibility for 2004–2005), had a higher percentage of African Americans (33.0% vs. 29.4% pilot pharmacies and 31.4% vs. 25.2% nonpilot pharmacies) and slightly lower percentages of non-Latino White patients (40.3% vs. 44.6% pilot pharmacies and 42.7% vs. 46.5% nonpilot pharmacies) and Latino patients (16.2% vs. 17.6% pilot pharmacies and 16.3% vs. 19.9% nonpilot pharmacies). While still predominantly male, the percentage of males was lower in the present study compared with the previous study (67.2% vs. 76.3% pilot pharmacies and 72.0% vs. 81.0% nonpilot pharmacies).

Most nonpilot pharmacy patients did not use pilot pharmacies to fill any ART prescriptions. For example, in 2007, 1,428 (88.9%) of nonpilot pharmacy patients filled no ART prescriptions at pilot pharmacies; 63 (3.9%) used a pilot pharmacy for 25%–49% of their ART claims; and 115 (7.2%) used a pilot pharmacy for 1%–24% of their ART claims. The proportion of cohort patients receiving the majority of their prescription medications (ART plus non-ART) at pilot pharmacies was 19.7% in 2005 and increased to 27.6% and 28.1% during 2006 and 2007 (Table 2). Pilot pharmacies had a slightly lower percentage of male patients than nonpilot pharmacies in 2006 and 2007 ($P=0.011$ and $P=0.056$, respectively). The pilot pharmacy group also had a larger proportion of Latino patients compared with the nonpilot group in 2006 and 2007 (e.g., 2007: 19.7% vs. 14.9% respectively, $P=0.006$) and a smaller percentage of non-Latino White patients (e.g., 2007: 35.7% vs. 44.8% respectively, $P=0.001$).

The percentage of patients who were adherent with ART was significantly greater for pilot pharmacies than non-pilot pharmacies, with the difference being greater than 20 percentage points each year (e.g., 2007: 69.4% vs. 47.3% respectively, $P<0.001$; Table 3). A much smaller percentage of patients using pilot pharmacies had excess fills than patients using other pharmacies (e.g., 2007: 12.9% vs. 35.5% respectively, $P<0.001$). In some years, significant differences were seen between groups in the number of patients classified as nonadherent or partially adherent; however, the magnitude of difference was less than 5 percentage points. Each year, the mean [SD] number of pharmacy visits to fill ART prescriptions was significantly greater for pilot pharmacy patients compared with nonpilot pharmacy patients (e.g., 2007: 15.2 [9.8] vs. 13.7 [6.8] respectively, $P<0.001$); however, the median number of visits (13) was the same for both groups each year.

A significantly greater percentage of pilot pharmacy patients used a PI-based ART regimen (NRTI + PI ± NNRTI) compared with nonpilot patients during 2005 and 2007 (Table 3). A significantly smaller percentage used an NNRTI-based regimen (NRTI + NNRTI) compared with nonpilot patients during 2007 (21.0% vs. 26.2%, respectively, $P=0.011$), but not during 2005 or 2006. During 2006, no pilot pharmacy patients were taking the contraindicated single NRTI treatment strategy, compared with 10 (0.6%) of nonpilot pharmacy patients ($P=0.050$); differences in the other years were not significant. Each year, a smaller proportion of pilot pharmacy patients was on contraindicated ART regimens compared with nonpilot pharmacy patients (e.g., 2007: 8.9% vs. 12.2% respectively, $P=0.027$).

The percentage of patients who used only a single ART medication strategy in a year was significantly greater for pilot pharmacies versus non-pilot pharmacies, with the difference being approximately 22 percentage points each year (e.g., 2007: 71.7% vs. 49.1%, respectively, $P<0.001$; Table 3). The percentages of patients experiencing opportunistic infections were similar, approximately 35%, for pilot and nonpilot pharmacy patients each year ($P=0.809–0.945$). Logistic regression indicated that the most important factors associated with likelihood of adherence were use of a pilot pharmacy

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**Table 2**: HIV/AIDS Patient Demographics: Pilot and Nonpilot Pharmacies, 2005–2007

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pilot (N=5,359)</td>
<td>Nonpilot (N=5,236)</td>
<td>P Value*</td>
</tr>
<tr>
<td>Number of pharmacies</td>
<td>10</td>
<td>5,359</td>
<td>NA</td>
</tr>
<tr>
<td>Number (% study patients)</td>
<td>439 (19.6)</td>
<td>1,795 (80.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Mean [SD] (range) age in years</td>
<td>44.7 [8.1]</td>
<td>45.4 [7.8]</td>
<td>0.096</td>
</tr>
<tr>
<td>Number (% male)</td>
<td>295 (67.2)</td>
<td>1,293 (72.0)</td>
<td>0.204</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Latino White</td>
<td>177 (40.3)</td>
<td>767 (42.7)</td>
<td>0.359</td>
</tr>
<tr>
<td>African American</td>
<td>145 (33.0)</td>
<td>563 (31.4)</td>
<td>0.502</td>
</tr>
<tr>
<td>Latino</td>
<td>71 (16.2)</td>
<td>293 (16.3)</td>
<td>0.939</td>
</tr>
<tr>
<td>Other race/ethnicity</td>
<td>46 (10.5)</td>
<td>172 (9.6)</td>
<td>0.571</td>
</tr>
</tbody>
</table>

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

HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; NA = not applicable; SD = standard deviation.
Antiretroviral Therapy Adherence, Medication Use, and Health Care Costs During 3 Years of a Community Pharmacy Medication Therapy Management Program for Medi-Cal Beneficiaries with HIV/AIDS

### Table 3: Prescription Medication Use: Pilot and Nonpilot Pharmacies, 2005–2007

<table>
<thead>
<tr>
<th>Category</th>
<th>Pilot</th>
<th>Nonpilot</th>
<th>P Value*</th>
<th>Pilot</th>
<th>Nonpilot</th>
<th>P Value*</th>
<th>Pilot</th>
<th>Nonpilot</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>439</td>
<td>1,795</td>
<td>NA</td>
<td>617</td>
<td>1,017</td>
<td>NA</td>
<td>628</td>
<td>1,606</td>
<td>NA</td>
</tr>
<tr>
<td>Mean [SD] median (range)</td>
<td>13 (1-55)</td>
<td>13 (1-80)</td>
<td></td>
<td>13 (1-62)</td>
<td>13 (1-55)</td>
<td></td>
<td>13 (1-54)</td>
<td>13 (1-63)</td>
<td></td>
</tr>
</tbody>
</table>

Number (% of Patients by Category

<table>
<thead>
<tr>
<th>ART adherence level (%)</th>
<th>Pilot</th>
<th>Nonpilot</th>
<th>P Value*</th>
<th>Pilot</th>
<th>Nonpilot</th>
<th>P Value*</th>
<th>Pilot</th>
<th>Nonpilot</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherent (MPR 80%-120%)</td>
<td>289 (65.8)</td>
<td>772 (43.0)</td>
<td>&lt;0.001</td>
<td>443 (71.8)</td>
<td>725 (44.8)</td>
<td>&lt;0.001</td>
<td>436 (69.4)</td>
<td>759 (47.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partially adherent (MPR 50%-79%)</td>
<td>51 (11.6)</td>
<td>162 (9.0)</td>
<td>0.231</td>
<td>64 (10.4)</td>
<td>150 (9.3)</td>
<td>0.990</td>
<td>73 (11.6)</td>
<td>137 (8.5)</td>
<td>0.125</td>
</tr>
<tr>
<td>Nonadherent (MPR less than 50%)</td>
<td>35 (8.0)</td>
<td>149 (8.3)</td>
<td>0.096</td>
<td>33 (5.3)</td>
<td>145 (9.0)</td>
<td>&lt;0.001</td>
<td>38 (6.1)</td>
<td>140 (8.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Excess fills (MPR more than 120%)</td>
<td>64 (14.6)</td>
<td>712 (39.7)</td>
<td>&lt;0.001</td>
<td>77 (12.5)</td>
<td>597 (36.9)</td>
<td>&lt;0.001</td>
<td>81 (12.9)</td>
<td>570 (35.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ART medication regimen strategies (%)  

| Only 1 NRTI                      | 25 (5.7) | 117 (6.5) | 0.526 | 33 (5.3) | 91 (5.6) | 0.796 | 30 (4.8) | 83 (5.2) | 0.704 |
| Multiple NRTI                    | 105 (23.9) | 508 (28.3) | 0.065 | 146 (23.7) | 416 (25.7) | 0.315 | 132 (21.0) | 421 (26.2) | 0.011 |
| NRTI+ NNRTI                      | 308 (70.2) | 1,157 (64.5) | 0.024 | 438 (71.0) | 1,097 (67.8) | 0.151 | 465 (74.0) | 1,092 (68.0) | 0.005 |
| Used at least 1 contraindicated ART regimen | 47 (10.7) | 266 (14.8) | 0.026 | 55 (8.9) | 221 (13.7) | 0.002 | 56 (8.9) | 196 (12.2) | 0.027 |

Count of ART medication regimen strategies used

- 1 strategy: 296 (67.4) vs. 827 (46.1) <0.001
- 2 strategies: 115 (26.2) vs. 670 (37.3) <0.001
- 3 or more strategies: 28 (6.4) vs. 298 (16.6) <0.001

At least 1 opportunistic infection 158 (36.0) vs. 635 (33.4) = 0.809

*P values for Pearson chi-square test for categorical variables and t-test test for continuous variables.

+Number of visits that included the filling of at least 1 ART prescription.

### Table 4: Logistic Regression Analysis of Factors Associated with ART Adherence, 2005–2007

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot pharmacy use</td>
<td>2.74</td>
<td>2.44</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>Male</td>
<td>1.06</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Ethnicity

- African American | 1.15 | 1.01 | 1.30 | 0.017 |
- Latino | 1.45 | 1.25 | 1.67 | <0.001 |
- Other | 1.18 | 0.99 | 1.40 | 0.067 |

*Unit of analysis was the patient-year (i.e., each patient contributed 1 observation for each of the 3 years), with n = 3,424 in the adherent category (MPR 80%-120%) and n = 3,278 in the other adherence category, which included patients who were nonadherent (MPR less than 50%), partially adherent (MPR 50%-79%), or had excess fills (MPR more than 120%). R-square = 0.0648; c-statistic = 0.613.

#Ethnicity reference category was Non-Latino White.

ART = antiretroviral therapy; MPR = medication possession ratio.

### Notes

- (odds ratio [OR] = 2.74, 95% CI = 2.44-3.10), and Latino or African American ethnicity (OR = 1.45, 95% CI = 1.25-1.67 and OR = 1.15, 95% CI = 1.03-1.30 respectively; Table 4).

In the generalized linear model analyses, the predicted mean (standard error [SE]) total costs per patient were not significantly different in the pilot versus other pharmacy group in any year (Table 5). The largest expenditure categories were medications, other services, and inpatient services. During each year, the predicted mean [SE] total medication cost per patient was greater in the pilot group than the nonpilot group (e.g., 2007: $29,955 [5679] vs. $25,690 [5362], respectively, P<0.001). The difference was driven largely by the difference in non-ART medication costs, which were approximately 30%-40% greater in pilot pharmacy groups each year (e.g., 2007: $10,815 [5538] vs. $8,190 [5252] respectively, P<0.001). Examination of the types of non-ART medications utilized (categories with costs exceeding $500 per patient in each year, 2005–2007, in either the pilot or nonpilot pharmacy group) indicated that the difference in non-ART costs was primarily and consistently attributable to greater use of...
### TABLE 5
Generalized Linear Model Analyses of Predicted Pharmacy and Medical Costs Per Patient Controlling for Age, Gender, and Ethnicity, 2005–2007

<table>
<thead>
<tr>
<th>Cost category</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE) Cost ($)</td>
<td>Mean (SE) Cost ($)</td>
<td>P Value&lt;sub&gt;b&lt;/sub&gt;</td>
</tr>
<tr>
<td>Total medication</td>
<td>26,797 (703)</td>
<td>22,544 (290)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ART medication</td>
<td>16,807 (403)</td>
<td>15,526 (183)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-ART medication</td>
<td>9,887 (579)</td>
<td>7,014 (200)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outpatient</td>
<td>2,734 (313)</td>
<td>3,808 (207)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital outpatient</td>
<td>112 (11)</td>
<td>44 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lab and x-ray</td>
<td>389 (34)</td>
<td>402 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>3,626 (274)</td>
<td>5,044 (185)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>35,546 (1,093)</td>
<td>33,501 (505)</td>
<td>0.079</td>
</tr>
</tbody>
</table>

<sup>a</sup>N of cases = 2,234 in each year. Goodness-of-fit for total cost equations: Pearson chi-square, 2005 = 0.8094, 2006 = 1.0418, 2007 = 0.7632.

<sup>b</sup>Assessed using Wald chi-square test for regression coefficient.

AIDS = acquired immune deficiency syndrome; ART = antiretroviral therapy; ER = emergency room; SE = standard error.

Gastrointestinal agents, analgesics, and psychotherapeutic drugs in the pilot pharmacy group compared with the nonpilot pharmacy group (Table 6).

The 2 remaining large expenditure categories, inpatient and other services, were significantly lower for pilot patients than nonpilot patients each year (Table 5). For example, predicted mean (SE) expenditures for inpatient services in 2007 for the pilot and nonpilot groups were $3,083 ($293) versus $5,186 ($300), respectively (P < 0.001). Although significantly lower costs for other services were observed for the pilot pharmacy group compared with the other pharmacy group each year (P < 0.001), the difference was not consistently attributable to a few specific services; the other category included more than 30 types of services, such as professional services provided by allied health care providers (e.g., chiropractor, optometrist, and psychologist), and facility services (e.g., adult day care, rehabilitation centers, and skilled nursing facilities). Although not a large contributor to total cost, the mean (SE) costs per patient for hospital outpatient services (which includes emergency room visits) were significantly lower for pilot than nonpilot pharmacy patients during each year (e.g., 2007: $96 [89] vs. $248 [14], respectively, P < 0.001).

During the 3-year study period, payments by the California DHCS to pilot pharmacies for MTM services provided to study patients were $430,141 in 2005 (n = 439 patients), $620,284 in 2006 (n = 617), and $657,752 in 2007 (n = 628). Thus, the average annual DHCS payment for MTM services per pilot pharmacy study patient was about $1,000 each year ($980, $1,005, and $1,047, respectively).

### Discussion

The present study assessed the results of a novel compensation program for community pharmacies offering MTM services for patients with HIV/AIDS enrolled in Medi-Cal over a 3-year period. Overall, the results of our initial evaluation (2005 data only, and including 53.3% Medicare dual-eligibles) were sustained in this group of patients who continued to receive care at pilot pharmacies through Medi-Cal from January 1, 2005, through December 31, 2007.

A greater percentage of pilot pharmacy patients were adherent to their ART medication regimens compared with patients using nonpilot pharmacies, with the difference being greater than 20 percentage points each year. After controlling for age, gender, and ethnicity, the odds of adherence for pilot pharmacy patients were more than twice those of nonpilot pharmacy patients. The fact that the proportion of patients who were partially adherent or nonadherent remained fairly constant in both groups is troublesome because these patients are at risk of developing ART resistance that could diminish their longer-term therapy options. As in 2005, a much smaller percentage of patients using pilot pharmacies had excess fills than patients using other pharmacies during 2006 and 2007. A reasonable expectation is that the greater percentage of adherent patients in pilot pharmacies will result in improved clinical outcomes given studies that have reported an association of improved adherence with reduced viral load.

There were some slight differences in the percentage of males and the race/ethnicity mix of pilot versus nonpilot pharmacies in 2006 and 2007, with pilot pharmacies having fewer males, fewer non-Latino White patients, and more Latino...
patients than nonpilot pharmacies, although the largest difference was less than 10 percentage points. Therefore, in this study cohort, the demographic profile of HIV/AIDS patients receiving medications at pilot pharmacies was generally similar to that of HIV/AIDS patients receiving medications at nonpilot pharmacies in California.

In 2005 and 2007, a larger percentage of pilot pharmacy compared with nonpilot pharmacy patients used PI-based ART medication regimens, although in 2006 the difference was not statistically significant. Each year, the percentages of patients using only a single ART medication strategy were greater for pilot pharmacy patients, and fewer pilot pharmacy patients were on contraindicated regimens. Remaining on a single type of medication regimen strategy is important because exposing patients to more drugs and drug classes increases the likelihood of developing ART resistance. These findings suggest that ART medications were being managed more successfully in pilot pharmacy patients, giving them more future treatment options.

Contrary to our hypotheses, 2 outcomes (opportunistic infection rate and total annual cost per patient) were not significantly lower in pilot pharmacy patients. The proportion of patients experiencing opportunistic infections (approximately one-third) was similar between the 2 groups each year despite having a greater proportion of adherent patients and patients on PI-based regimens in pilot versus nonpilot pharmacies. Although the reasons for this finding cannot be determined from our data, it could be lack of sufficient follow-up time to develop opportunistic infections which are usually observed in patients with advanced disease. Although the total annual cost per patient was similar in each group each year (e.g., approximately $39,000 in 2007), the mix of expenditures differed. Non-ART medication costs were appreciately greater in the pilot pharmacy group each year, while expenditures for inpatient services were significantly lower for pilot than non-pilot patients. Higher non-ART medication use comprised greater use of gastrointestinal agents (e.g., antiemetics and anti-emetic medications), analgesics, and psychotherapeutic medications. The greatest magnitude of difference was observed for analgesics, for which the average expenditure per pilot pharmacy patient was more than twice that of a nonpilot pharmacy patient during each of the 3 years. Analgesics are often used to treat pain of peripheral neuropathy, a common neurological complication associated with HIV infection. Antiemetics are often used to treat nausea, a side effect that may occur with ART medications. Thus, pilot pharmacy patients appear to be receiving more non-ART medications to mitigate commonly occurring adverse effects of HIV and its treatment. This finding is consistent with the reduction in drug-related toxicities reported for HIV patients receiving MTM services in a primary care clinic. Thus, the role of the pharmacist in proactively managing adverse drug reactions may increase medication costs but improve compliance and long-term patient outcomes.

Including the additional amount paid by the California DHCS (average of approximately $1,000 per pilot pharmacy study patient per year because of the $9.50 per prescription payments for MTM services) would increase the total cost for pilot patients by less than 3%. Of note, the California Legislature made changes to the pilot program effective July 1, 2008, requiring that California’s DHCS pay the $9.50 only if ART medications are being managed more successfully in pilot pharmacy patients, giving them more future treatment options.
2007 for MTM services (based on all prescriptions) would result in an estimated average payment of $400 per patient, which would add approximately 1% to the total cost of pilot pharmacy patients. Examination of data in subsequent years would be needed to determine if total costs remain similar in each group. Additionally, if our finding that more pilot patients are being maintained successfully on a single (or fewer) treatment regimen each year extends over many years, then the ART drug costs in the pilot group longitudinally may remain relatively stable over time, while the nonpilot pharmacy group ART medication costs would be expected to increase as the nonpilot pharmacy patients utilize more ARTs, newer ARTs, and more intensive salvage regimens.

Although this study spanned a 3-year period, the ultimate long-term benefit of patients being more adherent on appropriate combined ART regimens and utilizing more non-ART medications would require longer follow-up and remains to be studied.13 Regardless of whether cost offsets occur, the full value realized from the resources devoted to pilot pharmacy patients should ultimately be assessed on the basis of quality-adjusted life years (QALYs) gained over time. Since HIV is now considered a chronic disease that is treatable over decades, outcomes beyond medical claims data, such as maintenance of employment, fewer sick days, improved productivity, and patients’ quality of life should be explicitly considered and measured.

Limitations
First, the present study was an evaluation of an ongoing program and as such may be subject to selection bias, since patients were not randomly assigned to pilot versus nonpilot pharmacies. Although the 2 groups of patients were similar with regard to demographics, it is not possible to clearly determine to what extent the results we have observed are due to the true pilot program effect or to unobserved differences in patients using pilot versus nonpilot pharmacies. Second, a more rigorous quasi-experimental (pre-intervention vs. post-intervention with comparison group) study design was not possible, since pilot pharmacies had been offering MTM services prior to the Medi-Cal compensation program. A third limitation is the availability of only self-reported data regarding MTM services at pilot pharmacies. Data regarding pharmacy services provided at the nonpilot pharmacies, which could have been providing some MTM services beyond the California requirement to offer counseling on new prescriptions, were also unavailable. Although possible, most likely the nonpilot pharmacies did not offer the types of specialized MTM services for patients with HIV/AIDS that would have been comparable to the MTM services provided by the pilot pharmacies.11 Fourth, some patients classified as nonpilot pharmacy patients also had prescriptions filled at pilot pharmacies. However, we found that 88.9% of nonpilot pharmacy patients filled no ART prescriptions at pilot pharmacies, and despite this crossover usage, we still noted differences in the nonpilot versus pilot pharmacy patients.

Fifth, as in any study that relies on retrospective analysis of administrative claims data, use of the Medi-Cal database does not allow measurement of important clinical outcomes, such as viral load and immune status, which would be indicative of patients’ clinical status and disease progression or severity. Sixth, patients who had been dually eligible for Medicare were automatically switched to Medicare Part D for their prescription drugs as of January 1, 2006, and thus were not available for follow-up in this Medi-Cal database, although they may continue to be patients of the pilot pharmacies. Similarly, the Medi-Cal patients do not represent the entire patient load of either the pilot or nonpilot pharmacies. Thus, results may not generalize to patient populations covered by Medicare or by commercial insurance, which might differ from the present study sample with respect to demographics, disease characteristics, and medical care patterns.

Conclusions
Over a 3-year intervention period, patients with HIV/AIDS filling ART prescriptions at MTM pilot pharmacies consistently had higher ART adherence rates, fewer excess fills, and fewer contraindicated regimens than nonpilot pharmacy patients. In addition, more pilot pharmacy patients remained on a single type of ART regimen each year of the study, thus decreasing the likelihood of developing drug resistance and preserving therapeutic options in the future. There were no significant differences between the 2 groups in mean total all-cause health care cost per patient. The results of this novel pilot program should help health care plans understand the possible value of MTM for patients with HIV/AIDS and spur continued evaluation of MTM services provided in community pharmacies.

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Concept and design were performed by Gilmer, Hirsch, Miller, and Rosenquist. Data were collected by Gonzales, with the assistance of Miller and Hirsch, and interpreted by Best, with the assistance of Hirsch and Gilmer. The manuscript was written by Hirsch, with the assistance of Gonzales, Gilmer, and Rosenquist, and revised by Best, with the assistance of Gonzales and Hirsch.

REFERENCES


Antiretroviral Therapy Adherence, Medication Use, and Health Care Costs During 3 Years of a Community Pharmacy Medication Therapy Management Program for Medi-Cal Beneficiaries with HIV/AIDS

APPENDIX Antiretroviral Therapy Medication List by Category

**Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTI)**
- Abacavir sulfate
- Abacavir sulfate/lamivudine
- Abacavir/lamivudine/zidovudine
- Didanosine/mag/Al NaCB/sodium citrate
- Didanosine
- Didanosine/calium carbonate/magnesium
- Didanosine/sodium citrate
- Emtricitabine
- Lamivudine
- Lamivudine/zidovudine
- Stavudine
- Zalcitabine
- Zidovudine
- Tenofovir disoproxil fumarate
- Emtricitabine/tenofovir

**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)**
- Delavirdine mesylate
- Efavirenz
- Nevirapine

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

**Fusion Inhibitor**
- Enfuvirtide

*Buffering agents, magnesium hydroxide, aluminum sodium carbonate, sodium citrate.*
Why Hypotheses Informed by Observation Are Often Wrong: Results of Randomized Controlled Trials Challenge Chronic Disease Management Strategies Based on Epidemiological Evidence

Kathleen A. Fairman, MA

“My afraid I have to make the same points I’ve made over and over. An epidemiologic relationship between glucose level and risk of cardiovascular events does not mean [that] lowering glucose levels with an intervention will have the desired effect. … There are no shortcuts. We just don’t know what we’re doing until an adequate randomized trial is done.” —Cardiologist Robert Califf, commenting in a popular press interview on the first results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.¹

For researchers and clinicians engaged in the important business of trying to prevent cardiovascular events in patients with type 2 diabetes, 2010 was a year of eye-opening surprises. The revelations began early with the March 2010 release of results from the blood pressure control component of the ACCORD randomized controlled trial (RCT).² Initiated in 2001 by the National Heart Lung and Blood Institute (NHLBI), ACCORD was an important landmark clinical trial for patients with type 2 diabetes and risk factors for cardiovascular disease; it represented the first large, experimental investigation of several key treatment guidelines that were based on sound epidemiological evidence but had never been subjected to the more rigorous test of an RCT.³ ACCORD study subjects had type 2 diabetes, with a hemoglobin A1c level of at least 7.5%, and met cardiovascular risk criteria including (a) aged 40 years or older with cardiovascular disease or (b) aged 55 years or older with atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 cardiovascular disease risk factors (obesity, smoking, dyslipidemia, or hypertension).²

Of the 10,251 ACCORD study subjects, 4,733 met clinical criteria for inclusion in the blood pressure control component of the trial (systolic blood pressure [SBP] between 130 and 180 millimeters mercury [mmHg], taking 3 or fewer antihypertensive medications, and “the equivalent of a 24-hour protein excretion rate of less than 1.0 [grams]”). Patients were randomized to “intensive” therapy targeted to SBP less than 120 mmHg (n = 2,362) or “standard” therapy targeted to SBP less than 140 mmHg (n = 2,371). Patients were treated using “strategies that are currently available in clinical practice” and “drug classes … shown to result in a reduction in cardiovascular events among participants with diabetes.”⁴ At 1-year follow-up, mean SBPs were 119.3 (95% confidence interval [CI] = 118.9-119.7) mmHg and 133.5 (95% CI = 133.1-133.8) mmHg in the intensive- and standard-therapy groups, respectively, a difference that was “significant and sustained” throughout the study. However, in a mean 4.7 years of follow-up, the SBP differences did not translate into significant improvements in the primary endpoint outcome, a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or cardiovascular death; annual rates were 1.87% in intensive therapy and 2.09% in standard therapy (hazard ratio [HR] = 0.88, 95% CI = 0.73-1.06, P = 0.20). Additionally, serious adverse events attributable to antihypertensive treatment, including hypotension, bradycardia or arrhythmia, and hyperkalemia, were more common in the intensive- than standard-therapy arm (3.3% vs. 1.3%, respectively, P < 0.001).⁵

On the day of the announcement of the ACCORD blood pressure study results on March 14, 2010, presenters at an American College of Cardiology scientific session shared startling preliminary findings from a retrospective observational analysis of data from the International Verapamil SR-Trandolapril (INVEST) study of treatment with an angiotensin-converting enzyme (ACE) inhibitor and/or diuretic plus either a calcium channel blocker or beta-blocker for patients with hypertension and coronary artery disease.⁶ Conducted by Cooper-DeHoff et al. (2010), the observational analysis assessed the rate of cardiovascular events, including the primary composite outcome of nonfatal MI, nonfatal stroke, or all-cause death, in a subset of INVEST patients who also had diabetes (type not specified, n = 6,400), comparing those who achieved “tight” control (SBP of less than 130 mmHg, n = 2,255), “usual” control (SBP of 130 mmHg to less than 140 mmHg, n = 1,970), or “uncontrolled” SBP (140 mmHg or more, n = 2,175).⁷ Notably, the “tight” target was strongly supported by treatment guidelines in place at the time, including those of the American Diabetes Association (ADA), the seventh report of the Joint National Committee (JNC-7), and the American Heart Association (AHA).⁶,⁷,⁸ Yet, during a mean follow-up of approximately 2.6 years per patient, not only did tight control fail to decrease cardiovascular event rates compared with usual control; it was associated with slightly higher all-cause mortality. Although uncontrolled blood pressure was associated with an increase in the primary outcome compared with usual control (19.8% vs. 12.6%, respectively, HR = 1.46, 95% CI = 1.25-1.71, P < 0.001), rates for the usual control and tight control groups did not significantly differ (tight control = 12.7%, HR = 1.11, 95% CI = 0.93-1.32, P = 0.24).
And, in an extended follow-up analysis of the 5-year period following the close of the INVEST study, rates of all-cause mortality were 22.8% for patients with tight control and 21.8% for patients with usual control (HR = 1.15, 95% CI = 1.01-1.32, P = 0.04). The results of the observational analysis were striking: each 1% reduction in A1c was associated with hazard decreases of 21% for diabetes-related death (95% CI = 15%-27%), 14% for MI (95% CI = 8%-21%), and 37% for microvascular complications (95% CI = 33%-41%). For patients in preventing cardiovascular events and may actually cause harm. A follow-up analysis of ACCORD's intensive glycemic control component was published in March 2011, about 3 years after termination of the tight glycemic control arm of the trial for patient safety reasons. The extended analysis over a total of 5 years of follow-up supported the previous (2008) finding of an increase in all-cause death without a significant benefit on the primary study outcome (a composite of nonfatal MI, nonfatal stroke or cardiovascular death) for patients randomized to an “intensive” treatment arm (A1c target less than 6.0%, median before termination 6.4%), compared with patients randomized to “standard” treatment (A1c target of 7.0%-7.9%, median before termination 7.5%). Specifically, among patients treated with the intensive strategy for a mean of 3.7 years and transitioned to standard care for the remainder of the study (mean 1.2 years), the 5-year primary outcome rate was 2.1%, compared with 2.2% for patients who received standard treatment for all 5 years (P = 0.12), and all-cause mortality rates were 1.5% and 1.3%, respectively (P = 0.02). Perhaps more importantly, the ACCORD investigators still had no explanation for the findings. “We just don’t understand why we are seeing this mortality signal,” noted the lead investigator in a March 2011 interview, “and it is not for lack of looking. We’ve looked at severe hypoglycemia and it’s not that, and it also doesn’t seem to be caused by the rapid fall of [A1c] levels. There is no clear explanation emerging for this observation.”

**Epidemiological Evidence and Refuted Guidelines: ACCORD as a Case in Point**

One of ACCORD’s most important objectives was to test the “lower-is-better” view of A1c in type 2 diabetes which, at the time the trial was launched in 2001, had never been tested in an RCT but was widely held because of observational studies showing an association between higher A1c and poor outcomes. Among these was a study by Stratton et al. (2000) that is notable for its high quality. In a retrospective observational analysis of data gathered in the United Kingdom Prospective Diabetes Study (UKPDS), Stratton et al. categorized 3,642 patients with type 2 diabetes by A1c level, measured using an appropriate time-varying method. Cox proportional hazards regressions assessed the rates of negative patient outcomes (e.g., diabetic complications, MI, death) for patients at higher versus lower levels of A1c, controlling for numerous factors including demographics, smoking, LDL-C, triglyceride level, albuminuria, and SBP. Poisson regressions assessed incidence rates of patient outcomes, controlling for demographics and duration of diabetes.

The results of the observational analysis were striking: each 1% reduction in A1c was associated with hazard decreases of 21% for diabetes-related death (95% CI = 15%-27%), 14% for MI (95% CI = 8%-21%), and 37% for microvascular complications (95% CI = 33%-41%). For patients following the close of the INVEST study, rates of all-cause mortality were 22.8% for patients with tight control and 21.8% for patients with usual control (HR = 1.15, 95% CI = 1.01-1.32, P = 0.04). There were even more surprises on the same day with the release of the results of the lipid-lowering component of ACCORD, a development that was later listed by the AHA and American Stroke Association as one of the “top 10 advances in cardiovascular research in 2010.” ACCORD investigators randomized a subset of patients who met clinical eligibility criteria (low-density lipoprotein cholesterol [LDL-C] of 60 to 180 milligrams per deciliter [mg per dL]; high-density lipoprotein cholesterol [HDL-C] less than 55 mg per dL for women and blacks or less than 50 mg per dL for all others; and triglyceride level below 750 mg per dL for patients not already receiving lipid-lowering therapy or below 400 mg per dL for patients receiving lipid-lowering therapy) to treatment with simvastatin + placebo (n = 2,753) or simvastatin + fenofibrate (n = 2,765). In a mean of 4.7 years of follow-up, the annual rates of the primary composite outcome (nonfatal MI, nonfatal stroke, or cardiovascular death) were 2.2% and 2.4% in the fenofibrate and placebo groups, respectively (P = 0.32). Study groups did not significantly differ on any secondary endpoint outcome, including “major coronary disease event” (a composite of nonfatal MI, unstable angina, or cardiovascular death), death from any cause, or congestive heart failure.

Noting that “when a study does not support the central hypothesis, it is critical to examine potential reasons for this outcome,” ACCORD investigators reported the results of numerous pre-specified subgroup analyses, finding only the possibility of an interaction of treatment with sex (benefit for men and possible harm for women) and “a suggestion of heterogeneity according to baseline lipid levels: patients who had both a triglyceride level in the highest third and an [HDL-C] level in the lowest third … appeared to benefit from fenofibrate, whereas all other patients receiving fenofibrate did not.” Although ACCORD investigators noted that their findings were consistent with prevailing treatment guidelines “that recommend treatment for patients with hypertriglyceridemia and low [HDL-C] levels that persist despite statin therapy,” the AHA deemed the results a significant advance because they “will be helpful for targeting specific treatments that best reduce CVD risk in people with diabetes.”

**Follow-Up to ACCORD Affirms Earlier Findings**

Also during 2010, researchers in both ACCORD and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) continued to investigate the underlying causes of their previously reported puzzling findings that intensive glycemic control in patients with type 2 diabetes does not appear to be helpful.
with an A1c less than 6%, the unadjusted rate of diabetes-related deaths per 1,000 person-years of follow-up was 5.5, compared with 11.5 for patients whose A1c was within the accepted target range at the time, 7.0%-7.9%. Patients with A1c less than 6% experienced better outcomes than patients with A1c of 7.0%-7.9% on several other key measures, including all-cause mortality (11.1 vs. 18.7, respectively), fatal or nonfatal MI (10.1 vs. 16.6), and the development of complications related to diabetes (24.9 vs. 43.6). Although the research team cautioned that study results represented epidemiological associations, not necessarily a causal relationship between antidiabetic treatment to normal A1c and positive outcomes, they nonetheless concluded that “there is no specific target value of [A1c] for which one should aim but...the nearer to normal the [A1c] concentration the better” and that “any reduction in [A1c] is likely to reduce the risk of complications, with the lowest risk being in those with [A1c] values in the normal range (< 6.0%).”16

Viewed against the backdrop of the exceptionally promising findings of Stratton et al., the ACCORD trial results were understandably disappointing to clinicians and researchers, who were described as “flummoxed” in a media account published after termination of the intensive glycemic control experiment in February 2008. Yet, although the ACCORD trial results were, in a sense, surprising because of the strength of the observational evidence used to develop the study hypothesis, some knowledgeable observers noted that the replacement of treatment protocols based on observational results with new protocols based on stronger randomized evidence is a predictable and oft-repeated pattern in medical science. One observer summed up the ACCORD results by saying that “once again, the most sound of scientific and biologic plausibility has been refuted by a large clinical-outcomes trial.” The research literature is replete with such examples of evolving evidence, including research into the benefits of hormone replacement therapy in postmenopausal women, treatment algorithms for chronic kidney disease, and influenza vaccination of persons aged 65 years or older to prevent mortality.17

Indeed, the blood pressure control guidelines that were supported by so many key organizations, yet contradicted by ACCORD, were originally based on epidemiological analyses. ADA guidelines noted in 2010 that because these analyses showed “that blood pressure > 115/75 mmHg is associated with increased cardiovascular event rates and mortality in individuals with diabetes,” a “target blood pressure goal of < 130/80 mmHg is reasonable if it can be achieved safely.” A 2002 ADA guideline, in place at the approximate time of ACCORD’s initiation, noted that “there is no threshold value for [blood pressure], and risk continues to decrease well into the normal range.”

Why Are Informed Hypotheses Refuted So Often?

Replacement of initial epidemiological observation with more rigorous experimental evidence is common, desirable, and inherent to good scientific progress. Yet, the pattern is still somewhat puzzling on the surface. Why is observational evidence seemingly so likely to produce an erroneous conclusion? A look at some of the more common explanations suggests the seriousness of the problem and provides guidance for improvement.

1. Regression to the Mean (RTM). Although not a factor in the epidemiological research leading to the guidelines for patients with type 2 diabetes that were ultimately refuted by ACCORD, RTM has plagued many an observational analysis of interventions to improve outcomes in chronic disease care. The cause of RTM is “within-subject variability,” that is, random fluctuations in natural phenomena measured repeatedly in any person or other research subject. Because of within-subject variability, “when observing repeated measurements in the same subject, relatively high (or relatively low) observations are likely to be followed by less extreme [values] nearer the subject’s true mean.” Thus, when a group of study subjects is selected on the basis of abnormally high values on any measure (e.g., elevated A1c or SBP), a decline in the elevated values on average is mathematically expected; the same is true of increases in groups initially selected for abnormally low values (e.g., HDL-C). These changes are expected regardless of any intervention.

For example, Domurat (1999) studied an intensive disease state management (DSM) program (endocrinologist care, case management, routine screenings, and patient education) for patients with diabetes in a managed care organization. The DSM program was targeted to the highest-risk 30% of patients with diabetes who had “multiple hospital, emergency department, or urgent clinic admissions or visits,” recent complications of diabetes, comorbidities (e.g., uncontrolled hypertension or “general debility”), “poor understanding of disease self-care,” or other risk factors. In addition to better screening rates (e.g., for proteinuria, lipids) and lower hospitalization rates for the DSM patients, Domurat found that among both DSM patients and a comparison group of patients with diabetes who did not participate in the DSM program, patients whose laboratory results were within goal at baseline on average experienced worsened outcomes from baseline to follow-up (e.g., mean A1c declined from 7.0% to 7.5% in DSM), whereas among patients not in goal at baseline, outcomes improved (e.g., mean A1c declined by 1.3 points from 10.7% to 9.4% in DSM and by 2.4 points from 11.1% to 8.7% in usual care). Similar RTM patterns have been noted in other DSM program analyses but were often misinterpreted by study authors as programmatic effects. In contrast, in the Medicare Health Support (MHS) Chronic Disease Pilot Program, which randomized Medicare beneficiaries with heart failure or diabetes to a...
DSM program or a control (usual care) group, improvements in patient outcomes (hospitalization rates, health care costs) were observed in both study groups. A statistical analysis by MHS evaluators, Cromwell et al. (2008), appropriately assessed whether the declines were greater in the MHS DSM group compared with the control group, finding no significant between-group differences. Although previously reported weak observational analyses had calculated enormous (up to 14:1) return-on-investment estimates for DSM programs, the randomized MHS pilot results did not meet a key contractual requirement on-investment estimates for DSM programs, the randomized MHS pilot results did not meet a key contractual requirement set by the Centers for Medicare & Medicaid Services, “at least budget neutrality through the pilot’s first 12 months,” resulting in termination of the project in 2008. Notably, Cromwell et al. observed in an early report that “it appears that both disease groups are regressing to the mean with fewer subsequent admissions for the condition that qualified beneficiaries for the program,” and that the organizations providing DSM “may have substantially overestimated the success of their intervention in reducing other hospital admissions—at least relative to a randomly matched comparison group also regressing-to-the-mean.” When randomization is not possible, mathematical formulae to adjust observational results for RTM are available, but these are seldom used in the published managed care pharmacy literature.

2. Confounding. Among the most ubiquitous problems in observational research is confounding, sometimes called spurious association, in which the observed relationship between an independent variable and the outcome measures is partially or entirely attributable to a different factor that is systematically related to both the independent variable and the outcome. Sometimes, the problem is the “healthy adherer effect," in which both adherence to placebo and adherence to beneficial treatment are associated with positive outcomes. When observational analyses indicate that adherence to a particular treatment predicts positive outcomes, the results could be attributable to the treatment itself or to other causal factors for the outcome that are related to (but not caused by) treatment adherence (e.g., healthier diet, self-protective behaviors). Sometimes, the measured predictor is a marker for the confounding factor, severity of disease. For example, in an analysis that compared patients with versus without anemia, Nissenson et al. (2005) found that services clearly attributable to anemia (e.g., transfusions) represented only about 5%-11% of the between-group all-cause health care cost difference. The authors suggested 2 possible interpretations: either their classification algorithm had failed to measure the true cost of anemia, or anemia was a marker for advanced stage or severity of the underlying disease that qualified the patient for entry into the study sample, such as chronic kidney disease, human immunodeficiency virus, or congestive heart failure.

An interesting recent example of potential confounding because of a marker independent variable was provided in a study by Zoungas et al. (2010), which assessed the possibility that severe hypoglycemia had caused harm in patients assigned to the intensive glucose-lowering arms of ACCORD, ADVANCE, and the Veterans Affairs Diabetes Trial. In their analysis of the relationship between severe hypoglycemia and risks of macrovascular or microvascular adverse events in the ADVANCE study sample, Zoungas et al. found that severe hypoglycemia was associated not only with the risk of major macrovascular events (HR = 2.88, 95% CI = 2.01-4.12), major microvascular events (HR = 1.81, 95% CI = 1.19-2.74), cardiovascular death (HR = 2.68, 95% CI = 1.72-4.19), and all-cause death (HR = 2.69, 95% CI = 1.97-3.67), but was also significantly associated with a variety of respiratory, digestive, and skin conditions (P < 0.001). Noting the “range of adverse clinical outcomes” with which severe hypoglycemia was associated, Zongas et al. suggested that “it is possible that severe hypoglycemia contributes to adverse outcomes, but these analyses indicate that hypoglycemia is just as likely to be a marker of vulnerability to such events.”

3. Overreliance on Multivariate Analysis. Although performing multivariate analyses to adjust for confounding variables is important, sole reliance on multivariate statistical analysis is not a recommended method because bias and “residual confounding,” that is, confounding not reflected in measured variables, are possible. This problem has several implications. First, both adjusted and unadjusted results should be calculated and presented to enable readers to determine the effect of statistical adjustment on study findings. Second and related, a measure of the overall quality of the statistical model should be calculated and reported. Poor quality, such as a linear regression analysis that explains only 1% of the variance (i.e., R² = 0.01) or a logistic regression analysis that performs little better than random assignment in accurately predicting group membership (i.e., C-statistic of 0.50-0.60) is a sign that the analytic results may be compromised by unmeasured confounders. Third, interpretation of observational evidence should be cautious, taking into account the possibility of residual confounding. Common problems in statistical analyses performed to adjust for confounding factors in observational research include failure to explain covariate adjustments transparently, use of propensity-score matching without assessing the accuracy of the logistic regression model used in calculating the propensity score to predict treatment selection, and/or matching cohorts based solely on demographics and plan design rather than on relevant clinical factors.

4. Failure to Investigate Specific Associations. High-quality observational studies investigate the specific nature of the process underlying the association between the predictor variables and study outcomes, for example, whether an association of adherence with statins and all-cause health care costs is
attributable to hospitalizations for MIs and heart failure, versus hospitalizations for accidents or another outcome unlikely to be caused by statin treatment. Measurement of only all-cause utilization, rather than disease-specific utilization, in assessing study outcomes makes interpretation problematic.\textsuperscript{35}

In a related problem, one also sometimes sees research reports in which an author suggests that one factor might influence another, but actually measures and reports a different factor entirely. For example, in a 2007 study of drug therapy for depression, the authors noted an association between treatment with particular “first-line” drugs and favorable all-cause health care utilization patterns (increased physician visits, reduced hospitalizations, and no significant differences in emergency room [ER] visits).\textsuperscript{36} The authors speculated that the favorable side-effect profiles of the drugs might have improved antidepressant adherence, resulting in better outcomes; however, they did not provide any analyses to support that conclusion, such as an analysis of depression-related health care utilization or a “dose-response” analysis comparing outcomes for drugs with better versus worse side effects. Similarly, a cross-sectional analysis by Goldman et al. (2006) measured the associations between (a) copayments and medication compliance and (b) compliance and hospital and ER use; the authors then performed a simulation analysis of the changes in ER and hospital use that might be expected from copayment changes but did not actually analyze the relationship between either copayment (cross-sectionally) or copayment change (longitudinally) and hospital or ER utilization. Nonetheless, the authors concluded that changing copayments according to “therapeutic need” would “reduce hospitalizations and [ER] use.”\textsuperscript{37}

Less common but also problematic is the failure in retrospective analysis of administrative claims to investigate the time sequence in which events occurred,\textsuperscript{30} sometimes drawing conclusions that would potentially require the predictor event to occur after the study outcome. For example, in a retrospective observational analysis of patients with type 1 or type 2 diabetes in primary care, Menzin et al. (2010) measured the association between glycemic control, defined as average A1c value (sum of all A1c values obtained for each patient over a follow-up period of 1 to 5 years, divided by the number of tests), and diabetes-related hospitalizations during the same period.\textsuperscript{38} Although the hospitalizations could have occurred prior to the A1c tests intended to predict them, the study authors concluded that their results “showed a significant, positive, and graded relationship between 1-point A1c intervals and rates of diabetes-related hospitalizations.”\textsuperscript{38} Similarly, a frequently cited study by Sokol et al. (2005) assessed associations between medication adherence for several chronic conditions and medical utilization in several categories (disease-related and all-cause medical costs and hospitalizations), concluding that “for some chronic conditions, increased drug utilization can provide a net economic return when driven by improved adherence with guidelines-based therapy.”\textsuperscript{39} However, because the medication adherence and medical outcomes were measured during the same 12-month period, patterns of adherence or nonadherence could have occurred after the hospitalizations that they were intended to predict.

5. Selection Effect. A special category of confounding is selection effect, in which at least 1 factor associated with group selection is also systematically associated with study outcomes. Studies of programs to improve chronic disease care management have been affected considerably by this problem, often coupled with and exacerbated by an RTM effect, for 2 reasons.

First, patients may self-select into care management programs because they are especially motivated to improve their health outcomes; researchers may attribute the outcomes to the DSM program when, in reality, the outcomes may be partially attributable to the additional motivation. For example, in the Asheville Project studies of medication therapy management provided in community pharmacies, pre-intervention versus post-intervention comparisons were used.\textsuperscript{40-42} A 2008 report of an Asheville Project program for patients with hypertension and/or dyslipidemia noted that study patients “agreed to complete education classes related to cardiovascular risk reduction and to be matched with a participating care manager/coach with whom they would meet on a regular, long-term basis . . . as frequently as once a month.”\textsuperscript{42} Thus, the analysis was, in effect, limited to patients sufficiently motivated to make a substantial time commitment to chronic disease care. In the MHS, patients randomized to DSM could choose whether to participate; those participating were, on average, “healthier” and “less costly” at baseline than patients who were randomized to DSM but opted out.\textsuperscript{23}

Second, DSM programs sometimes target the highest-risk subsets of patients, commonly imposing program selection criteria such as recent hospitalization or emergency room use.\textsuperscript{10,21} When patients with extremely high resource utilization are selected for a program, the natural phenomenon of RTM is intensified, often erroneously making program results appear dramatic when a nonequivalent comparison group is used. Linden provides an interesting illustration of this phenomenon in an analysis of the average health care costs for patients with coronary artery disease who were enrolled in a health plan that provided no health management programs, such as DSM. Among those in the top cost quintile in 2001, mean costs dropped precipitously in 2002—by a remarkable $24,000—whereas for all other plan members (bottom 4 quintiles), costs increased by a modest $920 from 2001 to 2002.\textsuperscript{19} An observational analysis of a DSM program targeted to the highest-risk quintile would have found greatly improved outcomes for the DSM group compared with the lower-risk non-DSM patients, but the “results” of the analysis in Linden’s
example were achieved solely because of the differential effects of RTM on patients selected for high versus low baseline utilization (and without any DSM program at all).

6. No Reason Identified (Yet): Erroneous Conclusions Despite High Quality. In assessing observational results, researchers often point to criteria for assessing causality in epidemiologic studies. Although specific criteria vary, the most common and classic (dating back to analyses of the relationship between smoking and lung cancer in the 1960s) are as follows:43,44

- Consistency of association—a pattern that is consistently observed in multiple studies is more likely to be causal than a pattern documented in isolated studies;
- Strength of association—a statistically strong relationship is more likely to be causal than a weak one;
- Dose-response—a relationship is more likely to be causal if increasing doses of the predictive factor are associated with an increase in the outcome;
- Plausibility—a relationship is more likely to be causal when a plausible biologic explanation for it is known; and,
- Temporality—for A to cause B, A must precede B.

Despite the compelling logic of these 5 criteria, it is important to recognize that the Stratton et al. observational analysis of the relationship between A1c and complications of diabetes, which contributed to the ultimately refuted “lower-is-better” paradigm for A1c, met all 5. And, numerous analyses of seemingly every conceivable explanation for the negative results of “lower-is-better” in ACCORD have as of yet been unable to explain the findings. A March 2010 status report from the NHLBI noted that ACCORD researchers would “continue to analyze the ACCORD data to try to understand why these ‘intensive’ interventions did not reduce the rates of cardiovascular outcomes as hypothesized,” examining participant characteristics and drug effects, potentially to “generate ideas for future studies.”3 Thus, one of the many important lessons to be learned from ACCORD is methodological: even high-quality epidemiologic analyses may lead to conclusions about causality that ultimately prove to be erroneous, resulting in progression of knowledge.

Observation: It’s (Only) a Start

In a 2008 commentary on the need to assess quality of evidence in making treatment recommendations and decisions, developers of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for assessing evidence quality in treatment guideline creation reminded us that poor-quality evidence translated into weakly supported guidelines has at times led to suboptimal patient care and even to patient harm.45 Among the examples cited by the GRADE team was U.S. Food and Drug Administration (FDA) approval of the antiarrhythmic agents encainide and flecainide “on the basis of the drugs’ ability to reduce asymptomatic ventricular arrhythmias associated with sudden death;” however, “because arrhythmia reduction reflected only indirectly on the outcome of sudden death,” the quality of the evidence was low. An RCT conducted after approval showed that the drugs increased the rate of sudden death, and “appropriate attention to the low quality of the evidence would have saved thousands of lives.” Similarly, the GRADE team argued that “expert recommendations lagged a decade behind the evidence from well conducted [RCTs] that thrombolytic therapy achieved a reduction in mortality in [MI].”46

For patients and clinicians, the stakes in the assessments of scientific evidence about treatments for chronic disease are high. As editorialists Montori and Fernández-Balsells (2009) noted in their call for “an evidence-based about-face” on glycemic control in type 2 diabetes: “Although we should not dismiss potentially effective approaches (for example, early tight glycemic control for patients with newly diagnosed diabetes), we require additional research to confirm or refute such approaches before we impose them on patients.”46

Sometimes, the results of observational studies and RCTs are consistent, as were the secondary analysis of INVEST data by Cooper-DeHoff et al.5 and the ACCORD blood pressure RCT;2 but sometimes, they are not, and it is not possible to predict RCT outcomes with certainty. In addition to reminding us—again—of the importance of evidence grading systems in policymaking, recent RCT findings from ACCORD, ADVANCE, and rigorous studies of chronic disease management interventions should highlight the importance of humility in our interpretations, especially of epidemiological associations and other observational evidence.

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Why Hypotheses Informed by Observation Are Often Wrong: Results of Randomized Controlled Trials Challenge Chronic Disease Management Strategies Based on Epidemiological Evidence


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A Systematic Review of the Impact of Treatments on Quality of Life, Work Productivity, and Adherence in Multiple Sclerosis

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BACKGROUND: Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system and is one of the most common causes of neurological disability. Although no curative treatments exist for MS, the development and availability of new immunomodulator drugs has increased optimism in curbing the progression of the disease. However, these treatments are associated with side effects that in turn impair the patient’s quality of life (QoL). While most MS treatments have been shown to be well tolerated in clinical trials, patients may find long-term, chronic use to be inconvenient, especially with injectable drugs, or have side effects that in turn impair the patient’s quality of life (QoL). While most MS treatments have been shown to be well tolerated in clinical trials, patients may find long-term, chronic use to be inconvenient, especially with injectable drugs, or have side effects that in turn impair the patient’s quality of life (QoL).

OBJECTIVE: To review studies assessing the impact of treatments on QoL, work productivity, and adherence among patients with MS.

METHODS: MEDLINE, EMBASE, Cochrane Library Databases, Evidence-Based Medicine Reviews, and International Pharmaceutical Abstracts were searched from January 1990 to March 2010. Articles were included in the final review if they evaluated the impact of MS treatments on patients’ humanistic outcomes.

RESULTS: The initial search yielded 85 articles. After a detailed review, only 10 articles met the inclusion/exclusion criteria and were subjected to the final review. Seven studies dealt with QoL, 2 with adherence, and only 1 with work productivity. Interferon beta 1a and 1b were found to improve patient’s QoL, whereas treatment side effects were not shown to lead to drug discontinuation or interfere with QoL. Only 27%-41% of patients were reported to be adherent (medication possession ratio > 85%) and had significantly lower risk of relapse compared to a less adherent group. Glatiramer acetate was associated with a significant improvement in fatigue symptoms and a reduction in absence from work.

CONCLUSIONS: Overall, the humanistic impact of MS treatments does not appear to have been fully explored in the U.S. population. A need exists for longitudinal studies to assess the global impact of MS therapies on patient’s QoL, adherence, ability to work, and work productivity. Understanding the intangible and indirect costs of MS treatment will aid in the valuation of newer MS agents. Decision makers and patients need greater empirical evidence to understand the value and impact of new and existing MS therapies.

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Adherence to Antiretroviral Therapy and the Association with Risk of Hospitalization Among Commercially Insured HIV Patients in the United States

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BACKGROUND: A lower daily pill burden has been shown to improve adherence to antiretroviral therapy (ART).

OBJECTIVE: To assess differences in ART adherence according to the number of pills prescribed per day and to evaluate the relationship between adherence and hospitalization risk.

METHODS: Commercially insured patients in the United States from the MarketScan claims database with a diagnosis of HIV/AIDS between June 1, 2006, and December 31, 2008, and who received a complete ART regimen (i.e., 2 nucleoside/nucleotide reverse transcriptase inhibitors [NRTIs] along with a third agent [non-NRTI: protease inhibitor, CCR5 antagonist, or integrase inhibitor]) were included. Patients were grouped according to the daily ART pill count: 1, 2, or 3 or more pills a day and were required to receive the regimen for at least 60 days. Outcomes included adherence (absolute and at pre-specified thresholds) and frequency of hospitalization. Adherence was measured as a proportion (medication possession ratio), calculated as the total days supplied divided by the days between the start and end of the regimen. Logistic regressions were undertaken to assess the relationship between pills per day, adherence, and hospitalization while controlling for demographics, comorbidities (including substance abuse and mental illness), and ART-naive versus experienced status.

RESULTS: 10,620 patients met the study inclusion criteria, of whom 43.0%, 48.8%, and 52.3% received 1, 2, or 3 or more pills a day, respectively. 1,562 (12.8%) patients were excluded because they were dispensing an incomplete regimen. Approximately 45% of patients receiving a 1 pill a day regimen achieved ≥95% adherence versus 40% of patients receiving 2 pills a day, and 36% of patients receiving 3 or more pills a day. Based on logistic regression results, patients receiving 1 pill a day were 47% more likely to reach a 95% adherence threshold versus patients receiving 3 or more pills a day (odds ratio [OR] = 1.47, P < 0.001). Regardless of the number of pills received per day, patients were nearly 40% less likely to have a hospitalization if they were adherent to therapy (OR = 0.62, P < 0.001). Patients receiving 1 pill a day were 20% less likely to be hospitalized versus patients receiving 3 or more pills a day (OR = 0.81, P < 0.01).

CONCLUSIONS: After controlling for potential confounding factors, we found receiving a 1 pill a day ART regimen correlated with better adherence and a lower likelihood of hospitalization.

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Adherence, Persistence, and Medical Costs Associated with the Use of Clinically Effective Doses of Antipsychotic Medications in Patients with Bipolar Disorder

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BACKGROUND: Subtherapeutic dosing of second-generation antipsychotics (SGAs) in patients with bipolar disorder may result in...
suboptimal disease control. Evidence is needed to better understand the clinical and economic outcomes of patients receiving clinically effective doses of SGAs.

**OBJECTIVE:** To compare adherence, persistence, and costs in patients receiving clinically effective doses of SGAs.

**METHODS:** Patients with bipolar disorder diagnoses (ICD-9-CM codes 296.0x, 296.1x, 296.4x, 296.6x, 296.81) taking an oral SGA were identified in Medicaid claims databases. They were followed for 18 months (6-month pre-index, 12-month post-index). For patients on effective dosing utilization, adherence (medication possession ratio [MPR] $\geq 80\%$), and persistence (days of therapy before a 30-day gap) were calculated. These rates were compared utilizing a logistic and Cox proportional hazard model, respectively. Four post-index costs were calculated: mental health prescription costs, all prescription costs, all mental health costs, and all costs. Costs were compared using a generalized linear model with a gamma distribution and log-link function. A significance level of $P<0.05$ was used for all analyses. Ziprasidone was used as the comparator group.

**RESULTS:** 2,446 patients met inclusion criteria, with 45% ($n=1,102$) taking clinically effective doses after 2 months: aripiprazole 77%, ziprasidone 58%, olanzapine 52%, risperidone 50%, and quetiapine 26%. Of these patients, 58% ($n=642/1,102$) were adherent with their SGA treatment: ziprasidone 62%, aripiprazole 60%, olanzapine 58%, risperidone 58%, and quetiapine 55%. However, there were no significant differences for adherence by index medication. Median time-to-non-persistence was 96 days for all SGAs; 112 days for quetiapine, 117 days for ziprasidone, 93 days for aripiprazole, 95 days for risperidone, and 72 days for olanzapine. Patients taking olanzapine were more likely to discontinue their medication compared with patients taking ziprasidone (HR = 1.35, 95% CI = 1.03-1.79, $P=0.032$). Compared to ziprasidone, mental health-related prescription costs ($P<0.002$) and all prescription costs ($P=0.003$) were statistically lower for the risperidone group. There were no statistical differences between the groups for mental health-related or all-cause costs.

**CONCLUSIONS:** Less than 50% of patients started on an SGA were taking clinically effective doses 2 months after initial therapy. Of these patients, less than two-thirds were adherent for 1 year after their SGA start date. Although patients taking risperidone had lower prescription costs, there were no other significant cost differences compared to ziprasidone.

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**Assessing Self-Reported Quality of Life and Productivity Among Employees with Select Auto-Immune Inflammatory Disorders**

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**BACKGROUND:** Auto-immune inflammatory disorder (AIID) is a concept collectively used to describe a group of conditions that share common inflammatory pathways. The prevalence of AIID diseases is 4%-7% in the United States, and an individual with 1 AIID has a greater risk of having another AIID. The most examined of the diseases in this category are rheumatoid arthritis (RA), with a national U.S. prevalence between 0.5%-1.0%; ankylosing spondylitis (0.2%-0.9%); psoriasis (0.34%-2.0%); Crohn’s disease (0.12%-0.20%); ulcerative colitis (0.25%-0.50%); and psoriatic arthritis (0.10%-1.0%). While these autoimmune disorders represent complex disease states with varying and unrelated symptoms, they all evidence a common pathology and underlying causality. Yet, the diseases that represent AIIDs are generally considered as separate entities by payers, employers, and health care professionals. Biologics such as anti-TNF agents are most commonly used in the management of all of the 6 AIIDs. These medications carry a direct medical cost burden for both employers and payers. Both employers as well as payers can benefit from understanding the total health care and economic burden of AIIDs as these conditions have shown signs of notable impact in working age populations (mean ages between 44-55 years of age). In order to get a complete picture of total health care costs, productivity, work loss, disability, and indirect costs of lost productivity must also be considered, including employee self-reported work loss such as presenteeism. Few studies have looked at the total health care costs burden of AIIDs from an employer’s perspective. AIIDs are known to result in absenteeism and disability and are high-cost drivers for employers, but their impact on presenteeism and related factors such as quality of life are not well understood.

**OBJECTIVE:** To assess the impact of AIIDs on workforce productivity through employee self-reports at a large self-insured employer.

**METHODS:** A 15- to 20-minute survey was conducted during the 2009 annual flu shot campaign at Navistar, Inc., to obtain a representative sample of its U.S. active employees. Participants were asked about their health status, health risks/behaviors, disease status and severity/symptoms, job satisfaction, and work productivity. Three auto-immune conditions were selected for analysis: RA, psoriasis, and irritable bowel disease (IBD).

**RESULTS:** Of the active employees, 4,974 (49.8% response rate) completed the survey—3,370 (67.8%) via the online version and 1,604 (32.2%) via a paper version. 206 (4.2%) reported being diagnosed with
RA, 148 (3.0%) with psoriasis, and 62 (1.2%) with IBD. A total of 26 employees reported 2 or more of these diagnoses. Notable levels of job dissatisfaction (36%) and stress (22%) were reported across all 3 conditions. Nearly 75% of the RA cohort reported symptoms in the higher severity range versus 18% for psoriasis and 27% for the IBD cohort (P < 0.01). The RA cohort also reported, on average, a greater number of comorbidities (P < 0.01). Aggregated AIID scores on health and productivity outcomes showed a significant worsening with higher symptom severity (see table).

CONCLUSIONS: As reflected in these symptom severity stratifications, a feature reflecting a unique strength of the self-report method, AIID scores exert a notable burden on workforce health (physical and mental), health-based utilities, and productivity in this workforce. Symptom severity and comorbidities play key roles in this burden. Self-reported quality of life and productivity can be used to measure health and productivity of the workforce.

SPONSORSHIP: This research was conducted by Centocor Ortho Biotech Services, LLC.

Assessment of Contraceptive Budget Impact in a U.S. Health Plan Formulary Setting

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BACKGROUND: Current available contraceptive methods vary greatly in efficacy and overall costs. Although long-acting methods, such as intrauterine systems/devices (IUS/IUD) and implants, may have higher upfront medication costs than short-acting methods, such as oral contraceptives (OC), the latter may incur greater medical failure-related costs due to their dependence on user compliance.

OBJECTIVE: To develop a framework to estimate the potential cost savings from the introduction of an IUS in a U.S. health plan’s formulary setting.

METHODS: A budget impact model (BIM) was developed to assess the potential cost savings using a before-and-after comparison approach. Multiple contraceptive methods, up to a maximum of 8, can be selected across an adjustable time horizon between 1 and 5 years. The number of women using contraception was calculated from the U.S. Census and the National Survey of Family Growth. Contraceptive failure rates (i.e., pregnancies, induced abortions, live births, spontaneous abortions, and ectopic pregnancies) were derived from product labeling and published literature. Total costs included drugs, administration, physician visits, and contraceptive failures. Pharmacy costs were based on wholesale acquisition cost (WAC), whereas medical costs were based on Medicare Reimbursement Rate for physicians. Model outputs included annual health plan cost, per member per month (PMPM) costs, and per treated member per month costs.

RESULTS: Assuming a 5% weighted increase in the number of women using IUS from branded OC, generic OC, injectable contraceptive, vaginal ring, transdermal patch, and implant in a hypothetical cohort of 1 million plan members for a 3-year time frame, the model estimates a reduction in total annual cost by $1.8 million and 1,066 contraceptive failures, translating into a cost savings of $0.05 PMPM. Potential cost savings could range from $0.02 PMPM to $0.10 PMPM, depending on different possible scenarios.

CONCLUSIONS: Long-acting contraception methods, such as IUS, are highly effective in preventing large numbers of unintended pregnancies leading to cost savings of the health plan formulary budget.

SPONSORSHIP: This research was funded by Bayer HealthCare Pharmaceuticals, Inc., Wayne NJ.

Assessment of Medication Utilization Before and After Initiation of Pregabalin Utilizing a Pharmacy Claims Database

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BACKGROUND: Pregabalin is indicated as adjunctive therapy for adult patients with partial onset seizures, management of neuropathic pain associated with painful diabetic peripheral neuropathy, the management of pain associated with postherpetic neuralgia, and the management of fibromyalgia. Patients treated for these conditions often require multiple medications.

OBJECTIVE: To use pharmacy claims to assess the use of selected medications prescribed in addition to pregabalin.

METHODS: De-identified data were extracted from a pharmacy claims database for 4 plans (n = 414 patients) with differing co-pays for pregabalin. The pregabalin claim served as the index event, and patients were their own controls. Changes in adjunct medication utilization for 6 drug classes were evaluated 6 months pre- and post-initiation of pregabalin therapy.

RESULTS: Total cost of therapy increased by approximately 50% (range 38%-67%) per patient with the addition of pregabalin. On average, at least 1 medication was added to a patient’s profile in addition to pregabalin. Use of anti-anxiety agents, antidepressants, and non-narcotic analgesics did not seem to be impacted by the addition of pregabalin. Utilization of anti-inflammatory analgesics and musculoskeletal therapy agents was inconsistent. Utilization of migraine medications decreased in all plans. Utilization did not seem to be associated with co-pay. The number of patients receiving opioids decreased in the majority of plans; however, costs for opioids were mixed. Patients who received greater than a 20-day supply of opioids typically filled these prescriptions following the pregabalin index date (range 16-27 days). Doses for opioids and anticonvulsants increased in all plans. The average starting dose of pregabalin for all plans was ~150 mg per day. The average dose for the last prescription of pregabalin was less than 300 mg per day. The reduction of gabapentin utilization following the initiation of pregabalin was lower than expected ranging from 5%-31% following pregabalin initiation. In all plans, medication possession ratios (MPRs) were greater than 0.8 for pregabalin, indicating good adherence. There was no association between pregabalin dose and adherence.

CONCLUSIONS: Analysis of the pharmacy claims data of 4 plans demonstrated an increase in total costs with the addition of pregabalin and failed to show a consistent reduction in medication utilization including gabapentin.

SPONSORSHIP: This research was conducted by informedRx, an SXC Company, Lisle, IL, without external funding.

Association Between Medication Nonadherence and Indirect Costs Among Patients with GERD

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BACKGROUND: Although proton pump inhibitors and other medications may effectively treat gastro-esophageal reflux disease (GERD), nonadherence to such treatments may have an impact on work productivity thereby potentially leading to a higher indirect cost.

OBJECTIVE: To assess medication adherence and total indirect costs among GERD diagnosed patients on pharmacotherapy showing diurnal and nocturnal heartburn symptoms (group 1), diurnal-only symptoms (group 2), and nocturnal-only symptoms (group 3), along with the association between medication adherence and indirect costs.
METHODS: Data were analyzed from January 1, 2010, through June 30, 2010 (N=50,000 waves), using the National Health and Wellness Survey, a nationally representative dataset of U.S. adults. Medication adherence was assessed among the 3 groups using the GERD-specific Morisky Medication Adherence Scale (0=adherent vs. 1=nonadherent). Absenteeism (hours of work missed due to health) and presenteeism (hours missed due to on-the-job impairment because of health) among the 3 groups were included in annual total indirect cost calculations using the Work Productivity and Activity Impairment questionnaire. The association between total indirect costs and adherence was estimated using a generalized linear regression model specifying a negative binomial distribution, controlling for several potential confounders.

RESULTS: A total of 4,344 patients were included, group 1: n = 2,847; group 2: n = 486; and group 3: n = 1,011. Group 1 patients were younger (53.1 (SD = 13.9) vs. 59.3 (15.0) vs. 58.1 (13.7) years, P < 0.001), comprised of more African-Americans (7.9% vs. 5.8% vs. 5.9%; P < 0.01), smokers (22.2% vs. 13.8% vs. 15.6%; P < 0.01), and reported significantly lower levels of adherence (58.9% vs. 66.6% and 62.9%; P < 0.001) versus group 2 and 3 patients, respectively. The annualized unadjusted 2010 total indirect costs was significantly higher for group 1 patients [$4,343 (SD = $9,508)] versus group 2 [$3,729 (SD = $9,208)] and 3 patients [$3,449 (SD = $8,503)], P < 0.001. The multivariate regression model predicted that medication nonadherence was associated with 20.0% higher total indirect costs ($9,997.1 vs. $8,248.6, P = 0.016).

CONCLUSIONS: The results suggest that in comparison to GERD patients with diurnal-only and nocturnal-only heartburn symptoms, the high annualized total indirect costs associated with patients with diurnal and nocturnal symptoms could be potentially mitigated through improved medication adherence.

SPONSORSHIP: This research was funded by Eisai, Inc., Woodcliff Lake, NJ.

Association of Chemotherapy-Induced Peripheral Neuropathy with Chemotherapy Treatment and Costs for Metastatic Breast Cancer Patients: A Claims Database Analysis
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BACKGROUND: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting toxicity of many chemotherapy agents but is poorly quantified, and effects on treatment and health care costs are not well understood.

OBJECTIVE: To examine the incidence of CIPN and the association with chemotherapy treatment and health care costs among women with metastatic breast cancer.

METHODS: A claims-based analysis was conducted using data from January 2005 to December 2008 from a national commercial health insurer. Patients aged 18 years and older, with at least 2 claims each for breast cancer and metastatic disease, and who received chemotherapy, were identified. The first chemotherapy episode (first chemotherapy administration to the last without a gap of 60 days or more), was examined. No specific ICD-9-CM codes exist for CIPN. Patients were identified with CIPN if they had codes for peripheral neuropathy; all others were in the No-CIPN cohort. Descriptive statistics compared characteristics and all-cause health care costs between cohorts. Multivariate analyses examined CIPN association with dose delay, dose frequency change, medication switching, and discontinuation.

RESULTS: Among 1,821 patients identified, 70 (3.8%) had evidence of CIPN. Demographics were similar between cohorts except that CIPN patients had a higher Charlson comorbidity index (6.94 vs. 6.64, P = 0.01). Compared to the No-CIPN cohort, CIPN patients had significantly longer chemotherapy episodes, which resulted in higher health care costs ($100,293 vs. $59,123, P = 0.001). A greater proportion of CIPN patients received drugs or procedures associated with CIPN management: anticonvulsants (36% vs. 26%), physical therapy (27% vs. 12%), occupational therapy (14% vs. 4%), electromyography (6% vs. < 1%), nerve conduction (7% vs. < 1%), neurologist visit (19% vs. 6%), P < 0.05. Multivariate analyses demonstrated that CIPN patients were more likely to switch from index chemotherapy (OR = 2.69, 95% CI = 1.62-4.47). There was no difference between cohorts for dose delay, dosing interval modification, or discontinuation.

CONCLUSIONS: Since no CIPN codes exist, the incidence here is conservative, and CIPN is likely under-reported in clinical practice. CIPN patients more often experience changes in administered chemotherapy from index agents (likely the planned regimen), have longer chemotherapy episodes, and incur higher health care costs.

SPONSORSHIP: This research was funded by Eisai, Inc., Woodcliff Lake, NJ.

Assuring Safe and Cost-Effective Buprenorphine Use
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BACKGROUND: Since January 2009, the number of members who have had Suboxone/ Subutex/ buprenorphine pharmacy claims has increased 4-fold. This increase shows a growth in the number of members who have an opioid drug addiction problem and/or an increase in the number of members using Suboxone/ Subutex/ buprenorphine as addiction treatment. Most often, the Suboxone/ Subutex/ buprenorphine prescriptions are written by a provider different than the provider prescribing opioids and/or tramadol. A drug utilization review (DUR) application identifies fully insured members who have Suboxone/ Subutex/ buprenorphine pharmacy claims and concurrent opioid and/or tramadol pharmacy claims.

OBJECTIVE: To notify the Suboxone/ Subutex/ buprenorphine provider via letter or telephone about the simultaneous Suboxone/ Subutex/ buprenorphine and opioid and/or tramadol use. The program attempts to ensure safe and cost-effective Suboxone/ Subutex/ buprenorphine use.

METHODS: Through the DUR application, letters are mailed, including a medication history profile and a fax prescriber response feedback form. In addition, a toll-free telephone number is included where a fraud/abuse pharmacist, who is dedicated to overseeing Suboxone-opioid program, may be reached. The future operations of the Suboxone-opioid program will include outbound follow-up phone calls to the Suboxone/ Subutex/ buprenorphine prescribers, a process to evaluate denying future opioid pharmacy claims, locking the member into filling prescriptions at 1 pharmacy location, locking the member into obtaining prescriptions from only 1 provider, and referring members to behavioral health and/ or special investigations unit (SIU) areas when needed.

RESULTS: The number of opiate pharmacy claims for members who have Suboxone/ Subutex/ buprenorphine claims also increased since May 2009 from approximately 600 opioid and/or tramadol pharmacy claims per week to more than 1,000 opioid tramadol pharmacy claims weekly in June 2010. Since June 2010, when the Suboxone-opioid program was implemented, the number of opioid and/or tramadol pharmacy claims has remained steady at approximately 1,000 claims per week.

CONCLUSIONS: Implementation of the Suboxone/ opioid program in June 2010 has contributed over time to opioid and/or tramadol pharmacy claims not increasing. With future enhancements, the Suboxone-opioid program should have more capability to ensure
appropriate and safe Suboxone/ Subutex/ buprenorphine use while improving overall drug costs.

SPONSORSHIP: This research was funded by Aetna Health Insurance Company, Hartford, CT.

Barriers and Facilitators for Medication Adherence

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BACKGROUND: Literature has shown many patients do not adhere to prescribed medications. To help understand factors related to medication adherence, we conducted a survey of adherent and nonadherent patients.

OBJECTIVE: To determine factors that serve as barriers and facilitators to medication adherence for patients with diabetes and asthma.

METHODS: We identified all members > 18 years with at least 2 prescription fills for > 28 days supply from January 2007 to March 2009. We focused on medications (n=128) to treat depression, hypertension, hyperlipidemia, diabetes, asthma/COPD, multiple sclerosis, cancer, or osteoporosis. Diagnoses were identified by ICD-9-CM code and merged with pharmacy claims. Adherence was calculated by the medication possession ratio at a threshold of 80%. Adherence was lowest among those with diabetes (51%) and asthma (32%). We randomly selected 500 individuals with each condition to survey, half of whom were adherent and half who were not. Using the ASK-20 questionnaire as our basis, we added questions about facilitators and barriers to adherence.

RESULTS: Approximately 30% of patients forget to take their medications, 16% run out of medication because they don't refill in time, and 22% had taken a medication more or less than prescribed in the past month. Barriers most commonly noted were an irregular schedule (22%), having to take pills with food (13%), and being too busy to keep prescriptions filled (12%). Facilitators most frequently reported were taking medications at the same time daily (95%) and using a weekly pill reminder (47%). We are currently analyzing open-ended comments to identify additional barriers and facilitators. We will also conduct a subgroup analysis (e.g., by gender, age).

CONCLUSIONS: Building routine into medication-taking behavior appears to be a key factor for adherence. Finding ways to help patients in this effort is an important consideration for health plans to promote adherence. This study will help guide discussion within the health plan’s pharmacy team to enhance adherence and maximize the benefits of prescribed therapies.

SPONSORSHIP: This research was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Baseline Characteristics of Patients with Rheumatoid Arthritis Initiating Anti-TNF Therapy

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BACKGROUND: Large claims databases may be used for comparative effectiveness research (CER). However, nonrandom treatment selection may bias CER. Selection of anti-tumor necrosis factor (TNF) therapy for the treatment of rheumatoid arthritis (RA) may be influenced by patient demographics, history, and health status. Understanding differences in baseline patient characteristics may aid in the interpretation of CER.

OBJECTIVE: To describe differences in demographics and comorbid conditions in RA patients initiating adalimumab, etanercept, and infliximab across multiple large claims databases in the United States.

METHODS: Patients were identified at time of biologic initiation from 5 retrospective claims databases: HealthCore Integrated Research Database (July 2004 through October 2008), i3, a division of UnitedHealth Group (January 2005 through June 2006), IMS LifeLink Health Plan Claims Database (January 2004 through December 2007), MarketScan Commercial and Medicare Supplemental Claims Databases (January 2003 through June 2008); and Wolters Kluwer Pharma Solutions (WKPS) databases (January 2004 through December 2007). Inclusion criteria were aged ≥ 18 years, at least 2 RA diagnosis codes (ICD-9-CM codes 714.xx), with no biologic therapy in the 6 or 12 months prior to current therapy, and no select, inflammatory conditions. In the HealthCore, IMS LifeLink, and MarketScan datasets, patients also persisted on therapy for 1 year.

RESULTS: Across individual anti-TNF agents in all databases, 75% to 79% of patients were female. Infliximab patients were older and had a greater proportion of patients aged ≥ 65 years at initiation than adalimumab and etanercept patients. Infliximab patients also appeared to have greater comorbidity burden as measured by various adaptations of the Charlson Comorbidity Index.

CONCLUSIONS: Results across multiple databases substantiate that infliximab patients are older and experience greater comorbidity burden at time of anti-TNF initiation than adalimumab and etanercept patients. These baseline differences should be considered in any comparative effectiveness analysis.

SPONSORSHIP: This research was conducted by Centocor Ortho Biotech Services, LLC, Horsham, PA, without external funding.

Budget Impact of Erlotinib for Maintenance Therapy in Advanced Non-Small Cell Lung Cancer

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BACKGROUND: Erlotinib was recently approved for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy by the FDA.

OBJECTIVE: To assess the budgetary impact of adding erlotinib for maintenance therapy (MTx) in advanced NSCLC from a U.S. health plan perspective.

| TABLE Patient Characteristics by Anti-TNF Agent Across Multiple Databases |
|-----------------------------|-----------------------------|-----------------------------|
|                             | Adalimumab | Etanercept | Infliximab |
| Sample Sizes, n             |             |             |             |
| HealthCore                  | 621         | 1,281       | 938         |
| i3                          | 601         | 785         | 394         |
| IMS LifeLink                | 1,279       | 2,277       | 1,330       |
| MarketScan                  | 3,417       | 4,898       | 2,226       |
| WKPS                        | 11,791      | 19,034      | 13,080      |
| Aged 65 Years or Older      |             |             |             |
| HealthCore                  | 10%         | 7%          | 41%         |
| IMS LifeLink                | 17%         | 17%         | 42%         |
| i3                          | 10%         | 7%          | 13%         |
| MarketScan                  | 23%         | 20%         | 32%         |
| WKPS                        | 25%         | 21%         | 45%         |
| Comorbidity Index, Mean     |             |             |             |
| HealthCore (Deyo-Charlson)  | 1.2         | 1.3         | 1.3         |
| i3 (Charlson-Quadit)        | 1.2         | 1.2         | 1.3         |
| MarketScan                  | 1.4         | 1.4         | 1.4         |
| WKPS                        | 0.8         | 0.8         | 1.3         |

TNF=tissue necrosis factor, WKPS=Wolters Kluwer Pharma Solutions.
METHODS: A budget impact model was developed to analyze the costs associated with adding erlotinib MTx to a hypothetical U.S. health plan with 500,000 members. Treatment durations and dosing were derived from randomized controlled trials, FDA labeling, and National Comprehensive Cancer Network guidelines. Treatment patterns and assumptions were based on market research data and publicly available sources, including the Surveillance Epidemiology and End Results (SEER) registry and published articles. Cost data were obtained from the 2010 Centers for Medicare & Medicaid Services payment rates and a drug-pricing database. Sensitivity analyses were conducted to assess uncertainty.

RESULTS: Adding erlotinib MTx to the formulary was estimated to increase overall health plan expenditures by $0.012 per member per month (PMPM). The main driver of additional cost was the erlotinib drug cost (approximately $73,000 per 500,000-person health plan) with the estimated administration ($516) and side effect ($52) costs being relatively modest. The use of erlotinib MTx also shifted the use of subsequent therapies. One-way sensitivity analyses showed that the results were most sensitive to the proportion of members receiving MTx; however, the PMPM-added costs did not exceed $0.015.

CONCLUSIONS: At time of anti-TNF therapy initiation, infliximab patients are older, have more severe disease, carry greater comorbidity burden, and are more likely to have insurance through Medicare than adalimumab or etanercept patients. Comparative research of individual anti-TNF therapies should adjust for these population differences.

SPONSORSHIP: This research was conducted by Centocor Ortho Biotech Services, LLC, Horsham, PA, without external funding.

Clinical and Economic Outcomes in Patients with Type 2 Diabetes Initiating Insulin Glargine Using Disposable Pen Versus Exenatide

METHODS: This retrospective study used data from a large U.S. managed care claims database and included type 2 diabetes patients initiating treatment with the 1:1 matched cohort (exenatide: 1,958); 626 patients were in the 1:1 matched cohort. The study endpoints included treatment persistence, A1c, health care utilization, and cost removed observed baseline treatment-group differences. Primary study endpoints included treatment persistence, A1c, health care utilization, and cost during the 1-year follow-up period and were compared between treatment groups.

RESULTS: A total of 2,339 patients were included in the study (IG pen: 381, exenatide: 1,958); 626 patients were in the 1:1 matched cohort with no significant differences in baseline characteristics between groups (54% male, mean age 54; A1c 9.2%). At the end of the 1-year follow-up, patients in the IG pen group were significantly more persistent in treatment compared with the exenatide group (48% vs. 13% in persistence rate and 252 vs. 144 days in persistent days, both P<0.001). They also had significantly lower A1c at the end of

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follow-up (8.02% vs. 8.32%, P=0.042) and higher A1c reduction from baseline (−1.23% vs. −0.92%, P=0.038). There were no significant differences in hypoglycemia rates and overall diabetes-related health care utilization and cost. Compared with the exenatide group, patients using the IG pen had significantly higher diabetes-related outpatient ($1,673 vs. $1,473, P=0.033) and diabetes supply ($282 vs. $161, P<0.001) costs, although these were offset by significantly lower diabetes pharmacy cost ($2,106 vs. $2,438, P=0.001).

CONCLUSIONS: This study suggests that in a real-world setting among type 2 diabetes patients who failed OADs, initiation of IG pen instead of exenatide may be associated with greater persistence and improved clinical outcomes without increased hypoglycemia or cost. These findings need to be confirmed in further clinical studies.

SPONSORSHIP: This research was funded by sanofi-aventis, Bridgewater, NJ.

Collaborative Pharmacist-Based Managed Care Community Project to Improve Medical Services and Prescription Drug Utilization in Diabetic Patients

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BACKGROUND: Diabetes has the fifth highest mortality in the United States with $132 billion spent annually on treatment. Few studies have incorporated a pharmacist-based managed care collaborative effort to control cost associated with diabetes treatment.

OBJECTIVE: To evaluate managed care initiated pharmacist-based diabetes management program to improve medical services and prescription drug utilization.

METHODS: This short-term longitudinal, retrospective study used data collected in a managed care-associated community pharmacy project in 2007 and 2008. Selected pharmacists were trained to provide diabetes management, including prescription drug use and lifestyle and diet modification counseling, to patients visiting participating pharmacies from January to December 2008. Prescription and medical claims data for cases and controls (matched on baseline gender, age ±5 years, hemoglobin A1c ±0.1%, and cholesterol levels at index) was obtained. Cases with 3 or more follow-up visits to pharmacists were included. Differences in resource utilization and cost between cases and controls were compared using descriptive statistics and t-tests [SAS version 9.2].

RESULTS: A total of 66 (20.4%) cases and 258 (79.6%) controls were identified. Mean (SD) age for cases and controls was 47.37 (11.98) and 47.43 (13.09) years, respectively. There were 54.69% and 50.78% females among cases and controls, respectively. Cases had significantly more (P<0.001) drug claims per patient in 2008 (46.5±54.9) than in 2007 (33.0±53.9) and compared to controls (25.1±40.6) in 2008 (P<0.001). Reciprocally, drug cost per patient for cases was significantly (P<0.001) higher in 2008 ($4,759.3±3,060.4) than in 2007 ($3,011.6±$2,118.5) and compared to controls ($2,897.2±$3,584.7) in 2008. However, medical claims per patient for cases in 2008 (54.9) did not differ significantly from 2007 (53.9) and from controls in 2008 (40.6). Similarly, medical cost per patient for cases although lower in 2008 ($11,549.7) did not differ significantly from 2007 ($14,669.4) and from controls in 2008 ($15,951.5). Although not significant, total cost per patient in cases was lower in 2008 ($16,309.0) than in 2007 ($17,681.1) and compared to controls ($18,848.7) in 2008. However, controls had significantly higher total cost (P<0.05) in 2008 ($18,848.7±$46,234.5) than in 2007 ($13,730.23±$27,724.5).

CONCLUSIONS: Although pharmacist-based diabetes management intervention increases short-term costs associated with prescription drug utilization, overall economic burden associated with diabetes may be reduced due to reduced medical service utilization and costs.

SPONSORSHIP: This research was conducted by the University of Houston, College of Pharmacy, Houston, TX, without external funding.

Communicating Value-Based Incentives to Promote Mail Order Services

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BACKGROUND: Reducing cost shares for chronic medications in value-based (VB) prescription benefit designs has been shown to improve adherence and provide savings for members and organizations alike. Some health plans tie financial incentives to their preferred pharmacies (e.g., mail order), possibly limiting the volume of members who may want to take advantage of the prescription benefit. Incentives alone may not directly increase preferred pharmacy utilization. However, raising awareness of potential savings may motivate members to switch pharmacies for lower cost shares.

OBJECTIVE: To evaluate the impact of communicating specific savings to members via personalized letters on the utilization of Group Health (GH) Cooperative’s preferred pharmacies.

METHODS: Claims data were used to identify members with the VB benefit filling prescription VB drugs from nonpreferred, contracted pharmacies. These drugs would be discounted to a zero dollar copay if filled by the GH mail order pharmacy or with a $5 copay when filled through a GH clinic pharmacy. Ninety-two eligible subjects were randomly assigned to the control or intervention groups. All subjects were sent personalized letters. Ninety-two eligible subjects were randomly assigned to the control or intervention groups. All subjects were sent personalized letters.

OUTCOMES were the proportions of prescriptions filled at mail order or in GH’s preferred pharmacies post-intervention, with the patient as the unit of analysis and weights proportional to the total number of post-intervention prescriptions. Estimated marginal means were reported for 10 separate regressions run for 2 outcomes and 3 time periods: 45, 90, and 135 days post-intervention. Covariates included baseline

### Linear Regression Analysis of Pharmacy Utilization Post-Intervention

<table>
<thead>
<tr>
<th>Pharmacy Type</th>
<th>Post-Intervention</th>
<th>Control %</th>
<th>P Value</th>
<th>Effect % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mail Order</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 Days</td>
<td>18.9</td>
<td>10.9</td>
<td>0.227</td>
<td>8.0 (-5.1 to -21.1)</td>
</tr>
<tr>
<td>90 Days</td>
<td>16.9</td>
<td>11.1</td>
<td>0.238</td>
<td>5.8 (-3.9 to -15.6)</td>
</tr>
<tr>
<td>135 Days</td>
<td>23.4</td>
<td>15.4</td>
<td>0.104</td>
<td>8.0 (-1.7 to -15.6)</td>
</tr>
<tr>
<td>Preferred Pharmacies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 Days</td>
<td>37.0</td>
<td>26.8</td>
<td>0.109</td>
<td>10.2 (2.3 to 22.7)</td>
</tr>
<tr>
<td>90 Days</td>
<td>29.1</td>
<td>24.4</td>
<td>0.391</td>
<td>4.7 (-6.1 to -13.5)</td>
</tr>
<tr>
<td>135 Days</td>
<td>41.9</td>
<td>30.8</td>
<td>0.042</td>
<td>11.0 (0.4 to -21.7)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
RESULTS: After controlling for comorbidities, pharmacy dispense rates and individual prescription numbers, the letters had a positive but statistically insignificant effect on mail order through 135 days post-intervention and a statistically significant improvement on preferred pharmacy prescription dispense rates at 135 days.

CONCLUSIONS: The intervention was associated with a positive effect on preferred pharmacy prescription dispense utilization. However, the true effect of sending personalized letters on mail order pharmacy dispense rates cannot be determined by this study, which was limited by a small sample size and short duration of time.

SPONSORSHIP: This research was conducted by Group Health Cooperative, Seattle, WA, without external funding.

Comparison of Health Care Costs for Gout Patients by Uric Acid Level

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BACKGROUND: The costs of morbidity associated with gout are high, and disease severity impacts these costs. More studies are needed to assess and understand the relationships between costs and other factors, such as serum urate levels (sUA) and comorbidities, in patients with gout.

OBJECTIVE: To summarize the costs associated with the utilization of medical and pharmacy services for patients with gout by sUA levels.

METHODS: Retrospective analysis was conducted using lab, pharmacy, and medical service claims data (January 1, 2005-June 30, 2010) for patients 18 years and older enrolled in a regional staff model health plan. Inclusion criteria were at least 2 sUA and at least primary gout diagnosis (ICD-9-CM codes 274.xx), and/or at least 1 prescription for gout-specific medications, which included allopurinol, colchicine, probenecid, probenecid/colchicine, and febuxostat. Patients with a diagnosis for malignancies were excluded. Reimbursed costs (including both plan and patient costs) for 1-year post-first sUA (index date) were summarized for 3 cohorts based on sUA: (a) <6 mg per dl; (b) 6-8.99 mg per dl, and (c) ≥9 mg per dl.

RESULTS: 449 patients met inclusion criteria (Cohort 1: n=75, mean age =62 years, 71% male; Cohort 2: n=305, mean age =61 years, 78% male; Cohort 3: n=69, mean age =62 years, 58% male). One-year post-index gout-specific prescription costs were $52, $47, and $40 ($P<0.05), respectively; all prescription costs were $1,510, $1,947, and $2,317, respectively, for the 3 cohorts (NS). Gout-related medical service (inpatient and outpatient) costs for the 3 cohorts were $442, $360, and $603 ($P<0.05), respectively. all-medical service costs were $8,521, $9,352, and $13,444 ($P<0.05), respectively, for the 3 cohorts.

CONCLUSIONS: Patients with more advanced gout disease (i.e., higher sUA) utilized less gout-specific medication but more medical services. The next step is to assess utilization patterns, including medication adherence and comorbidities for these patients.

SPONSORSHIP: This research was funded by Takeda Pharmaceuticals North America, Inc., Deerfield, IL.

Comparison of Rates of Inhaled Corticosteroid (ICS) Initiation and Total ICS Claims Between Member and Prescriber Communication over 6 Months

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BACKGROUND: National asthma guidelines recommend inhaled corticosteroids (ICSs) as first-line agents for controlling persistent asthma. ICSs decrease the frequency and severity of asthma exacerbations while increasing quality of life. Patients who overutilize their short-acting beta-2 agonists (SABAs) rescue inhalers typically require ICS.

OBJECTIVE: To compare rates of patient versus physician communication in adding ICSs to patients with uncontrolled asthma.

METHODS: 120,536 patients’ pharmacy claims were examined to identify those with uncontrolled asthma (≥6 SABA claims in 12 months) without an ICS in October-December 2009. Patients meeting inclusion criteria received 1 of 2 methods of communication. Group 1 (G1) (n=103) received a direct mailing encouraging use of ICSs, while Group 2 (G2) (n=102) patients’ prescribers received facsimiles recommending ICSs. Six months claims data from January-June 2010 were collected for the evaluation period. Medi-Span Generic Product Identifier (GPI) codes were used to identify new claims and total ICS claims. The rate of ICS initiation and average total ICS claims were then compared between G1 and G2.

RESULTS: Of the individuals who filled an ICS, 88% of G1 and 87% of G2 initiated their ICS claims within 90 days following communication. Fifty-nine percent of G1 and 52.2% of G2 had their first ICS claims within 30 days of intervention. G1 filled 137 claims, while G2 filled 114 claims in the evaluation period. After 6 months, 48% of G1 and 44.7% of G2 had at least 1 ICS claim. Patients with initial fill of ICS in the first month had an average total claim count of ICSs of 3.76 in G1 and 3.04 in G2. Patients with initial fill of ICS in the second month had 1.43 claims and 2.33 for G2. Patients with initial fill of ICS in the third month had 1.43 total claims in G1 and 1.25 in G2.

CONCLUSIONS: Both communication methods were similar in effectiveness to initiate an ICS. The majority of the impact from the communications was apparent in the first 90 days. Limitations of the study include missing or incorrect contact information and only using pharmacy claims to identify patients. Mailings and facsimiles produced comparable results, but the additional cost of mailings due to postage may be a barrier to the intervention. Identifying patients through pharmacy claims data and contacting physicians via facsimiles may be used in other chronic disease states to initiate necessary medications.

SPONSORSHIP: This research was conducted by American Health Care, Rocklin, CA, without external funding.

Comparison of Suboptimal Treatments Identified from Claims Data Alone with a Medication Therapy Management Patient Interview

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BACKGROUND: Identifying suboptimal treatment for disease conditions is a common strategy used by medication therapy management (MTM) providers to detect medication-related problems. While there may be a tendency to rely solely on pharmacy claim databases and diagnosis codes supplied by the Centers for Medicare and Medicaid Services (CMS) to identify suboptimal treatments, some identified by claims data alone may be negated after confirming with the patient.

OBJECTIVE: To determine the change in information accuracy by comparing suboptimal treatments identified from claims data alone with a MTM patient interview.

METHODS: A retrospective study was performed on 100 medication reviews conducted by the University of Florida College of Pharmacy MTM Call Center during June and July 2010 for Medicare Part D beneficiaries who qualified for MTM services. Subjects met the following criteria for MTM: on 8 or more medications, 3 or more chronic conditions, and high annual drug costs. Before the interview, prescription
claims submitted in the past 120 days was available to the interviewer along with diagnosis codes provided by CMS. A suboptimal treatment was identified when 1 of the following scenarios occurred: diabetic without a statin or an angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB), heart failure without an appropriate beta-blocker (BB) or ACE inhibitor/ARB, long-term steroid use without an antiresorptive agent, and asthmatic without a rescue or a controller medication.

RESULTS: The study sample included both subjects older than 65 and younger than 65 who met Medicare eligibility due to a qualifying disability; many were dual eligible for Medicare and Medicaid. A total of 124 incidents of suboptimal treatments were identified in 68 patients based on examination of claims data alone, and 45.5% was negated after the MTM interview. The 2 most common reasons for negation were (a) patients denied having a medical condition identified from diagnosis codes (16.9%) and (b) patient self-reported taking the necessary medication or on another therapy (16.9%). 5 new suboptimal treatments were discovered for 4 patients based on the new conditions revealed from the interview.

CONCLUSIONS: The telephone patient interview confirmed 56.5% of the incidents after clarifying patients’ health conditions and medication use. From the interview, it was discovered that 9.8% of the targeted medical conditions was denied by the patients. These findings indicated the value of utilizing patient interviews in improving the accuracy of identifying suboptimal treatment for disease conditions.

SPONSORSHIP: This research was funded by Gold Standard/Elsevier and WellCare Health Plans, Inc., Tampa, FL.

Consistency of Maintenance Infliximab Weight-Based Dosing and Administration Patterns in Commercially Insured Patients with Rheumatoid Arthritis

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BACKGROUND: FDA-approved prescribing information recommends infliximab weight-based dosing and administration in rheumatoid arthritis (RA) of 3 mg per kg at 0, 2, 6 and every 8 weeks (or 4 if needed) with flexible dosing during maintenance based on patient response. Minimal real-world, weight-based dosing data are available and have historically come from chart review studies.

OBJECTIVE: To evaluate infliximab weight-based dosing and administration patterns in commercially insured patients with RA using a recently published, novel methodology of weight imputation.

METHODS: The IMS LifeLink database was utilized to analyze patients with an index medical claim of infliximab therapy initiated January 1, 2004, through December 31, 2007. Eligible patients were aged 18 years or older at index, had at least 2 RA diagnosis codes during infliximab treatment, and had at least 365 days infliximab persistence. Patients excluded had other selected inflammatory diseases, medical/pharmacy claims for anti-tissue necrosis factors (TNF) 6 months prior to the infliximab index date, a record of taking abatacept or rituximab while on infliximab, or receipt of infliximab in the hospital outpatient setting. Weights of RA patients from the GE Centricity electronic medical record database were imputed onto the commercial database through propensity score matching. Dosing was calculated as the number of mg per kg of infliximab administered at each infusion. Administration patterns included time between infusions. The fourth through eighth infliximab infusions were analyzed representing the maintenance period of the first treatment year.

RESULTS: A total of 1,330 RA patients receiving infliximab were identified from LifeLink. Mean (SD) age was 62 (0.37 years), 75% were female. 1,073 patients in LifeLink were matched, had weights imputed, and received at least 4 infliximab infusions. During the first year maintenance period, median and mean doses remained between 3.00-3.27 and 3.93-5.22 mg per kg, respectively (see table). Median time between administrations was 56 days for all maintenance infusions.

CONCLUSIONS: The observed infliximab weight-based dosing and administration schedule was consistent with FDA-approved prescribing information. These data suggest that RA patients are receiving relatively consistent maintenance doses of infliximab.

SPONSORSHIP: This research was funded by Centocor Ortho Biotech Services, LLC, Horsham, PA.

Cost-Effectiveness Analysis of Hyalgan versus Synvisc in the Treatment of Osteoarthritis

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BACKGROUND: Osteoarthritis (OA) is the most common and costly form of arthritis. Treatment goals for OA are to reduce pain, maintain and/or improve joint mobility, and limit functional impairment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common pharmacological treatment for OA. Hyalgan (sodium hyaluronate) and Synvisc (hylan G-F20) are viscosupplements aimed to restore viscosity and elasticity of the synovial fluid. These agents are often used after NSAID treatment has failed and also to postpone the time a patient would undergo total knee replacement (TKR) surgery. For the standard course of therapy, Hyalgan costs less than Synvisc, which has fewer injections.

OBJECTIVE: To evaluate the cost-effectiveness of Hyalgan compared to Synvisc in delaying the time to TKR surgery in patients with knee pain due to OA.

METHODS: Using a societal perspective, a 5-year Markov model evaluated the treatment of knee pain due to OA and the progression to TKR surgery using Hyalgan versus Synvisc in a cohort of 1,000 hypothetical patients. A literature search was conducted to derive estimates of probabilities and health utility scores. Costs were derived from the Federal Supply Schedule and Center for Medicaid and Medicare Services. Using a cycle length of 6 months, treatments were compared based on discounted total costs and discounted quality-adjusted life years (QALYs) at 3% per cycle. Parameters were then varied in a 1-way sensitivity analyses.

RESULTS: The average cost per QALY for the treatments were $2,940 and $2,390 for Hyalgan and Synvisc, respectively; thus, Synvisc has a lower cost with greater QALYs gained compared to Hyalgan. Sensitivity analyses revealed that the model was most sensitive to variations in efficacy rates and number of injections per course of therapy. A 25% decrease in Hyalgan’s efficacy rate and number of injections resulted in a decrease in incremental cost-effectiveness ratio of about 600% and 100%, respectively.

CONCLUSIONS: When comparing the base case standard course of therapy, Synvisc cost less per QALY gained compared to Hyalgan.
However, if the number of Hyalgan injections is fewer, it may be more cost-effective than Synvisc. This study is limited by the amount of current evidence provided by literature.

SPONSORSHIP: This research was funded by the San Diego Clinical and Translational Research Institute, San Diego, CA.

■■ Cost-Effectiveness of Fingolimod in the Treatment of Patients with Relapsing Remitting Multiple Sclerosis

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BACKGROUND: Multiple sclerosis (MS) carries a substantial economic burden that impacts managed care plans. The number of relapses experienced by a MS patient is a significant predictor of the total costs of care. Reducing the frequency and severity of relapses may decrease overall costs. Fingolimod is a new once-daily oral disease-modifying therapy (DMT) indicated for the treatment of patients with relapsing forms of MS.

OBJECTIVE: To estimate the cost per relapse avoided with oral fingolimod 0.5 mg in a hypothetical managed care plan from a U.S. commercial payer perspective.

METHODS: This Microsoft Excel-based model estimated the cost-effectiveness of fingolimod based on the number of incidents and prevalent patients with relapsing remitting multiple sclerosis (RRMS) receiving first-line disease-modifying therapy (DMT) in a U.S. health plan. Treatment comparators included fingolimod, subcutaneous (SC) and intramuscular (IM) interferon-beta agents (IFNβ-1a and IFNβ-1b), and glatiramer acetate. The analysis calculated the cost per relapse avoided for each of the products over 2 years (including drug acquisition costs, direct costs of managing relapses, and monitoring costs) divided by the number of relapses avoided. Cost data were derived from published sources (inflated to US$2010) and were modifiable to reflect a plan's actual costs. The relative risk reduction for each DMT was obtained from the respective placebo-controlled clinical trials, and the average number of relapses for an untreated patient was obtained by pooling the number of relapses from the placebo arms of the interferon clinical trials.

RESULTS: Fingolimod was the most cost-effective DMT with a 2-year cost per relapse avoided of $74,843, followed by SC IFNβ-1b ($84,509), SC IFNβ-1a ($93,529), SC IFNβ-1b ($96,117), glatiramer acetate ($111,398), and IM IFNβ-1a ($138,199). Univariate sensitivity analysis showed that the cost per relapse avoided for fingolimod showed the results were most sensitive to drug acquisition cost of fingolimod and number of relapses in untreated patients.

CONCLUSIONS: Fingolimod had the lowest cost per relapse avoided compared with other DMTs frequently used in first-line therapy. This cost-effectiveness was due to its efficacy in reducing relapses in clinical trials.

SPONSORSHIP: This research was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ.

■■ Cost-Effectiveness of Pharmacist Provided Care for the Treatment of Adult Pharyngitis

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BACKGROUND: There are over 12 million ambulatory care visits for acute pharyngitis annually in the United States. Group A streptococcus (GAS) is a leading cause of acute pharyngitis in adults. Current guidelines recommend diagnosis through culture or rapid antigen diagnostic test (RADT). Owing to the reliability of RADT and relatively straightforward treatment, community pharmacists may provide cost-effective care for disease states such as GAS pharyngitis.

OBJECTIVE: To evaluate the cost-effectiveness of a community pharmacist-as-provider program for the diagnosis and treatment of pharyngitis caused by GAS.

METHODS: A cost-effectiveness analysis from a societal perspective was conducted by expanding an existing model to compare treatment for adult pharyngitis patients. In addition to the 5 physician-provided treatment strategies compared in the previous model, the episodic costs and benefits of treatment provided by pharmacists using RADT and walk-in clinics using RADT were also considered. Model parameters were derived through a comprehensive review of literature and from the Centers for Medicare and Medicaid Services (CMS) physician fee schedule. Utilities were expressed in quality-adjusted life days (QALDs) to account for the relatively short duration of most cases of pharyngitis.

RESULTS: Using a cost-effectiveness threshold of $137 QALD, GAS treatment provided by a pharmacist was the most cost-effective treatment (see table). Pharmacist treatment dominated all of the other methods except physician culture and physician RADT with follow-up culture. The incremental cost-effectiveness ratio (ICER) for physician culture was $6,042 per QALD gained and $4,075 per QALD for physician RADT with follow-up culture (see table). At a pharmacist cost above $55.66, walk-in clinics become the most cost-effective option.

CONCLUSIONS: This model suggests that pharmacists may be able to provide a cost-effective alternative for the treatment of pharyngitis caused by GAS in adult patients.

SPONSORSHIP: This research was conducted by University of Nebraska Medical Center, College of Pharmacy, Omaha, NE, without external funding.

■■ Cost-Effectiveness of 2 Disease-Modifying Therapies for Treatment of Multiple Sclerosis

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BACKGROUND: The multiple sclerosis (MS) treatment landscape has recently changed with the introduction of an oral agent to the current armamentarium of physician-administered and self-injected agents. Oral fingolimod was approved by the FDA for the treatment of patients with relapsing forms of MS. Clinical efficacy, safety, and economic data comparing fingolimod to those agents already on the market will become increasingly important.

OBJECTIVE: To determine the cost-effectiveness of natalizumab versus fingolimod in patients with MS.
METHODS: A decision analysis was developed (U.S. payer perspective) to capture direct medical costs (US$2010) over a 2-year time horizon. Two-year costs of treating patients with MS were modeled in terms of drug acquisition costs (published wholesale acquisition cost [WAC]), administration and monitoring costs (published reimbursement rates), and costs of treating MS relapses (literature-based estimates, adjusted to US$2010). Effectiveness was assessed in terms of MS relapses avoided from placebo-adjusted relapse rates for natalizumab and fingolimod reported in the AFFIRM and FREEDOMS trials, respectively. Estimated standard errors were used to create distributions for model parameters and a probabilistic sensitivity analysis with 1,000 Monte Carlo simulations was conducted in a net-benefit framework.

RESULTS: Mean 2-year estimated treatment cost for natalizumab was $86,461 versus $98,748 for fingolimod. Patients receiving natalizumab had a mean of 0.74 relapses avoided per 2 years versus 0.59 for fingolimod. Natalizumab cost per relapse avoided was $117,164, and fingolimod cost per relapse avoided was $168,754. Natalizumab dominated fingolimod in the incremental cost-effectiveness analysis (less costly and more effective). In the probabilistic analysis, natalizumab was cost-effective (less costly and more effective) as compared with fingolimod in terms of cost per relapse avoided.

CONCLUSIONS: From a U.S. payer perspective, natalizumab was more cost-effective (less costly and more effective) as compared with fingolimod in terms of cost per relapse avoided.

SPONSORSHIP: This research was funded by Biogen Idec Inc., Cambridge, MA.

Cost of Warfarin-Associated Bleeding in Atrial Fibrillation

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BACKGROUND: Bleeding is a major complication of warfarin therapy. Assessing the cost of warfarin-associated bleeding will assist in the economic evaluation of novel anticoagulants aimed at reducing bleeding risk.

OBJECTIVE: To assess the cost of warfarin-associated bleeding in atrial fibrillation (AF) patients.

METHODS: Medical and pharmacy claims from AF patients (ICD-9-CM code 427.31) in the MarketScan database from January 2003 to December 2007 were analyzed. Eligible patients had at least 1 warfarin prescription (Rx) or AF diagnosis in the 4 months prior to AF index date, had filled a warfarin prescription within 30 days of AF diagnosis, and had 12 months follow-up data after index warfarin Rx. Intracranial hemorrhage (ICH) and gastrointestinal (GI) bleeding (based on ICD-9-CM codes) were assessed. Major GI bleeding was defined as a GI bleed associated with hospitalization. Annual costs for patients with and without bleeding after index warfarin Rx were compared using Poisson regression, controlling for demographics, insurance status, and comorbidities.

RESULTS: Data from 47,458 patients were analyzed, of which 201 (0.4%), 926 (1.9%), and 1,811 (3.8%) had an ICH, a major GI bleed, and a minor GI bleed, respectively after index warfarin Rx. Patients with bleeding claims were older and had more comorbidities than patients without bleeding claims (P < 0.01). Patients with an ICH or a major GI bleed had more hospitalizations (P < 0.05) and a longer length of stay (P < 0.01) than patients without bleeding claims. Patients with an ICH or a major or minor GI bleed had more emergency department (P < 0.01) and outpatient visits (P < 0.01) than patients without bleeding claims. Mean (SD) health care costs in the 12 months after warfarin index Rx were $41,903 ($56,654) for ICH, $40,586 ($65,164) for major GI bleed, $24,347 ($56,488) for minor GI bleed, and $24,129 ($36,425) for patients without bleeding claims. Bleeding claims accounted for 49.6%, 30.2%, and 2.6% of annual cost in ICH, major GI bleed, and minor GI bleed patients, respectively. On average, 51.4%, 34.5%, and 12.3% of annual costs occurred within 30 days after the first ICH, major GI, and minor GI bleeding claim, respectively. Poisson regression showed that annual costs were 61.6%, 48.7%, and 0.2% higher (P < 0.001) for patients with ICH, major GI, and minor GI bleed, respectively than patients with no bleeding claims.

CONCLUSIONS: ICH and major GI bleed associated with warfarin therapy are costly and identify an opportunity for novel anticoagulants to reduce health care costs and potentially improve patient outcomes.

SPONSORSHIP: This research was funded by Daiichi-Sankyo, Parsippany, NJ.

Costs of Contraceptive Coverage and Pregnancy Care: An Actuarial Analysis


BACKGROUND: Covering pregnancy and delivery care is a significant cost to commercial insurers and employers. According to published estimates, almost half of this cost is attributable to unintended pregnancies that result from nonuse or misuse of contraception or contraceptive failure despite correct use.

OBJECTIVE: To examine the costs of covering pregnancy and delivery care and prescription contraceptives (oral contraceptives [OCs] and intrauterine devices [IUDs]) for a commercial population.

METHODS: We relied on the 2008 MedStat MarketScan Database as the main source used in this study. Approximately 19 million members generated the data used in our analysis, representing a typical under-65 commercially insured population, and approximately 5.7 million members are childbearing-age females (aged 15 to 49 years). Females with at least 1 claim associated with pregnancy and/or delivery were identified from the 5.7 million females of childbearing age. Also identified were females with at least 1 prescription OC claim based on NDC codes and women with IUD care based on HCPCS code J7300 or J7302 or insertion/removal CPT code 58300 or 58301 or a combination of IUD insertion/removal (J7300) and OC (58300) claims. The prevalence rates and resulting average costs (trended to 2010) of oral and IUD contraception and pregnancy/delivery per member per month (PMPM) and per female of childbearing age per month (PFPCM) were demographically adjusted to reflect results of a typical commercially insured population.

RESULTS: About 6.5% (n = 370,642) of approximately 5.7 million females of childbearing age had at least 1 claim related to pregnancy and/or delivery care; 19.0% (n = 1,074,881) of childbearing-age females had an OC claim, and 1.2% (n = 68,989) had IUD care. The cost for pregnancy and delivery care was $14.64 PMPM (4.3% of total costs); OCs, $1.72 PMPM (0.5% of total costs); and IUD care, $0.26 PMPM (0.88% of total costs). The PFPCM was approximately 3 times higher than the PMPM cost as it is spread across only females of childbearing age.

CONCLUSIONS: The costs to cover pregnancy and delivery care and prescription contraceptives in a commercial population have important implications for payers and employers, especially if the payers and employers advocate the public health goal to reduce the number of unintended pregnancies.

SPONSORSHIP: This research was funded by Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ.
Cost Savings Through Retrospective Authorization for Factor VIIa Use

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**BACKGROUND:** Thromboembolic events leading to uncontrolled bleeding is the major cause of morbidity in acute trauma. Since the introduction of recombinant factor VIIa (Novoseven) and other acute bleeding management modalities, physicians are now afforded options previously unknown to emergency and surgical practice. Managed care organizations are currently grappling with defining appropriate use of these bleeding control therapies and subsequent payment for their use in the hospital setting. The implementation of authorization guidelines may aid prescribers in the responsible use of these products and help control medication costs.

**OBJECTIVE:** To conduct a retrospective review and analysis of submitted claims to a managed care organization for off label usage of recombinant factor VIIa and determine the impact of peer reviewed authorization guidelines on the total payments for the medication.

**METHODS:** Data were collected on the in-patient utilization of factor VIIa for non—FDA-recognized indications for claims submitted between June 1, 2009, to August 31, 2010. Peer-reviewed guidelines were used by a managed care organizations Bleeding Disorder case manager to determine the need for further review by the plan medical director for medical necessity for each claim. Claims submitted by acute care facilities during this time period were gathered and reviewed to verify the actual physician order, medication dose, documentation of administration, and clinical assessment for the need for off-label use of factor VIIa.

**RESULTS:** Of 42 submitted claims between June 1, 2009, and August 31, 2010, 19 claims were approved due to diagnosis and clinical outcome, resulting in a total payment by the organization of $185,030.28. The 23 claims that were declined using the peer-reviewed guidelines saved a total of $482,414.68. Further appeals were ultimately upheld by the reviewing medical director, resulting in no change of payments.

**CONCLUSIONS:** More than half of all submitted claims were not found to meet clinical criteria for use based on peer-reviewed guidelines. The managed care plan that implemented this process reduced the reimbursement for factor VIIa by a significant margin over the study period. Instituting peer-reviewed authorization guidelines may decrease managed care reimbursement for claims submitted with off-label indications for recombinant factor VIIa.

**SPONSORSHIP:** This research was performed by PerformRx, Philadelphia, PA, without external funding.

Cost Utility Analysis of Romiplostim Versus Splenectomy in the Treatment of Chronic Refractory Immune Thrombocytopenic Purpura

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**BACKGROUND:** The use of romiplostim was approved by the FDA in 2009 for the treatment of chronic immune thrombocytopenic purpura (ITP) refractory to intravenous immunoglobulins (IVIG), corticosteroids or splenectomy. In cross-study comparisons for ITP, romiplostim is associated with higher overall response rates while possessing a greater safety profile relative to the above pharmaceutical therapies. It has been suggested that romiplostim may even be used prior to splenectomy, the only treatment that offers the potential for long-term remission.

**OBJECTIVE:** To assess the incremental cost utility associated with treatment of chronic refractory ITP using romiplostim prior to splenectomy (romiplostim-first) compared to using splenectomy prior to romiplostim (splenectomy-first).

**METHODS:** A lifetime semi-Markov model with 3% discounting of costs and effects was used to project the cost-effectiveness of using romiplostim-first compared to using splenectomy-first. Efficacy data were drawn from studies of adult (aged 18 years or older), chronic, refractory ITP patients of both genders and all races. A payer’s perspective was adopted in the analysis. All costs were assessed in US$2010.

**RESULTS:** The use of splenectomy prior to romiplostim dominated by yielding a greater degree of quality adjusted life-years gained (0.02 QALYs more) with lower lifetime costs ($129,444) both in the base-case as well as in all univariate sensitivity analyses.

**CONCLUSIONS:** Despite higher up front costs associated with splenectomy, the potential for long-term remission as well as lower costs of maintenance on remission in splenectomy likely caused the splenectomy-first strategy to be the more cost-effective therapy in our analysis. Although romiplostim represents an advance in the treatment of patients with chronic refractory ITP, further studies clearly demonstrating its cost-effectiveness relative to splenectomy will be necessary if it is to be used as a preferred second-line agent.

**SPONSORSHIP:** This research was performed at the University of Southern California School of Pharmacy, Los Angeles, without external funding.

Determinants of Nonadherence to Prescription Medications for Diabetes and Lipid-Related Conditions: A Systematic Review

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**BACKGROUND:** Very few systematic reviews to date have attempted to synthesize the available evidence on determinants of nonadherence.

**OBJECTIVE:** To summarize the evidence on the impact of a broad range of determinants on nonadherence to prescription medications for diabetes and lipid-related conditions.

**METHODS:** Articles were identified through searches conducted on MEDLINE and EMBASE. The search was limited to English-language, peer-reviewed articles that employed multivariate testing of determinants of nonadherence to oral prescription medications for diabetes and lipid-related conditions in adults.
RESULTS: Based on the inclusion criteria, a total of 66 studies were included: 41 for type 2 diabetes and 25 for lipid-related conditions. Mutable factors significantly correlated with therapy discontinuation included the following individual factors (unfavorable patient beliefs, depressive symptoms, comorbid conditions, smoking, lack of exercise); environmental factors (lack of friends/social network); medication-related factors (number of medications, dosing frequency, side-effects, switching of therapy); and health-system factors (lack of communication with physician, lack of satisfaction with physician, high out-of-pocket cost). Immutable factors significantly correlated with therapy discontinuation included: individual factors (younger age, nonwhite race, male gender, lower household income); disease-related factors (lower disease severity); and medication-related factors (new to therapy). Mutable factors significantly correlated with missed/skipped doses included the following: individual factors (low self-efficacy for taking medication, self-perceived barriers to medication taking, depressive symptoms, lack of exercise, psychological distress, irregular meal habits); medication-related factors (number of medications, dosing frequency, side effects); and health-system factors (lack of trust in physician, lack of health insurance, high out-of-pocket cost). Immutable factors significantly correlated with missed/skipped doses included the following: individual factors (lower age, nonwhite race, male gender, not married, lower household income) and disease-related factors (higher disease severity).

CONCLUSIONS: A vast majority of determinants found to be significantly correlated with either therapy discontinuation or missed/skipped doses were mutable rather than immutable factors. Researchers as well as clinicians can target mutable factors identified in this review to develop interventions aimed at increasing patients’ adherence.

SPONSORSHIP: This research was funded by Merck & Co., Inc., Whitehouse Station, NJ.

### Diabetes Medication Adherence Association with Hospitalizations and Total Cost of Care

**Gleason PP, Starner CI, Zhou S, Ritter S, Prime Therapeutics, LLC, 1305 Corporate Center Dr., Eagan, MN 55121; pgleason@primetherapeutics.com, 612.777.3190**

**BACKGROUND:** Poor medication adherence has been reported to be associated with worse medical outcomes and increased medical costs. However, minimal data are available quantifying outcome and cost differences between individuals adherent and nonadherent to diabetes mellitus (DM) medications.

**OBJECTIVE:** To compare 1-year all-cause hospitalization rates, medical costs, and pharmacy costs among individuals adherent and nonadherent to their DM medications.

**METHODS:** Using retrospective pharmacy and medical claims from a 1.3 million member commercial plan, members continuously enrolled from 2007 through 2009 with 2 separate DM office visits or a DM hospitalization in 2008 with a DM medication supply or DM with microvascular disease were followed for 1 year. All DM drug claims were assessed to identify members as adherent (proportion of days covered [PDC] 80% or greater) or nonadherent (PDC < 80%). Due to medical and pharmacy cost skewness, individuals exceeding the 99th percentile were excluded. All medical and pharmacy claim total allowed amounts (plan and member) were summed to determine total cost of care. Statistical assessment of the relationship between adherence and all-cause hospitalization was done with chi-square (unadjusted) and logistic regression adjusting for age, sex, Charlson risk score, insulin use at baseline, unique drug classes used at baseline, high-deductible health plan enrollment, and zip code income. For costs, t-test (unadjusted) and multiple linear regression were performed using the same covariates.

**RESULTS:** Of the 15,043 members meeting all inclusion criteria, 11,108 (73.9%) were adherent and 3,935 (26.1%) nonadherent. The adherent group was associated with a significantly lower hospitalization rate (odds ratio of 0.69, 95% confidence interval, 0.61 to 0.78), significantly lower medical costs ($1,010), higher pharmacy costs $1,582, but higher total cost of care $372.

**CONCLUSIONS:** Individuals adherent to DM medication had an associated 2.8 percentage point lower hospitalization rate or 31% lower risk of hospitalization. Although medical costs were lower, higher pharmacy costs resulted in higher total costs of care.

**SPONSORSHIP:** This research was conducted by Prime Therapeutics, LLC, Eagan, MN.

### Direct Health Care and Workplace Productivity Costs of Back and Neck Pain with or Without a Neuropathic Component Compared to Other Medical Conditions in a Large Integrated Database for 2005


**BACKGROUND:** Productivity costs for common medical conditions such as back and neck pain and depression are considerably greater than direct health care (inpatient and outpatient) costs; thus, both direct health care and productivity costs should be considered when economic impacts are evaluated in an employed population.

**OBJECTIVE:** To quantify the direct and indirect (productivity) costs associated with back and neck pain and compare with costs associated with other common medical conditions.

**METHODS:** We used 2005 Marketscan, an integrated commercial database containing health and productivity management (HPM) and health care utilization, including inpatient, outpatient, and pharmacy claims (direct costs); HPM (indirect costs) contains absenteeism, short-term disability (STD), and workers’ compensation (WC) for employees. Adult employees with continuous eligibility in 2005 were enrolled. ICD-9-CM codes identified medical conditions, including back and neck pain without (nociceptive pain, NOCI) or with a neuropathic component (mixed pain, MIXED). Absenteeism data were adjusted for nonreporting of salaried employees. Regressions

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**TABLE**

<table>
<thead>
<tr>
<th>Diabetes Medication Adherence Association with Hospitalizations and Total Cost of Carea</th>
</tr>
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<tbody>
<tr>
<td><strong>1-Year Outcomes Assessment</strong></td>
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<tr>
<td><strong>Adherent (PDC 80% or Greater)</strong></td>
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<tr>
<td><strong>Nonadherent (PDC &lt; 80%)</strong></td>
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<tr>
<td><strong>Multivariate Model P Value</strong></td>
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<tr>
<td>All-cause hospitalization rate, n (%)</td>
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<tr>
<td>1,066 (9.6%)</td>
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<tr>
<td>488 (12.4%)</td>
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<tr>
<td>&lt; 0.001</td>
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<tr>
<td>All medical costs,b mean [SD]</td>
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<tr>
<td>$7,079 [$12,990]</td>
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<tr>
<td>$8,089 [$13,915]</td>
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<tr>
<td>&lt; 0.001</td>
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<tr>
<td>All pharmacy costs, mean [SD]</td>
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<tr>
<td>$4,699 [$3,528]</td>
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<tr>
<td>$3,117 [$3,244]</td>
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<tr>
<td>&lt; 0.001</td>
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<tr>
<td>Total cost of care (medical and pharmacy), mean [SD]</td>
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<tr>
<td>$11,777 [$14,216]</td>
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<tr>
<td>$11,206 [$15,096]</td>
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<td>&lt; 0.001</td>
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</tbody>
</table>

aHospitalization rate compared by logistic regression, and costs compared by linear regression.

bAll medical costs are allowed amounts (plan and member paid) from all facility and professional claims including office visits, hospitalizations, procedures, laboratory testing, ancillary, etc.

PDC = proportion of days covered, SD = standard deviation.
improves upon the accuracy of using claims data alone in identifying health condition and medication usage are collected.

evaluated absenteeism, STD, WC, and total health care costs.

RESULTS: A total of 2,046,332 employees (male = 59.2%; mean age 40.2±11.6 years) were analyzed. NOCI (9.4%), and MIXED (3.0%) hypertension (9.9%), diabetes (3.7%), sleeping disorders (2.2%), and depression (1.1%) were the most prevalent medical conditions among these employees. Direct costs for MIXED and NOCI were $3,787.9±37.7 and $1,700.6±22.1 compared to $2,035.6±21.3 (hypertension), $2,399.5±32.5 (diabetes), $2,239.8±41.9 (sleeping disorders), and $1,354.0±59.0 (depression). Absenteeism for MIXED was 25.3 hours ($431.9) and 22.4 ($382.4) for NOCI, compared to 27.7 (hypertension), 19.3 (diabetes), 17.5 (sleeping disorders), and 20.4 (depression). The mean STD days was 65.5 ($8,944.7) for MIXED and 54.0 ($7,374.2) for NOCI compared to 48.0 for other reasons. Mean WC days for all back and neck conditions were 18.2 ($3,485.4) and amounted to $3,296.6 per claim compared to 17.4 ($2,376.1) for other medical conditions. Total annual costs associated with MIXED and NOCI were $20,946.5 and $17,239.2, respectively.

CONCLUSIONS: Among the conditions studied, direct health care cost was highest in MIXED. The total cost of back and neck pain (MIXED and NOCI combined) exceeds that of other conditions and was largely driven by costs associated with STD as well as WC and absenteeism.

SPONSORSHIP: This research was funded by Ortho-McNeil Janssen Scientific Affairs, LLC, Raritan, NJ.

<table>
<thead>
<tr>
<th>Problem Category</th>
<th>Before Patient Interview</th>
<th>After Patient Interview</th>
<th>% Negated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-drug interaction</td>
<td>240</td>
<td>45</td>
<td>81.2</td>
</tr>
<tr>
<td>Drug-disease interaction</td>
<td>235</td>
<td>72</td>
<td>69.4</td>
</tr>
<tr>
<td>Drug-age interaction</td>
<td>46</td>
<td>28</td>
<td>39.1</td>
</tr>
<tr>
<td>Nonadherence</td>
<td>195</td>
<td>32</td>
<td>83.6</td>
</tr>
<tr>
<td>Therapy duplications</td>
<td>50</td>
<td>17</td>
<td>66.0</td>
</tr>
<tr>
<td>Suboptimal treatment</td>
<td>124</td>
<td>70</td>
<td>43.5</td>
</tr>
<tr>
<td>Medication missing a clear indication</td>
<td>31</td>
<td>2</td>
<td>93.5</td>
</tr>
</tbody>
</table>

MTM = medication therapy management.

Identification of medication-related problems was based on prescription claims and diagnosis codes alone, and telephonic patient interview can be utilized as a supplement to claims databases.

SPONSORSHIP: This research was funded by Ortho-McNeil Janssen Scientific Affairs, LLC, Raritan, NJ.

Disagreements on Medication Nonadherence Between Prescription Claims and Patient Reports from Medication Therapy Management Interviews

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BACKGROUND: Medication adherence is an essential component in therapeutic outcomes optimization, and patients who are nonadherent to prescribed medications represent opportunities for pharmacist interventions. While there may be a tendency for medication therapy management (MTM) providers to rely solely on pharmacy claims databases to identify nonadherent patients, sometimes claims data may not accurately reflect patients' actual medication-taking practices.

OBJECTIVE: To evaluate the extent to which patient interviews confirm presumed nonadherence identified from prescription claims data alone.

METHODS: A retrospective study was performed on 100 medication reviews conducted during June and July 2010 for Medicare Part D beneficiaries who qualified for MTM services. Enrollment criteria for MTM are 8 or more Part D covered chronic medications, 3 or more chronic diseases, and high annual drug costs. Before each MTM interview, diagnosis codes provided by Centers of Medicare and Medicaid Services and prescription claims submitted within 120 days prior to the interview were used to identify medication-related problems. During the interview, the pre-identified problems are evaluated with the patient, and new information relevant to patient's health condition and medication usage are collected.

OBJECTIVE: To determine whether a telephonic patient interview improves upon the accuracy of using claims data alone in identifying medication-related problems.

METHODS: A retrospective study was performed on 100 medication reviews that were conducted during June and July 2010. The following categories of medication problems were investigated: drug-drug interaction, drug-disease interaction, drug-age interaction, adherence, therapy duplications, suboptimal treatment, and medication use without a clear indication based on diagnosis code.

RESULTS: The sample included both subjects older than 65 and younger than 65 who met Medicare eligibility due to a qualifying disability; many were dual eligible for Medicare and Medicaid. A total of 195 adherence issues were identified in 61 patients before interview, and 83.6% was negated after interview based on patients' self-reports of medication-taking practices. Within the group of negated issues, the 3 most common reasons for negation were the following: the medication had been discontinued (45.4%), patients reported to be actively taking the medications (39.3%), and refill pattern changed due to a dose change (4.9%). 10 new adherence issues were discovered for 10 patients based on the patient interviews. The new issues were due to medication not being taken as prescribed according to patients' self-reports.

CONCLUSIONS: The telephonic patient interview confirmed only 16.4% of the adherence issues identified from prescription claims data. The
apparent discrepancy between poor refill patterns revealed from the claims data and patients’ self-reports on medication-taking practices suggests the need for further study. Results from the evaluation indicate the insufficiency of basing adherence issues on prescription claims alone, and the need to utilize the patient interview as a supplement to the prescription claims database.

**SPONSORSHIP:** This research was funded by Gold Standard/Elsevier and WellCare Health Plans, Inc., Tampa, FL.

#### Dosing Patterns During First 18 Months of Infliximab Treatment in Patients with Rheumatoid Arthritis

**Table:** Mean [SD] Infliximab Dosing (mg) During First 18 Months of Treatment Across 3 Databases

<table>
<thead>
<tr>
<th>Infliximab users</th>
<th>HealthCore</th>
<th>Premier Perspective</th>
<th>WKPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 938</td>
<td>n = 2,185</td>
<td>n = 14,507</td>
</tr>
<tr>
<td>Dose 1</td>
<td>302.8 [131.0]</td>
<td>338.2 [156.8]</td>
<td>336.0 [128.8]</td>
</tr>
<tr>
<td>Dose 2</td>
<td>302.1 [115.3]</td>
<td>331.6 [140.9]</td>
<td>341.5 [131.9]</td>
</tr>
<tr>
<td>Dose 3</td>
<td>312.3 [124.7]</td>
<td>351.3 [149.6]</td>
<td>363.5 [138.5]</td>
</tr>
<tr>
<td>Dose 5</td>
<td>332.4 [135.9]</td>
<td>362.6 [154.2]</td>
<td>373.9 [142.1]</td>
</tr>
<tr>
<td>Dose 6</td>
<td>345.4 [141.6]</td>
<td>371.6 [155.7]</td>
<td>382.3 [145.8]</td>
</tr>
<tr>
<td>Dose 7</td>
<td>355.7 [139.3]</td>
<td>377.6 [160.6]</td>
<td>388.6 [147.9]</td>
</tr>
<tr>
<td>Dose 8</td>
<td>369.4 [157.4]</td>
<td>383.5 [162.5]</td>
<td>394.3 [149.6]</td>
</tr>
<tr>
<td>Dose 9</td>
<td>376.9 [150.5]</td>
<td>390.1 [171.8]</td>
<td>399.5 [152.1]</td>
</tr>
<tr>
<td>Dose 10</td>
<td>385.8 [164.5]</td>
<td>393.1 [165.1]</td>
<td>402.2 [152.9]</td>
</tr>
<tr>
<td>Dose 11</td>
<td>390.9 [168.9]</td>
<td>395.3 [167.6]</td>
<td>405.5 [153.6]</td>
</tr>
<tr>
<td>Dose 12</td>
<td>399.1 [166.2]</td>
<td>397.0 [169.8]</td>
<td>409.2 [155.0]</td>
</tr>
</tbody>
</table>

WKPS = Wolters Kluwer Pharma Solutions databases.

**CONCLUSIONS:** Data from multiple real-world databases suggest that infliximab doses in patients with RA was consistent with FDA-approved prescribing information and remained relatively stable during the first 18 months of therapy. It may be important to consider multiple data sources when examining biologic dosing patterns.

**SPONSORSHIP:** This research was funded by Centocor Ortho Biotech Services, LLC, Horsham, PA.

#### Early and Sustained Remission Associated with Normalized Physical Function and Health-Related Quality of Life and Significantly Improved Productivity in Patients with Active Psoriatic Arthritis Treated with Golimumab: GO-REVEAL 2-Year Data

**Background:** Controlling disease activity to remission is crucial to regain a normal life in the management of rheumatoid arthritis (RA). The long-term impact of disease remission in patients with psoriatic arthritis (PsA) need to be evaluated using patient-reported outcomes.

**Objective:** To evaluate the impact of golimumab (GLM) on disease remission, physical function, work productivity, and health care utilization in patients with PsA over 2 years.

**Methods:** GO-REVEAL was a multicenter, randomized, placebo-controlled study. Adult patients with active PsA (n = 405) were randomized to GLM (50 mg or 100 mg) every 4 weeks or placebo. At week 16, patients with inadequate response entered early escape. All placebo-treated patients received GLM 50 mg from week 24. Clinical responses were analyzed using 20% improvement by the American College of Rheumatology criteria (ACR20) and 75% improvement by the Psoriasis Area and Severity Index (PASI75).

**Results:** At baseline, mean age was 47.0 years, and 63% of patients were male. Baseline HAQ was 1.02, and PASI score was 7.8. Compared to placebo, a greater proportion of patients treated with GLM achieved DAS28 remission as early as week 4 (16.3% vs. 3.6%, P < 0.001) and week 14 (30.6% vs. 1.9%, P < 0.001). Increased remission was observed over time with over 50% of patients treated with GLM achieving remission at week 104. A greater proportion of GLM-treated patients achieved ACR20 and PASI75 response, a normalized physical function (HAQ≤0.5) or quality of life, or had significantly improved work productivity compared to placebo-treated patients at week 14 (all P values <0.01). These improvements were sustained over time through weeks 52 and 104. A greater proportion of patients in DAS28 remission also achieved normal physical function or had significantly improved work productivity from baseline at weeks 52 and 104, when compared to those not in remission. Improvement in employability, reduced time lost from work by patients and caregivers, and reduced health care utilization were observed at weeks 52 and 104, especially among those who achieved DAS28 remission. The overall safety profile of GLM through week 104 was similar to other anti-TNFα agents used for the treatment of PsA.

**Conclusions:** GLM treatment induced early and sustained remission (DAS28 <2.6), resulting in long-term improvements in physical function, health-related quality of life, work productivity, and reduction in health care utilization in PsA patients.

**Sponsorship:** This research was funded by Centocor Ortho Biotech Services, LLC, Horsham, PA, without external funding.
Economic Impact of Copayment Waivers on a Generic to Generic Conversion Program

Gorski B, Prasla K,* Godley P, Chaddock J, Scott and White Health Plan, 2401 S. 31st St, Temple, TX 76508; lprasla@swmail.sw.org, 254.298.6154

BACKGROUND: Health plans provide generic medications to beneficiaries at significantly lower costs than brand name drugs. The costs of generic medications can vary considerably. Scott & White Health Plan (SWHP), a regional Texas health plan, identified the price of felodipine as significantly higher than that of amlodipine due to a maximum allowable cost (MAC) in place. Because of established comparative effectiveness, SWHP implemented a 2-step initiative to convert patients from felodipine to amlodipine. The first initiative used a dynamic interchange process to convert patients to amlodipine at point-of-sale after patient and physician consent. The second initiative offered copay waivers to patients who did not convert to amlodipine through the first initiative.

OBJECTIVE: To measure the economic impact of copayment waivers on a generic-to-generic conversion program.

METHODS: 662 patients were contacted through mailings and offered the opportunity to convert from felodipine to amlodipine and receive copay waivers from March 2010 to June 2010. Patients that converted to amlodipine were identified through pharmacy claims. Total plan paid costs for participating members were identified pre- and post-conversion to amlodipine. Plan savings were identified for index dates and projected to 1 year.

RESULTS: Of the 662 patients contacted, 85 patients converted to amlodipine. 42 patients were excluded from the denominator due to lack of prescriptions for amlodipine or felodipine for the past year; 3 patients were excluded from the numerator due to felodipine prescriptions post-conversion. 82 patients switched to amlodipine for a 13.2% conversion rate. Actual program savings for SWHP were identified as $11,330.13 over a 4-month period from March 1, 2010, to July 31, 2010. After adjusting for days supply, the program has a projected annual savings of $33,723.

CONCLUSIONS: In this previously contacted population, the copay waiver initiative showed significant year-long savings with only a 13% conversion rate. The SWHP population contains low market shares of felodipine to amlodipine patients (18%); in populations with higher market shares of felodipine, cost savings can be considerably higher. For generic drugs with established comparative effectiveness and MACs in place, generic-to-generic conversions through copay waivers offer novel ways for health plans to save costs.

SPONSORSHIP: This research was funded by Scott and White Health Plan, Temple, TX.

Effect of Azilsartan Medoxomil Versus Valsartan and Olmesartan Medoxomil on the Achievement of Systolic Blood Pressure Goals in Essential Hypertension


BACKGROUND: Healthcare Effectiveness Data and Information Set (HEDIS) measures define controlled hypertension as systolic/diastolic blood pressure (SBP/DBP) of <140/90 mm Hg. In 2009, about one-third of members of commercial health plans with diagnosed hypertension had uncontrolled blood pressure. Failure to reach SBP goals can reduce health plans’ HEDIS scores.

OBJECTIVE: To assess the percentage of patients with uncontrolled essential hypertension who would reach SBP goals with alternative angiotensin receptor blocker (ARB) therapies.

METHODS: A Monte Carlo simulation model was created to estimate the number of hypertensive patients with SBP >140 mm Hg who would achieve SBP goal when treated with azilsartan medoxomil 80 mg, valsartan 320 mg, or olmesartan medoxomil 40 mg for 12 months. A cohort of hypothetical patients with uncontrolled hypertension was created from National Health and Nutrition Examination Survey (NHANES) 1999-2006 and was assigned a baseline SBP. Follow-up SBP values were generated by randomly sampling from the mean and SD of the percentage change from baseline to final visit in sitting office SBP readings by using data from the azilsartan medoxomil clinical trial program. Mean (SD) relative changes in SBP were azilsartan medoxomil –10.45% (10.89%), valsartan –6.38% (10.23%), and olmesartan medoxomil –8.67% (10.53%). We assessed goal attainment assuming that adherence was alternatively perfect and that 48% of patients...
RESULTS: In this analysis, patient characteristics based on NHANES data were as follows: mean (SD) age 53 (14) years, 53% male, 13% with prior cardiovascular disease, and mean baseline SBP 159 (19) mm Hg. We estimated that 46.0% patients receiving azilsartan medoxomil would achieve SBP goal versus 34.4% for valsartan and 41.0% for olmesartan medoxomil, assuming perfect adherence. Accounting for medication nonadherence, 23.8%, 17.9%, and 21.4% of patients would reach SBP goals, respectively.

CONCLUSIONS: Our findings suggest that more patients treated with azilsartan medoxomil than with valsartan or olmesartan medoxomil are expected to reach SBP goal. Treatment with azilsartan medoxomil may serve to improve health plans’ HEDIS scores.

SPONSORSHIP: This research was funded by Takeda Pharmaceuticals North America, Inc., Deerfield, IL.

Evaluating Generic Alternatives in Medicare Part D Through Member Outreach

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BACKGROUND: A large Medicare Part D prescription drug plan in the Northeast wanted to encourage the use of alternative generic drugs over brand drugs, when appropriate, to reduce costs for both the plan and the members. Targeted drug classes included oral antihistamine, benign prostatic hyperplasia, antidepressants, antihypertensives, statins, triptans, sedatives, and bisphosphonates.

OBJECTIVE: To examine cost and member impact after implementing a member-focused communication encouraging members to ask their doctor about specific alternatives to approximately 30 brand drugs.

METHODS: The communication was directed to members with 3 messages in the May to early June time period of 2010. Message had 3 components: (a) identification to member of target drugs they were using for which an alternative was available; (b) a message that a lower cost generic alternatives was available; and (c) suggestion “to ask your doctor” if these alternatives would be “right for you”.

RESULTS: Preliminary results look promising using a 4-month pre-period (January-April 2010) and a 4-month post-period (June-September 2010). In the 4-month pre-period, $20,220,485 was spent in these classes for the target and alternate drugs (see table). In the post-period, $18,240,785 was spent for a savings of $1,977,760. Overall days supply declined 43,392 in this period, suggesting there was very little discontinuation of therapy.

CONCLUSIONS: Outreach successfully targeted members and caused a change in the drug used and resulted in savings to the plan and the members.

SPONSORSHIP: This research was funded by CVS Caremark, Pittsburgh, PA.

Encouraging Generic Alternatives in Medicare Part D Through Member Outreach

TABLE

<table>
<thead>
<tr>
<th>Therapeutic Category</th>
<th>Pre-Period Spend</th>
<th>Post-Period Spend</th>
<th>Net Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antihistamines</td>
<td>$856,152</td>
<td>$829,100</td>
<td>$27,052</td>
</tr>
<tr>
<td>BPH drugs</td>
<td>$2,428,967</td>
<td>$1,312,088</td>
<td>$1,116,879</td>
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<tr>
<td>Depression</td>
<td>$2,292,701</td>
<td>$2,257,450</td>
<td>$35,252</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>$1,503,107</td>
<td>$1,387,795</td>
<td>$115,313</td>
</tr>
<tr>
<td>Statins</td>
<td>$10,815,957</td>
<td>$10,412,729</td>
<td>$403,227</td>
</tr>
<tr>
<td>Triptans</td>
<td>$1,535,748</td>
<td>$1,301,531</td>
<td>$234,217</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>$605,305</td>
<td>$554,126</td>
<td>$51,179</td>
</tr>
<tr>
<td>Sedatives</td>
<td>$20,220,485</td>
<td>$18,242,725</td>
<td>$1,977,760</td>
</tr>
</tbody>
</table>

BPH = benign prostatic hypertrophy; post-period = June through September 2010; pre-period = January through April 2010.

Evaluating Age Edit and Smart Benefits in the Management of Topical Dermatological Agents

Xu L,* Pavek A, Kavety J, Etemad L, UnitedHealthcare Services, Inc., 5901 Lincoln Dr, Edina, MN 55436; ling_xu@uhc.com, 952.992.5370

BACKGROUND: Currently, UHCP uses an age edit to target noncovered indications (e.g., photodamage) of select topical dermatological agents (TDA). Theoretically, age can be used as a proxy for covered indications. Subsequently, only members over 29 years require prior authorization. The age edit of 29 years or older reduces member disruption but may allow for noncovered uses in members less than 29 years of age. Smart Benefits (SB) are a collection of new management tools being developed that use member-specific information from sources such as medical claims data to individualize benefits at the point-of-sale. By linking medical claims data with pharmacy claims adjudication, SB can reduce the need for manual coverage review.

OBJECTIVE: To assess the current age edit and the opportunity for Smart Benefits to improve TDA management in place of, or in conjunction with, the current clinical program.

METHODS: Using pharmacy and medical claims data, members with an attempted claim for TDA (topical tretinoin, Differin, and Tazorac) between January 1, 2009, through December 31, 2009, were identified. The date of the first attempted claim for a TDA was identified as the index date. In order to capture new users, members were excluded if a claim for the index drug occurred in the 6 months prior to the index date. ICD-9-CM codes for covered diagnosis—acne (706.1), psoriasis (696.0; 696.1), and precancerous skin lesion (702.0; 238.2; 239.2)—were identified during the period from July 1, 2008, through February 28, 2010. The date of service for the medical claim with the identified ICD-9-CM code was collected as was the associated date the claim posted to the system. Members were stratified by age and presence of an identified ICD-9-CM code.

RESULTS: A total of 128,502 members met the inclusion criteria. Members aged 14 to 21 years (benchmark age group) accounted for 37.2% of attempted claims. The prevalence of covered diagnosis in the 14–21 age group (85.4%) was higher when compared to all members aged 29 years or older (67.1%), but similar to the 26–33 age group (81.2%). While the percentage of members with a covered diagnosis decreased gradually from 85% to 57% between 14 to 58 years of age, the decline had no clear cut-point at any particular age. With regard to SB, ICD-9-CM codes were available for 76.1% of all members. Medical claims with a covered ICD-9-CM code had a date of service and post date prior to or on the TDA index date for 70.1% and 26.5% of members, respectively.

CONCLUSIONS: No single age point was a definitive proxy to identify members using TDA for noncovered indications. SB layered with the age edit can reduce the disruption caused by the age edit.

SPONSORSHIP: This research was funded by UnitedHealthcare Services, Inc., Edina, MN.

Evaluation of a Pharmacist-Led Medication Reconciliation Program in Post-Discharge Patients

Salamanovich SA, Trinh CT, Shimamoto MS, Mathew MK, Jung TS, Cheng I,* HealthCare Partners Medical Group, 19191 S. Vermont Ave, Ste. 200, Torrance, CA 90502; ichung@healthcarepartners.com, 310.354.4265

BACKGROUND: Patients admitted to hospitals commonly have new

FIGURE

Abstracts from Professional Poster Presentations at AMCP’s 23rd Annual Meeting & Showcase
medications prescribed and/or have changes to their existing medications upon discharge. As a result, discrepancies may occur between a patient’s discharge medication regimen and the home regimen. Duplicate therapy, incorrect dosages, and missing medications are all troubling possibilities. To recognize and avoid potential medication errors, a medication reconciliation program was implemented in a managed care organization during the transition of care.

**OBJECTIVE:** To evaluate the effectiveness of a pharmacist-led medication reconciliation program in reducing medication errors in patients discharged from an inpatient setting.

**METHODS:** This was a prospective observational study conducted at a 254-bed community hospital. Patients discharged from the hospital between September 2009 and April 2010 were referred to the pharmacy department for intervention. A PharmD candidate contacted patients by telephone and reviewed the patient’s discharge summary, pre-admission medications, and self-reported medications. Discrepancies were reviewed with a supervising clinical pharmacist to develop an action plan. A satisfaction survey for the program was administered to the patients’ primary care physicians (PCP) with a 5-point Likert scale (1 = strongly disagree and 5 = strongly agree).

**RESULTS:** A total of 286 patients were referred to the program. The average time of the medication reconciliation consultation was 9 minutes for each patient. Out of 3,153 medications reviewed, 937 (30.3%) required clinical pharmacist intervention. The most common interventions were (a) clarification of missing prescribed medications (i.e., patients took medications at home that were not mentioned in discharge summary medication list): n = 230, 24.0% of interventions; (b) dose/frequency correction: n = 167, 17.5%; (c) medication discontinuation (i.e., patients should have discontinued medication but continued at home): n = 159, 16.6%. Out of 20 clinicians, 11 responded to the survey. Overall, PCPs were satisfied with the program (score = 4.6) and agreed the program would reduce medication errors (score = 4.5).

**CONCLUSIONS:** Based on our analysis, there appears to be important pharmacist-led interventional opportunities within a medication reconciliation program for patients transitioning from hospital settings.

**SPONSORSHIP:** This research was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ.

**Evaluation of a Value-Based Insurance Design in a Large Retail Employer**

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**BACKGROUND:** As the cost of health care continues to rise faster than inflation, employers have responded by shifting cost to employees. As out-of-pocket costs increase, employees may forgo needed medical services or medications, which can lead to negative health consequences. This concern has prompted employers to implement more clinically sensitive approaches to reduce cost, such as value-based insurance design (VBID). Mercer Health & Benefits is offering a value-based benefit product called Dx-Rx Pairing. This program offers reduced copayments for certain chronic disease medications with concurrent enrollment in a disease management program.

**OBJECTIVE:** To measure adherence and utilization in 1,276 program enrollees and in those eligible but not enrolled (1:1 matched controls, n = 1,276).

**METHODS:** Adherence, defined by proportion of days covered (PDC), was calculated using incurred drug claims 1 year before and after implementation of Dx-Rx. We used regression analyses to compare the change in adherence. Costs and utilization were evaluated at 1 year and 1.5 years post-enrollment compared to baseline.

**RESULTS:** A large, national retailer implemented Dx-Rx as of April 1, 2008. In the intervention group, 800 patients received health education mailings (HEM), while 476 patients received nurse counseling (NC). The adherence results differed according to the type of intervention. For those who received NC, adherence significantly improved for members taking antihypertensives, diabetes medications, and statins (β = 0.050, P = 0.025; β = 0.108, P < 0.001; β = 0.058, P = 0.017). Among members who received HEM, PDC improved significantly only for members taking diabetes medications (β = 0.052, P = 0.019). The number of hospitalizations significantly decreased in the NC group compared to the controls at 1.5 years (P < 0.001); in contrast, the number of hospitalizations increased in the HEM group but remained steady in the matched controls (P = 0.003). Utilization differences were also reflected in the cost results, with total mean [SD] health care costs in the NC increased by $44 [$467] in enrollees versus $1,861 [$401] in the controls (P < 0.003). In the HEM group, the total health care costs significantly increased compared to the controls at 1.5 years ($1,261 [$199] increase in enrollees, $182 [$181] increase in controls, P < 0.001).

**CONCLUSIONS:** The Dx-Rx program may be effective in improving medication compliance and ultimately improving health care outcomes and reducing total health care costs when active counseling is provided to high utilizers of care.

**SPONSORSHIP:** This research was conducted by University of California, San Francisco, without external funding.

**Evaluation of PQA Draft Measures of MTM Performance**

Ward M,* Xu Y, Nau D, Kuhle J, Humana, Inc., 1412 Arbor vague Circle, Chapel Hill, NC 27514; mward@humana.com, 919.265.0275

**BACKGROUND:** The Medicare Prescription Drug Improvement and Modernization Act (MMA) of 2003 requires Medicare Part D sponsors to have a medication therapy management (MTM) program. The Pharmacy Quality Alliance (PQA) has identified 4 potential performance measures to evaluate the impact of MTM services.

**OBJECTIVE:** To assess the potential use of the 4 performance measures proposed by PQA for evaluating the impact of MTM services.

**METHODS:** This was a retrospective analysis using MTM program data, membership enrollment data, and pharmacy claims from a health plan with Medicare Advantage prescription drug plan (MA-PD) and prescription drug plan (PDP) members. Medicare members who were eligible for MTM services based on Centers for Medicare & Medicaid Services (CMS) MTM eligibility criteria in 2009 were included. MTM consultations included telephonic and face-to-face pharmacist consultations. The following 4 PQA testing measures were calculated: (a) percentage of MTM-eligible members who received a comprehensive medication review (CMR); (b) percentage of MTM-eligible members who received an MTM consultation and discontinued use of a high-risk medication present before the MTM consultation; (c) percentage of diabetic MTM-eligible members who received an MTM consultation and began use of an angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) not present before the MTM consultation; and (d) percentage of MTM-eligible members with uncontrolled asthma who received an MTM consultation and began use of an asthma controller medication not present before the MTM consultation.

**RESULTS:** Of the 634,261 MTM-eligible Medicare members identified in 2009, 32,917 (5.2%) received a CMR by a pharmacist. There were 7,556 unique member/high-risk medication combinations identified prior to MTM consultation, of which 99.1% were no longer present in the post-consultation period. Of the 2,204 diabetic members on a hypertensive medication who did not receive an ACE inhibitor/ARB prior to MTM consultation, 15.4% received an ACE inhibitor/ARB in the
post-consultation period. A small number of uncontrolled asthmatic members (n=36) were identified with no controller therapy prior to MTM consultation, of which 5.6% began use of a controller therapy medication in the post-consultation period.

CONCLUSIONS: The calculation of the 4 draft measures of MTM performance was feasible for a Medicare plan with MTM program data, drug claims, and the technical specifications from PQA. Additional research is underway to assess the appropriate use of these measures to evaluate and improve MTM services.

SPONSORSHIP: This research was funded by Pharmacy Quality Alliance, Inc., Fairfax Station, VA.

Evaluation of the AMCP Format Versus 3.0: Managed Care Customer Perspectives

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BACKGROUND: The AMCP Format for Formulary Submissions is designed to standardize the method by which manufacturers can respond to unsolicited requests from managed care organizations (MCOs) regarding the clinical value of their products, as well as relevant off-label indications, economic information, and comparison to similar products. The Format was developed in collaboration with manufacturers and MCOs to address the needs of providing and evaluating comprehensive evidence-based drug information. Initially published in 2000, the Format underwent a major revision in late 2009 with Version 3.0, specifically with reorganization of sections related to the value story for the product as well as inclusion of a broader range of supporting studies, cost-effectiveness research, treatment guidelines, and consensus statements.

OBJECTIVE: To (a) evaluate the value that managed care customers place on different parts of the dossier, (b) assess the level of knowledge regarding the changes in Version 3.0, (c) explore customer understanding of the concept of comparative effectiveness research (CER), and (d) identify areas for improvement that manufacturers can implement when developing product dossiers.

METHODS: Participants included MCO customers who had contacted Genentech’s Medical Communications Department to request medical information from 2008-2010. They were asked to participate in a voluntary, electronic survey developed through Survey Monkey.

RESULTS: There were 28 responses. The survey showed that 36% of respondents were familiar with Version 3.0. Only 22% of respondents said they preferred Version 3.0 over Version 2.1 or other formats, while 64% expressed no preference. Respondents indicated that the most useful sections of the dossier are Section 1.0 Executive Summary and Section 3.0 Supporting Clinical Evidence. Almost 70% of respondents preferred to receive dossiers in an electronic format (CD-ROM or e-mail). When asked to identify areas for improvement for product dossiers, respondents indicated the inclusion of CER, increase availability, and decrease bias.

CONCLUSIONS: MCOs place the highest value on clinical data and utilize the Executive Summary and clinical sections most frequently. Unpublished clinical data were cited as the most useful aspect of the dossier. There is limited knowledge of changes made in Version 3.0. Definitions of CER are wide ranging and often opposing. Customers cite dossier availability and inclusion of CER as their top needs for dossier improvements.

SPONSORSHIP: This research was funded by Genentech, a member of the Roche Group, South San Francisco, CA.

Examining Health Care Costs in Chemotherapy-Induced Nausea and Vomiting: A Retrospective Analysis

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BACKGROUND: Chemotherapy-induced nausea and vomiting (CINV) is a major adverse effect of cancer treatment. CINV can have a significant impact on patient and caretaker quality of life and may result in a decision to refuse additional chemotherapy. The 5-hydroxytryptamine subtype 3 receptor antagonists (5-HT3-RA), first introduced in 1994, are indicated for the prevention of CINV. Current NCCN guidelines recommend a combination of 5-HT3-RA, dexamethasone, and aprepitant (NK1) for patients undergoing highly emetogenic chemotherapy (HEC) and a 5-HT3-RA with dexamethasone for moderately emetogenic chemotherapy (MEC).

OBJECTIVE: To examine the rate of CINV and CINV-related health care costs incurred during the first month of chemotherapy by patients undergoing a HEC or MEC treatment regimen.

METHODS: This study was a retrospective cohort analysis using UnitedHealthcare’s (UHC) i3/Ingenix LabRx database. The data included both pharmacy and medical claims of UHC’s 8-10 million covered lives. Continuously enrolled adult patients newly diagnosed with breast, lung, or colon cancer, newly treated with a MEC or HEC regimen, who received prophylactic 5-HT3-RA treatment during the period April 1, 2008, and March 31, 2009, were identified. The index date was defined as Day 1 of chemotherapy, and patients were followed for 30 days after the index date. CINV was defined by a claim with a primary ICD-9-CM diagnosis code for nausea and vomiting or volume depletion. The primary outcomes of interest were the rate of CINV and CINV-related health care costs (pharmacy, inpatient, ED, and outpatient).

RESULTS: A total of 9,558 patients were identified, with 28.7% (n = 2,739) undergoing HEC treatment and 71.3% (n = 6,819) undergoing MEC treatment. The mean age was 55.8 (SD = 10.5), and 71.8% were female. For patients on a HEC regimen, 10.7% (n = 294) experienced CINV and incurred $4,776 in CINV-related health care costs. For patients on MEC, 13.2% (n = 901) experienced CINV with $4,829 in related costs. Mean all-cause total health care costs in the first 30 days of treatment for patients with CINV were $39,743 (SD = $28,860) compared to $34,696 (SD = $29,684) for patients without CINV (P < 0.001).

CONCLUSIONS: This retrospective analysis showed that patients who experienced CINV in the first month of chemotherapy incurred significantly higher total health care costs than patients without CINV. The costs reported here were similar to those found in recent published reports examining CINV.

SPONSORSHIP: This research was funded by Eisai, Inc., Woodcliff Lake, NJ.

Exenatide BID Observational Study: Results for Primary and Secondary Endpoints at 12-Month Analysis


BACKGROUND: Controlled clinical trials, open-label follow-up studies, and more recently retrospective studies utilizing large claims databases have provided information about efficacy, safety, and effectiveness of exenatide twice daily in patients with type 2 diabetes.

OBJECTIVE: To evaluate the clinical effectiveness of exenatide twice daily among patients with type 2 diabetes in a real-world setting.

METHODS: Patients were enrolled from 74 practice sites from September 2007 through January 2009 and followed for 12 months in this
prospective, single-arm naturalistic, multicenter observational study. The primary effectiveness endpoint was achieving or maintaining hemoglobin A1c of ≤7.0%, or an absolute drop of 0.5% from baseline. Quality of life (QOL) was assessed using the Impact of Weight on Quality of Life (IWQOL-Lite). McNemar’s and paired t-tests were performed to compare the measures between baseline and follow-up. All care was managed by the treating physician, with the protocol referring to the American Diabetes Association standards of medical care for type 2 diabetes.

**RESULTS:** A total of 452 patients were included in the primary study population. At baseline, patients (60% female) had mean (+SD) age of 55±11, duration of type 2 diabetes of 9±8 years, hemoglobin A1c of 8.0±1.7%, and body mass index (BMI) of 38.2±7.4kg/m2. Family history of type 2 diabetes was reported in 73.9% of patients; 61.5% had hypertension; and 47.1% had hyperlipidemia. At 12 months, 98 patients (21.7%) were receiving 5 mcg exenatide twice daily; 146 (32.3%) were receiving 10 mcg twice daily; and 208 (46.0%) had discontinued treatment. The A1c goal was achieved in 76.3% of the 118 patients with A1c measurement available at 12 months (see table). There was a mean improvement of 4.56 in the total IWQOL-Lite score at 12 months versus baseline (P<0.001, see table). There was significant drop in all IWQOL-Lite sub-scales, including physical, social, emotional, and QOL impairment domains, with the largest mean improvement observed in physical QOL (−14.78, P<0.001). On follow-up at 12 months, 76.3% of patients achieved their A1c goal versus baseline. There was also a significant improvement in physical function (−10.56 points, P<0.001), emotional function (−7.91 points, P<0.001), physical role (−13.44 points, P<0.001), and energy (−6.26 points, P<0.001). The A1c mean change from baseline was −0.80% (P<0.001), and BMI of 38.2 ± 7.4 kg/m² had a mean change of −0.83 kg/m² (P<0.001).

**CONCLUSIONS:** The exenatide twice daily observational study substantiated the clinical effectiveness of exenatide demonstrated in previous clinical trials and retrospective database studies.

**SPONSORSHIP:** This research was funded by Eli Lilly and Company, Indianapolis, IN.

### Factors Associated with Work Productivity

**Impairment in Subjects with Overactive Bladder**

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**BACKGROUND:** Overactive bladder (OAB) can negatively affect work productivity.

**OBJECTIVE:** To identify factors associated with impaired work productivity in subjects with OAB symptoms and estimate annual indirect costs of productivity loss.

**METHODS:** Of 24,866 respondents of the National Health & Wellness Survey, an internet-based questionnaire, 2,750 recontacted respondents completed a longitudinal survey. Eligible adults had an OAB Awareness Tool score of >14 (men) or >16 (women) or reported OAB prescription medication use. Analysis of proportions and a multivariate model (2-tailed P<0.05) identified factors associated with work productivity using the Work Productivity and Activity Impairment (WPAI) measure.

**RESULTS:** Of 476 employed respondents, 193 reported OAB Rx medication use, and 283 were untreated with prescription medication. Bivariate analyses showed significant (P<0.05) differences for treated versus untreated subjects for percent health-related impairment while working (20% vs. 47%) and percentage overall health-related impairment (33% vs. 48%). In multivariable analyses, (a) absenteeism was significantly associated with younger age, male gender, and black ethnicity; (b) presenteeism was significantly associated with OAB nontreatment, younger age, and Hispanic or Other ethnicity; and (c) overall loss of work productivity was significantly associated with OAB nontreatment, younger age, male gender, and Hispanic or Other ethnicity (see table). The effect of OAB nontreatment on overall work productivity loss remained significant when symptom severity and symptom impact were included as covariates. Annual indirect costs of impaired work productivity were $9,670 in treated and $17,477 in untreated subjects (P<0.001).

**CONCLUSIONS:** The strongest predictors of overall work productivity impairment in adults with OAB symptoms were age and lack of OAB treatment.

**SPONSORSHIP:** This research was funded by Pfizer Inc., New York, NY.

### Health Care Utilization and Costs During the First 3 Years After a Diagnosis of Fibromyalgia

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**BACKGROUND:** Fibromyalgia (FM) is a chronic condition characterized by widespread pain and other symptoms including fatigue, sleep disturbances, and cognitive effects. FM diagnosis is difficult, resulting in help-seeking behavior until the appropriate diagnosis is made. It is unclear how the FM diagnosis impacts health care resource utilization and costs relative to the pre-diagnosis period.

**OBJECTIVE:** To evaluate pharmacy prescribing patterns, health care resource utilization, and costs 1 year before and 3 years after a diagnosis of FM.

**METHODS:** This retrospective cohort analysis identified pharmacy and medical claims in the Humana database for individuals aged 18 years or older newly diagnosed with FM, defined as at least 2 claims with ICD-9-CM codes 729.1 or 729.0 between June 1, 2002, and March 1, 2005. Comorbidities, pharmacotherapy (stratified by pain-related and antidepressant) and 3 years after diagnosis. The strongest predictors of overall work productivity impairment in adults with OAB symptoms were age and lack of OAB treatment.
RESULTS: We identified 2,613 FM patients (73% female, mean age 58.5 ± 15.3 years, mean pre-diagnosis Charlson Comorbidity Index [CCI] 0.48 ± 1.05). Claims for pain-related medications peaked during the 6 months immediately after diagnosis and remained stable during follow-up. Recommended FM therapies increased post-diagnosis but remained less common than other pain-related therapies. Prescribing and costs for nonpain-related medications were higher than pain-related medications and increased throughout the entire study period. Total resource utilization and costs increased progressively through 6 months immediately after diagnosis (total mean costs per patient = $3,481), followed by a decline and plateau, but increased again during the final 6 months ($3,588). The CCI score increased over the study period, and there was substantial outpatient resource use for chronic conditions.

CONCLUSIONS: An FM diagnosis was associated with increased utilization and pain-related medication costs up to the first 6 months post-diagnosis followed by stabilization over 3 years. The increase in nonpain medications over the observation period, which accounted for the majority of pharmacy costs, may be related to an increasing prevalence of comorbid conditions and a small subset of high utilizers of health care resources.

SPONSORSHIP: This research was funded by Pfizer Inc., New York, NY.

Health Care Cost Outcomes for Alcohol Dependence: A Comparison of 4 Treatments

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BACKGROUND: Alcohol use disorders (including alcohol abuse and dependence) occur commonly in the general population, with an estimated past-year prevalence of approximately 8.5%. Since 2005, the National Institutes of Health has recommended that medication be considered for every patient with alcohol dependence. However, few patients with alcohol dependence are prescribed medications approved by the FDA. Currently 4 medications are approved by the FDA for the treatment of alcohol dependence: injected naltrexone (XR-NTX), oral naltrexone (oral-NTX), acamprosate, and disulfiram. However, relatively little data are available that evaluate comparative health care cost outcomes for these 4 treatments.

OBJECTIVE: To examine cost outcomes for alcohol-dependent patients treated with 1 of 4 different FDA-approved medications.

METHODS: This retrospective, propensity-score matched analysis examined persistence, utilization, and costs among 15,502 adult commercial members who had at least 1 medical or pharmacy claim for injected naltrexone (XR-NTX), oral naltrexone (oral-NTX), acamprosate, and disulfiram between 2006-2009, with at least 6 months pre- and post-index enrollment.

RESULTS: In the 6 months following the index treatment episode, patients treated with XR-NTX (n=661) had significantly longer persistence with treatment compared to patients on oral-NTX (n=2,391), disulfiram (n=3,492), and acamprosate (n=8,978, P<0.01 for all comparisons). XR-NTX was associated with a consistent pattern of lower rates of admission to inpatient services and lower costs (P<0.01). For total costs, including pharmacy costs of the agents, the total cost per capita was significantly lower for patients treated with XR-NTX ($6,757) versus acamprosate ($10,345, P<0.001) and was not significantly different versus oral-NTX ($6,595) or disulfiram ($7,107).

CONCLUSIONS: Limitations include nonequivalent baseline characteristics between the groups (addressed by propensity-score matching), and the need to conclude associative rather than causal relationships. Nevertheless, these data represent the largest and best-matched real-world comparison across these four agents to date. Treatment with XR-NTX was associated with (a) significantly greater refill persistence, (b) a significantly smaller percent of intensive service utilization, and (c) either significantly lower or no significant difference in combined net health care costs expended over a 6-month period, including the cost of the agents.

SPONSORSHIP: This research was funded by Alkermes, Inc., Waltham, MA.

Health Care Costs of Patients Switching or Dose Escalating Anti-Tumor Necrosis Factor (TNF) Therapy

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BACKGROUND: Switching among anti-tumor necrosis factor (TNF) agents has become common as patients and physicians seek better disease control. An alternative to switching is dose escalation. Cost implications of switching versus dose escalation are unknown.

OBJECTIVE: To examine all-cause and rheumatoid arthritis (RA)-specific health care costs of anti-TNF switching versus dose escalation.

METHODS: Patients treated with adalimumab, etanercept, or infliximab were identified from the MarketScan database (June 2004 through June 2009). Inclusion criteria were patients aged 18 years or older, diagnosed with RA (ICD-9-CM codes 714.xx), no biologic claim for 6 months pre-index, continuous plan enrollment for 12 months post-index, at least 3 doses of index biologic, and no other select inflammatory disorders. Switch was defined as a claim for nonindex anti-TNF during follow-up. Infliximab dose escalation was defined as at least 33% increase in number of vials in a claim or decrease in interval between infusions. Adalimumab and etanercept dose escalation was defined as a refill less than 28 days, increase in days supply per claim, or decrease in the number of days between refills of at least 7 days. Propensity score matching was applied to control for baseline differences. Generalized linear models with gamma distribution and logarithmic link were used for adjustment of baseline covariates.

RESULTS: The sample consisted of 2,587 patients (1,979 commercial/608 Medicare). In the unadjusted sample, all-cause and RA-specific costs are greater for patients that dose escalate versus switch (all-cause costs = $36,354 vs. $32,960, P<0.001; RA-specific costs = $21,837 vs. $19,447, P<0.001). After adjusting for age and comorbidity, all-cause costs are comparable for all patients ($32,493 vs. $31,885, P=0.484). RA-specific costs are lower for those that escalate ($17,667 vs. $20,341, P<0.001). Results from the commercial sample were similar to the overall sample. In the Medicare sample there were no significant differences between all-cause costs and RA-specific costs of switching versus dose escalation in the unadjusted sample; dose escalation was significantly less costly in the adjusted RA-specific costs sample ($15,488-escalate vs. $17,971-switch, P=0.008).

CONCLUSIONS: In this analysis, all-cause health care costs of switching agents versus escalating dose are similar when comparable patient samples are evaluated. The RA-specific costs of dose escalation are significantly lower than costs of switching. Adjustment of patient baseline differences may be needed when conducting comparative analyses of observational data.

SPONSORSHIP: This research was funded by Centocor Ortho Biotech Services, LLC, Horsham, PA, without external funding.
Health Care Resource Utilization and Costs Among Type 2 Diabetes Patients on Combination Oral Therapy: Step-Therapy, Loose, and Fixed-Dose Combinations

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**BACKGROUND:** The impact of different oral antidiabetic drug (OAD) combination treatments (fixed dose combination [FDC], loose dose combinations [LDC], or monotherapy with subsequent add-on step-therapy [ST]) on health care resources utilization (HRU) and costs among type 2 diabetes patients remains uncertain.

**OBJECTIVE:** To evaluate the impact of different OAD combination therapies on HRU and costs among type 2 diabetes patients.

**METHODS:** A retrospective claims database analysis was conducted for type 2 diabetes patients continuously enrolled in a national health plan from 2007 to 2009. Patients who previously used OAs or insulin were excluded. Eligible patients were assigned to 1 of the 3 cohorts (FDC, LDC, or ST). HRU and total healthcare and diabetes-related costs were measured during the 12-month follow-up period. Logistic regression, negative binomial model (NBM), and generalized linear models (GLM) were conducted, controlling for patient demographics and comorbidities.

**RESULTS:** 21,048 patients (8,416 FDC, 4,225 LDC and 8,407 ST) were included. FDC patients were younger than patients on ST (mean age: 53.3 vs. 55.8, *P* < 0.001) and LDC (53.3 vs. 55.0, *P* < 0.001) FDC patients had a lower Charlson-Quan score than ST (1.13 vs. 1.21, *P* < 0.001) but similar to LDC patients (1.13 vs. 1.15, *P* = 0.451). Compared to ST patients, FDC patients had significantly lower rates of inpatient stays (9.0% vs. 12.7%, *P* < 0.001) and emergency room (ER) visits (1.4% vs. 2.0%, *P* = 0.003). FDC patients had fewer diabetes-related ambulatory visits (2.7) than ST (3.7, *P* < 0.001) and LDC patients (3.2, *P* < 0.001). FDC patients had lower average diabetes-related costs ($1,641) than ST ($2,099, *P* < 0.001) and LDC patients ($1,909, *P* = 0.012). Logistic regression analysis showed that ST and LDC patients had significantly higher odds of inpatient or ER visits compared to FDC patients (step-therapy odds ratio = 0.366, *P* < 0.001; LDC odds ratio = 1.262, *P* < 0.001). NBM showed that FDC patients had significantly fewer adjusted diabetes-related ambulatory visits (2.79) compared to ST (3.59, *P* < 0.001) and LDC patients (3.20, *P* < 0.001). GLM demonstrated that FDC patients had significantly lower adjusted total health care costs ($8,745) compared to ST ($10,352, *P* < 0.001) and LDC patients ($10,294, *P* < 0.001).

**CONCLUSIONS:** In this analysis of type 2 diabetes patients, FDC treatment was associated with fewer inpatient, ER, and ambulatory visits and lower total and diabetes-related health care costs than treatment with dual therapy in nonfixed form.

**SPONSORSHIP:** This research was funded by AstraZeneca, Wilmington, DE.

**Health Care Resource Utilization and Costs Associated with Bevacizumab Versus Cetuximab in Second-Line Treatment of Metastatic Colorectal Cancer Patients**

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**BACKGROUND:** Targeted therapies such as bevacizumab (BV) and cetuximab (CX) are efficacious and increasingly used in metastatic colorectal cancer (mCRC). However, real-world comparisons of health care outcomes between these 2 drugs are unclear.

**OBJECTIVE:** To compare real-world health care resource utilization and costs of mCRC patients treated with BV versus CX in second-line therapy.

**RESULTS:** The study included 2,188 mCRC patients (second-line BV = 1,808, second-line CX = 380). The 2 groups were similar in demographics. During the 6-month period following second-line start, BV patients had fewer inpatient (0.5 vs. 0.7, *P* < 0.001) and outpatient visits (3.45 vs. 3.50, *P* = 0.014) than CX patients (see table). Treatment with BV, compared to CX, was associated with significantly lower 6-month total costs (adjusted difference: –$10,231, *P* = 0.020) and medical costs (–$10,796, *P* = 0.012). Median duration of second-line therapy was significantly longer for BV patients than CX patients (4.7 vs. 4.0 months). Average monthly costs while on second-line therapy was also lower in BV patients compared to CX patients in terms of total (–$6,219, *P* < 0.001) and medical costs (–$6,367, *P* < 0.001).

**CONCLUSIONS:** BV is associated with fewer health care resource utilization and lower health care costs compared to CX in second-line treatment of mCRC patients.

**SPONSORSHIP:** This research was funded by Genentech, a member of the Roche Group, South San Francisco, CA.

**Health-Related Characteristics of Low Versus Normal Folate Level in Women of Childbearing Age**

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**BACKGROUND:** Folate is an essential vitamin for good health. Women of childbearing age are a population subgroup for which it is especially important to maintain normal blood folate levels. The link between low blood folate levels and an increased risk of neural tube birth defects has been well established. However, little is known of the health care-related characteristics of women with low versus normal folate.

**OBJECTIVE:** To compare health-related characteristics among U.S. women of child-bearing age with low versus normal red blood cell (RBC) folate levels.
METHODS: Data from the National Health and Nutrition Examination Survey (NHANES) were used for this study from years 2003 to 2006. Based on NHANES definition, women of child-bearing age (ages 18-45 at the time of survey) were categorized in 2 groups: (a) normal red blood cell (RBC) folate level (≥ 140 ng per ml) and (b) low RBC folate level (< 140 ng per ml). All descriptive and bivariate statistics were analyzed with SAS 9.2.

RESULTS: Approximately 94% (n = 2,649) eligible subjects were defined as having normal folate level (NFL) versus 5.9% (n = 167) defined as low folate level (LFL). Compared to NFL, LFL were significantly younger (28 years vs. 30 years, P = 0.010), with a significantly greater proportion between the ages of 18 and 25 (55.7% vs. 39.9%, P < 0.001). A higher proportion were African American (55.1% vs. 22.3%, P < 0.010); had a lower proportion of health insurance (67.3% vs. 75.5%, P = 0.010), private insurance (39.5% vs. 53.1%, P < 0.010); and similar Medicaid/CHIP coverage (16.8% vs. 15.1%, P = 0.560). LFL also reported significantly (P < 0.050) higher coronary events such as a heart attack (8.1-fold) or stroke (3.6-fold), emphysema (4.9 fold), and arthritis (1.8-fold). In contrast, NFL reported a greater proportion of asthmatics (15.7 vs. 9.6, P < 0.010) and a lower proportion of members with health insurance coverage, and tend to have lower rates of private insurance coverage, and tend to have higher rates of chronic health conditions compared to women with normal folate levels.

SPONSORSHIP: This research was conducted by Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ, without external funding.

Impact and Pharmacist Response to a Point-of-Sale Therapeutic Duplication Program

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BACKGROUND: Therapeutic duplication (TD) is a frequently occurring drug-related problem. Because of the potential for additive drug toxicities, therapeutic duplication raises patient safety concerns and contributes to waste within the health care system.

OBJECTIVE: To (a) identify cases of potential TD at the point of sale, (b) reject duplicate claims but permit pharmacists to override the reject if necessary, and (c) qualitatively analyze program data including pharmacists’ responses to duplicate claims.

METHODS: A TD edit program was implemented at the point of sale for 4 therapeutic drug classes including statin cholesterol medications, proton pump inhibitors, SSRI antidepressants, and triptan migraine medications. Duplicate claims were rejected, and online messaging informed the pharmacy of the TD and provided information pertaining to the original duplicative prescription (drug name and date filled). Pharmacists were able to override the reject, if deemed clinically appropriate, and indicate the type of intervention made (if any) by using standard Professional Service and Result of Service codes.

RESULTS: During calendar year 2009, a total of 43,517 TDs were identified by the program. The percent of claims not overridden by the pharmacy varied by drug class and ranged from 33% (triptans) to 55% (statins). Results of pharmacist’s interventions for claims that were overridden are summarized in the Table and indicate that pharmacists frequently consulted with physicians to determine prescription appropriateness. Only 8% of TD rejects were overridden without a pharmacist intervention.

CONCLUSIONS: Based on the percent of rejected claims that were not overridden by a pharmacist, nearly half of the incidences of TD identified may have resulted from unnecessary medication use. Pharmacists appear to provide valuable interventions in addressing TDs, ultimately reducing the number of therapeutically inappropriate duplications encountered by patients and likely improving patient safety.

SPONSORSHIP: This research was funded by Aetna Health Insurance Company, Hartford, CT.

Impact of a Clopidogrel and Proton Pump Inhibitor Concurrent Use Retrospective Drug Utilization Review Provider Safety Letter

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BACKGROUND: Proton pump inhibitors (PPIs) may reduce the effectiveness of clopidogrel (Plavix) by decreasing conversion to its active metabolite and potentially increasing the risk for a subsequent cardiovascular event. Using retrospective drug utilization review (RDUR), health plans can send provider letters notifying them of members with potentially unsafe concurrent drug use and requesting the provider to re-evaluate the need for PPI therapy and consider an H2-blocker (except cimetidine).

OBJECTIVE: To assess concurrent clopidogrel and PPI utilization after a provider RDUR letter.

METHODS: This observational cohort study used pharmacy claims data from a 1.3 million-member commercial insurer. Provider letters were sent on December 23, 2009, for members with concurrent clopidogrel and PPI supply. A control population of 2.6 million commercially insured members was identified using the intervention group criteria; however, letters were not sent. At 180 days (June 23, 2010), members still enrolled were assessed for the presence of a PPI supply, clopidogrel supply, or both. Statistical comparisons were made using the chi-square test.

Impact of a Retrospective Drug Utilization Review Provider Safety Letter for Clopidogrel and PPI Concurrent Use

<table>
<thead>
<tr>
<th>Drug Supply at 180 days</th>
<th>Intervention</th>
<th>Control</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>post-Provider Letter</td>
<td>n = 1,316</td>
<td>n = 2,740</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clopidogrel and PPI</td>
<td>825 (62.7%)</td>
<td>1,924 (70.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>PPI only</td>
<td>124 (9.4%)</td>
<td>231 (8.4%)</td>
<td>0.324</td>
</tr>
<tr>
<td>Neither clopidogrel nor PPI</td>
<td>84 (6.4%)</td>
<td>167 (6.1%)</td>
<td>0.774</td>
</tr>
<tr>
<td>Clopidogrel and H2-blocker (no PPI)</td>
<td>70 (5.3%)</td>
<td>33 (1.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clopidogrel only</td>
<td>213 (16.2%)</td>
<td>385 (14.1%)</td>
<td>0.081</td>
</tr>
</tbody>
</table>
| H2-blocker = histamine-2 receptor antagonist, PPI = proton pump inhibitor.

aChi square test.
RESULTS: Of the 1,723 members with a provider intervention letter sent, 291 were no longer enrolled, and 116 had no clopidogrel or PPI claims after the mail date, leaving 1,316 analyzable members; the control group consisted of members for whom the safety edit was inactive. Control group members utilizing rosiglitazone with CIN were analyzed identically to the intervention group. ADT rate differences were tested using the chi-square statistic. A total of 294 patients met the inclusion criteria. Of these, 130, 97, and 67 patients fell into the no depression, controlled depression, and uncontrolled depression cohorts, respectively. Patients with untreated depression had a lower MPR than patients with controlled depression or no depression (76.6%, 79.2%, and 83.4%; P = 0.031).

RESULTS: In the intervention group, 30 per 100,000 (168) members had their rosiglitazone claim rejected due to the safety edit during the 180-day study period (see table); 138 (82.6%) due to concurrent insulin, 23 (13.7%) had no claims for ADT. At 30 days, the no ADT rate was significantly lower in the intervention (62.7%) versus control group (70.2%), P < 0.001. The 7.5 point difference translates into a number needed to intervene upon of 14 to affect 1 change (95% CI = 9.4-22.7).

CONCLUSIONS: This quality of care RDUR provider letter resulted in a significant 7.5% reduction in concurrent clopidogrel and PPI use, compared to a control group. The number needed to intervene upon was 14 at a cost of $17.22 per member no longer concurrently using clopidogrel and a PPI.

SPONSORSHIP: This research was funded by Blue Cross and Blue Shield of Florida, Jacksonville, FL.

Impact of a Rosiglitazone Safety Edit: Cohort Study

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BACKGROUND: Rosiglitazone prescribing information warns against concurrent insulin or nitrate (CIN) use due to increased risk of myocardial ischemic events. To prevent rosiglitazone and CIN use, a point-of-sale automated electronic safety edit was implemented for a 1.2 million-member commercially insured population on January 1, 2009. The edit rejected a rosiglitazone claim if CIN supply existed.

OBJECTIVE: To determine whether MS patients diagnosed with depression would have better adherence to DMT with an adequate course of antidepressants versus patients with inadequate antidepressant therapy.

METHODS: Six-month continuous enrollment in 2008 and 2009 who also received DMTs were identified from medical and pharmacy claims from a private midwestern insurer. From this data, a medication possession ratio (MPR) for the DMT, a diagnosis of depression, and measurement of antidepressant treatment adequacy were determined. Patients were grouped into 3 categories: no depression, controlled depression, and uncontrolled depression. The MPR was calculated for the calendar year of 2009. MPRs for the groups were compared using the Wilcoxon rank sum test and an ANOVA test that controlled for age, gender, length of DMT use, and specific DMT.

RESULTS: A total of 294 patients met the inclusion criteria. Of these, 130, 97, and 67 patients fell into the no depression, controlled depression, and uncontrolled depression cohorts, respectively. Patients with uncontrolled depression had a lower MPR than patients with controlled depression or no depression (76.6%, 79.2%, and 83.4%; P = 0.031).

However, after controlling for potential confounders, the effect of uncontrolled depression on post-index days 30, 60, 90, and 180 was not significantly different between groups (see table). At 30 days, the no ADT rate was not different between intervention and control groups (P = 0.119) and remained nonsignificant (P > 0.05) at 180 days.

CONCLUSIONS: A rosiglitazone point-of-sale automated safety edit did not result in increased ADT abandonment 60 days after the reject claim and potentially reduced myocardial ischemic event risk.

SPONSORSHIP: This research was funded by Blue Cross and Blue Shield of Florida, Jacksonville, FL.

Impact of Depression on Adherence to Disease-Modifying Therapies for Multiple Sclerosis

Deyle T, Klepser D,* Huether J, University of Nebraska Medical Center, College of Pharmacy, Department of Pharmacy Practice, 986043 Nebraska Medical Center, Omaha, NE 68198; dklepser@unmc.edu, 402.559.4927

BACKGROUND: Multiple sclerosis (MS) is a demyelinating disease of the central nervous system whose treatment often involves disease-modifying treatments (DMTs) to reduce exacerbations, decrease the formation of brain lesions, and slow disease progression. Despite the benefits of the DMTs, nonadherence to these medications is common. Untreated depression is a commonly implicated factor in nonadherence with a few reports that patients with new or worsening depression are at greater risk for discontinuing INF-β1b therapy. Additionally, adequate treatment of depressive symptoms has been shown to increase adherence in other drug classes such as the HMG-CoA-reductase inhibitors, but the relationship has not been well studied for DMTs.

OBJECTIVE: To determine whether MS patients diagnosed with depression would have better adherence to DMT with an adequate course of antidepressants versus patients with inadequate antidepressant therapy.

METHODS: In this retrospective cohort study, patients with continuous enrollment in 2008 and 2009 who also received DMTs were identified from medical and pharmacy claims from a private midwestern insurer. From this data, a medication possession ratio (MPR) for the DMT, a diagnosis of depression, and measurement of antidepressant treatment adequacy were determined. Patients were grouped into 3 categories: no depression, controlled depression, and uncontrolled depression. The MPR was calculated for the calendar year of 2009. MPRs for the groups were compared using the Wilcoxon rank sum test and an ANOVA test that controlled for age, gender, length of DMT use, and specific DMT.

RESULTS: A total of 294 patients met the inclusion criteria. Of these, 130, 97, and 67 patients fell into the no depression, controlled depression, and uncontrolled depression cohorts, respectively. Patients with uncontrolled depression had a lower MPR than patients with controlled depression or no depression (76.6%, 79.2%, and 83.4%; P = 0.031).

However, after controlling for potential confounders, the effect of uncontrolled depression on post-index days 30, 60, 90, and 180 was not significantly different between groups (P = 0.119) and remained nonsignificant (P > 0.05) at 180 days.

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SPONSORSHIP: This research was funded by Blue Cross and Blue Shield of Florida, Jacksonville, FL.

### TABLE

<table>
<thead>
<tr>
<th>Hierarchical Order</th>
<th>30 Days</th>
<th>60 Days</th>
<th>90 Days</th>
<th>180 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>n = 168</td>
<td>n = 222</td>
<td>n = 168</td>
<td>n = 222</td>
</tr>
<tr>
<td></td>
<td>8 (4.8%)</td>
<td>222 (100%)</td>
<td>9 (5.4%)</td>
<td>166 (74.8%)</td>
</tr>
<tr>
<td>Other antidiabetic drug†</td>
<td>134 (79.8%)</td>
<td>0</td>
<td>133 (79.2%)</td>
<td>34 (15.3%)</td>
</tr>
<tr>
<td>No supply of any antidiabetic drug</td>
<td>26 (15.5%)</td>
<td>0</td>
<td>26 (15.5%)</td>
<td>22 (9.9%)</td>
</tr>
</tbody>
</table>

Not all columns sum to 100.0% due to rounding.

†Supply of antidiabetic drug therapy (ADT) including insulin or any oral antidiabetic agent with the exception of rosiglitazone.

‡10 members on rosiglitazone and concurrent nitrate or insulin, 3 members on rosiglitazone only.

§4 members on rosiglitazone and concurrent nitrate or insulin, 48 members on rosiglitazone only.
depression status was no longer significant ($P=0.129$).

CONCLUSIONS: Adequate antidepressant use was not associated with a significantly greater improvement in DMT adherence despite a small decrease in MPR. Overall adherence to DMT was high across the groups, and it is possible that this study was underpowered to detect a difference.

SPONSORSHIP: This research was funded by University of Nebraska Medical Center, College of Pharmacy, Omaha, NE.

### Impact of Electronic Prescribing on Formulary Adherence Rates in an Integrated Health Plan

**Boals E,** Klepser D, Huerter J, Williams C, BlueCross and BlueShield of Nebraska, 7261 Mercy Rd., Omaha, NE 68180; elizabeth.boals@bchsne.com, 402.982.6595

**BACKGROUND:** E-health, including electronic prescribing, is an area of managed care pharmacy where potential value has been predicted, but actual value is largely unknown. Major health plans are paying a significant amount to third-party vendors to provide health care providers with information regarding plan eligibility, plan benefits, and prescription claim history. What is unknown is if this investment impacts formulary adherence and if payers are receiving value for the dollars spent.

**OBJECTIVE:** To compare the correlation between electronic prescribing rates and formulary adherence rates among providers practicing in Nebraska.

**METHODS:** The retrospective claims analysis compared the rates of generic utilization to various electronic prescribing rates. The analysis included Nebraska prescribers who had more than 120 prescription claims between October 1, 2009, and September 30, 2010. Claims were reviewed for the prescription origin code and formulary status. For the various subgroups, the median and mean generic prescribing rates were calculated and compared. This analysis also compared rates of brand formulary adherence to electronic prescribing rates.

**RESULTS:** When generic prescribing rates were compared among various levels of electronic prescribing, prescribers who were considered to not use electronic prescribing had an average generic utilization rate of 70%, while prescribers that had high numbers of electronic prescriptions had an average generic utilization rate of approximately 71%.

**CONCLUSIONS:** These results suggest that electronic prescribing currently may not be driving formulary adherence as much as could be expected. There could be many reasons why this analysis did not show significant differences in formulary adherence between high and low electronic prescribing rates, including generic utilization rate plateau, slow adoption of electronic prescribing, and physicians only using a part of electronic prescribing capabilities.

SPONSORSHIP: This research was funded by BlueCross BlueShield of Nebraska, Omaha, NE.

### Impact of Multiple Sclerosis on Patients: A Systematic Review of the Evidence

**Kamal KM,** Patel B, Atreja N, Zacher C, Duquesne University, 314 Bayer Learning Center, 600 Forbes Ave., Pittsburgh, PA 15282; kamalb@duq.edu, 412.396.1926

**BACKGROUND:** Multiple sclerosis (MS) is an unpredictable disease and results in increasing disability and cognitive impairment over time. This translates into reduced productivity, work disability, and economic hardship in patients with MS. In addition, MS symptoms severely compromise a patient’s quality of life (QoL). Thus, measurement of patient-reported outcomes in MS offers payers, clinicians, and other decision makers a better understanding of the patient experience and aids in the evaluation of the disease impact on patients and on society as a whole.

**OBJECTIVE:** To conduct a review of studies examining the impact of MS on patient’s QoL and work productivity.

**METHODS:** A systematic literature review was conducted on MEDLINE, EMBASE, Cochrane databases, Evidence Based Medicine Reviews and International Pharmaceutical Abstracts. All English articles published between January 1990 and March 2010 were identified. Search terms used alone or in combination included multiple sclerosis, loss of productivity, presenteeism, absenteeism, quality of life and health-related quality of life. Randomized clinical trials reporting only clinical outcomes, nonpharmacological treatments, psychometric studies, and review articles were excluded.

**RESULTS:** A total of 63 articles were retrieved in the initial search out of which 17 articles met the inclusion/exclusion criteria. The review of 11 QoL studies confirms the increasing humanistic burden of MS on patients, including physical, psychological, and social factors. Most studies showed that QoL in MS was low compared to the control group. Also, QoL was considerably impaired in the early stages of MS and was found to vary with age and disease duration. Women demonstrated
higher levels of global QoL and social coping compared to men. Results from 6 productivity studies confirmed the high economic burden of MS, with indirect cost greatly exceeding the direct cost in MS. Also, the loss of productivity and caregiver burden contributed a major percentage to the economic impact caused by MS.

CONCLUSIONS: This systematic review confirms the emerging importance of patients' perceived health status and QoL in MS. Despite significant investigations into the physical aspects of humanistic outcomes, very limited data are available on the impact of the disease on cognitive impairment, patient's emotional status, and interpersonal relationships. Also, there is a need to assess QoL in newly diagnosed patients. MS has a considerable economic impact on the health care system in terms of the loss of productivity on the part of patients and caregivers.

SPONSORSHIP: This research was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ.

■ Impact of Palivizumab Coverage Status and Use on RSV-Related Health Care Utilization

Champ AM, Klepser D,* Huether J, Williams C, University of Nebraska Medical Center, 986045 Nebraska Medical Center, Omaha, NE 68198; dklepser@ummc.edu, 402.539.4927

BACKGROUND: Respiratory syncytial virus (RSV) infections are a leading cause of hospitalizations in infants and children and are responsible for an increased risk of morbidity and mortality in infants born prematurely and those with chronic lung disease (CLD) or congenital heart disease (CHD). Because palivizumab is the only available product for prophylaxis of RSV infections in high-risk infants and is an expensive injectable immunoprophylactic agent, many third-party payers have implemented a prior authorization (PA) program for palivizumab based on the American Academy of Pediatrics (AAP) guidelines and FDA-approved package labeling.

OBJECTIVE: To compare RSV-related hospitalizations and events among groups determined by PA utilization, PA eligibility, and palivizumab utilization.

METHODS: A retrospective study was conducted utilizing claims data from 4 RSV seasons (2006-2010) from a 700,000-member midwestern third-party payer. All live births were analyzed, and each infant was placed into 1 of 5 groups determined by PA utilization, PA eligibility, and palivizumab utilization. RSV-related events and hospitalizations were identified utilizing ICD-9-CM codes, and rates were compared among the groups.

RESULTS: A total of 50,283 patient-seasons were included in this study. The event rates for each group are shown in the Table. Patients applying for the PA had higher rates of RSV-related health care utilization regardless of PA eligibility.

CONCLUSIONS: Policymakers need to consider why infants who were PA eligible did not apply for palivizumab coverage and determine why these infants had lower RSV risk compared with those infants that received medication. Possible explanations include increased surveillance of patients applying for the PA program or difference in risk among patients who could qualify for the PA and those who actually apply.

SPONSORSHIP: This research was performed by University of Nebraska Medical Center, Omaha, NE, without external funding.

Impact of Pregabalin Utilization Management: An Analysis of Rejected Pregabalin Claims

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BACKGROUND: Utilization management is a tool used by health plans to ensure appropriate use of medication. The impact of patients using pregabalin when exposed to utilization management is unclear.

OBJECTIVE: To investigate the impact of pregabalin management on medication utilization and cost.

METHODS: A retrospective database analysis comparing patients with and without restrictions for pregabalin was conducted. Members with a rejected claim due to prior authorization (PA), step edit (SE), or nonformulary (NF) between January 2006 and November 2008 were compared to a control group who filled pregabalin without facing such restrictions during the same period. The index date was the first date of the rejected claim while the date of the first approved pregabalin claim was the index date for the control group. All patients were naive to pregabalin and aged 18 or older with continuous enrollment 12 months pre- and 12 months post-index date. The outcome variable of interest was the total growth of medications within the market basket for pregabalin.

RESULTS: A total of 14,917 patients were identified in the case group and 26,592 in the control group. Groups were similar in age (55.4 for case versus 57.8 for control) and female percentage (65.2% for case versus 63.4% for control). Among patients in the case group, 59.2% had rejections due to SE, 28.6% due to PA, and 12.3% for NF. Of those with a rejected pregabalin claim, 29% filled pregabalin, 9.4% received duloxetine, and 44.3% received gabapentin with the first year post-rejection. More than one-third (34.2%) filled no prescription for pregabalin, gabapentin, or duloxetine. Regression analysis showed that in comparison to patients in the control group, rejections due to NF (~$288.1, P = 0.01) and PA (~$175.2, P = 0.02) had lower medication costs 1 year post-index date. No differences in cost were noted for plans with SE (~$105.7, P = 0.17).

CONCLUSIONS: Management strategies, especially NF and PA, can lead to cost savings. However, these savings may be due to one-third of patients not filling a prescription for pregabalin, gabapentin, or duloxetine after the rejected claim. Patient follow-up by health plans is warranted to avoid care disruption.

SPONSORSHIP: This research was funded by Pfizer Inc., New York, NY.

<table>
<thead>
<tr>
<th>TABLE</th>
<th>RSV-Related Claims and Hospitalizations by Palivizumab Coverage Status for 4 RSV Seasons (2006-2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA Status</td>
<td>Applied for Prior Authorization (PA)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>50,283</td>
</tr>
<tr>
<td>RSV-related claim (%)a</td>
<td>3,509 (0.65)</td>
</tr>
<tr>
<td>RSV-related hospitalization (%)a</td>
<td>326 (0.65)</td>
</tr>
</tbody>
</table>

aP < 0.05 for comparison between those who did not apply and were ineligible for the PA and all other groups.
bP < 0.05 for comparison between received palivizumab and PA eligible groups.
Impact of Prescription Cost-Sharing on Adherence to HIV Antiretroviral Therapy

Johnston SS, Juday T,* Selkirk D, Espindle D, Chu B, Bristol-Myers Squibb, 777 Scudders Mill Rd., Plainsboro, NJ 08536; Timothy.Juday@bms.com, 609.897.6534

BACKGROUND: No published research has assessed the impact of prescription cost-sharing for HIV combination antiretroviral therapy (cART) on adherence.

OBJECTIVE: To analyze the relationship between cART prescription cost-sharing and adherence to cART in treatment-naïve HIV patients initiating first-line cART.

METHODS: Retrospective observational cohort study using 2002-2008 data for commercially insured enrollees in a large U.S. claims database. Study participants were ART-naïve adults diagnosed with HIV and initiating first-line cART between January 1, 2003, and December 31, 2007 (initiation date = index). A 6-month pre-index period was used to establish cART naïveté and patient characteristics. A minimum 12-month post-index period extended until cART discontinuation (switch or at least 30-day therapy gap) or study end was used to construct a patient-quarter panel dataset with repeated quarterly measures of cART cost sharing per 30-days supplied of the entire cART regimen and adherence to cART (proportion of days that patient possessed all components of the cART regimen). Two panel data regressions with generalized estimating equations estimated the effect of quarterly cost sharing on the probability that patients had adherence ≥85% or ≥95%, respectively; regressions were adjusted for patients’ demographic, clinical, and insurance characteristics.

RESULTS: Study sample included 3,731 patients: mean age 41.1 years; 83.2% male; mean (SD) duration of post-index period 5.1 (4.2) quarters; mean (SD) daily cART pill count 3.2 (2.2). Mean (median) cost sharing per 30-days supplied of the entire cART regimen was $67 ($40). In the regression analyses, higher cost-sharing levels were associated with significantly lower odds of adherence ≥95% (P < 0.001), with the effect growing in magnitude over time. The Figure depicts 95% confidence intervals for predicted probabilities of adherence ≥95% across time since index at different cost-sharing levels. Results were similar for adherence ≥85%.

CONCLUSIONS: In this real-world study of commercially insured HIV patients, individuals with higher cost-sharing levels were less likely to maintain clinically meaningful levels of adherence with treatment, which may lead to potential adverse clinical and economic consequences.

SPONSORSHIP: This research was funded by Bristol-Myers Squibb, Plainsboro, NJ.

Implementation of a Web-Based Medication Therapy Management Solution for Community Pharmacists in a Medicaid Population

Sheen J,* Bollinger S, Smith S, Kemp-Cornelius J, Oestreich GL, Driver R, ACS, a Xerox Company, Rx Delivery Services, 2810 N. Parham Road, Ste. 210, Richmond, VA 23294; janelle.sheen@acs-inc.com, 314.368.9327

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SPONSORSHIP: This research was funded by Bristol-Myers Squibb, Plainsboro, NJ.


BACKGROUND: A web-based solution to assist in medication therapy management (MTM) was implemented for the MO HealthNet (formerly Missouri Medicaid) Program starting April 1, 2010, replacing a previously implemented pharmacist disease-management program.

OBJECTIVE: To describe the implementation of a web-based MTM solution for pharmacists in Missouri targeting actionable clinical issues.

METHODS: The MTM solution, part of a provider web portal, aggregates pharmacy and medical claims history and clinical data into a central location providing individualized recommendations to pharmacists. Prior to participating in the program, pharmacists were required to complete a 2-hour continuing education, web-based training program that focused on the basic foundation of providing MTM services. Pharmacists also received training on the MTM solution. From April to September 2010, health recommendations were identified weekly for MO HealthNet participants. Complete medical and pharmacy claims profiles were available to pharmacists with actionable alerts at the point of service. Nine clinical areas were targeted initially: general health, asthma, diabetes, hypertension, hyperlipidemia, heart failure, immunization, smoking cessation, and osteoporosis. Health recommendations were classified into 8 groups: assessments, education, laboratory monitoring, exams, self-management, therapy recommendations, drug-drug interactions, and immunizations. For example, some health recommendations for diabetes included lifestyle modifications, adherence with medications, glycated hemoglobin (HbA1c) test, and vision and foot screenings. Pharmacists were reimbursed for addressing health recommendations.

RESULTS: Ninety pharmacists were trained to utilize the solution during the implementation phase. Three percent of participants (98,674) received a recommendation with the total number being 770,273. The largest number of health recommendations were for diabetes (177,963), followed by hypertension (155,730), hyperlipidemia (68,881), and vaccines (66,470). Pharmacists resolved the most health recommendations relating to hypertension (69), followed by hyperlipidemia (51), osteoporosis (41), the health survey (40), and smoking cessation (36). A total of 175 claims were submitted for MTM services by 15 pharmacists for 148 participants. The program will continue to grow statewide.

CONCLUSIONS: DirectCarePro is a MTM solution that provides pharmacists with recommendations to facilitate individualized health improvements within a MTM program. The program will continue to expand as more pharmacists are trained.

SPONSORSHIP: This research was conducted by Affiliated Computer Services, Richmond, VA, without external funding.

Improved Patient Access and Fiscal Savings of Medically Indigent Services Program Prescription Services

Chuong TT, Ho S, Tidwell D, Klevens L,* Riverside County Regional Medical Center, 26520 Cactus Ave., Moreno Valley, CA 92555; tklevens@crs.riverside.gov, 951.486.4529

BACKGROUND: Residents enrolled in Riverside County’s Medically Indigent Services Program (MISP) have doubled since June 2006 to June 2009 from 8,136 to 17,459. However, the funding for the county’s program has remained stagnant in spite of the needs by the growing indigent population. Pharmacists’ initiatives taken by Riverside County Regional Medical Center’s (RCRMC) Department of Pharmacy have played a key role in reducing cost expenditures while enhancing the quality and safety of patient care.

OBJECTIVE: To evaluate the impact of pharmacist-managed services on (a) cost savings, (b) medication errors/noncompliance due to polypharmacy/poly-prescribers, (c) medication safety, and (d) quality of patient care.

METHODS: The MISP Prescription Services have increased cost savings for Riverside County by confining prescription dispensing to county-operated pharmacies and increasing Patient Assistance Program (PAP) enrollments. Mail order service was implemented concurrently to enable patients to have 90-days supply of medications delivered to their homes. As part of the mail order services, staff members called patients prior to their medication refill date to increase medication compliance. Continued efforts to maintain cost savings for MISP included tighter formulary management. This process consisted of establishing policies to limit MISP coverage to the most medically appropriate and cost-effective medications. Moreover, a closed formulary system allowed opportunities for cost savings from medication and diabetic supply contracts. The coordination and integration of care was most clearly exemplified by the ambulatory care pharmacists that assisted prescribers and patients with medication education and optimal utilization of medications. By improving the communication between pharmacy and clinics, prescribers were more likely to select formulary products, increase prescriptions to 90-days supply and improve patients’ access to refills.

RESULTS: In combination with PAP initiatives these tactics have generated an overall estimated cost reduction of $400,000 per month, with an overall savings of about $2.2 million in the first 6 months of implementation.

CONCLUSIONS: MISP Prescription Services may be applied to most health care organizations. Although the program covers 2.1 million county residents, it can be implemented on a smaller scale while retaining its effectiveness. By utilizing similar tactics such as managed formulary, an organization can expect to have immediate and long-term cost-savings benefit.

SPONSORSHIP: This research was funded by Riverside County Regional Medical Center, Moreno Valley, CA.

Incidence of Hypoglycemia and Resulting Impact on Direct Medical Costs in Type 2 Diabetes

Quilliam BJ,* Simeone JC, Ozbay B, Kogut SJ, University of Rhode Island, College of Pharmacy, 41 Lower College Rd., Kingston, RI 02881; bsquilliam@uri.edu, 401.874.2030

BACKGROUND: Despite advances in the management of diabetes, hypoglycemia remains an important complication of antidiabetic medication treatment.

OBJECTIVE: To estimate the rate of hypoglycemia and associated costs in a large national cohort of employment-aged patients with type 2 diabetes.

METHODS: We utilized the Medstat MarketScan database from 2004-2008 to assess rates and costs of hypoglycemia in a cohort of continuously enrolled, working-age patients with diabetes. We followed patients from cohort entry until the end of their continuous eligibility to identify the first instance of hypoglycemia requiring medical intervention (inpatient and/or outpatient). Using these data, we then calculated incidence rates (IR) of hypoglycemia and stratified these estimates by age and gender. We calculated inflation-adjusted total costs and per patient per month (PMPM) costs associated with medical interventions for hypoglycemia visits.

RESULTS: The study cohort comprised 536,581 members with approximately 1.21 million patient-years of follow-up. The overall IR of hypoglycemic events was 153.8 per 10,000 patient-years. The IR of hypoglycemic events was highest in adults aged 18-34 (218.8 per 10,000 patient-years) and adults aged 65+ (193.2 per 10,000 patient-years). Overall, patients had a 0.13% risk of an inpatient admission for hypoglycemia in the first year following cohort entry, a 0.35% risk of an emergency room (ER) visit, and a 1.49% risk of an outpatient visit. Over 85% of all hypoglycemia encounters took place in an outpatient setting. 10.9% occurred in an ER, and only 4.0% occurred in an inpatient setting. Total costs of hypoglycemia for this cohort were $52,223,675 over the study period.
BACKGROUND: The overall incidence of hypoglycemia was relatively low in this large claims database but was associated with high cost for inpatient intervention. Younger and older adults may require more assistance to prevent hypoglycemic episodes. Risk management strategies should concentrate on avoiding costly inpatient encounters.

SPONSORSHIP: This research was funded by Takeda Pharmaceuticals North America, Inc., Deerfield, IL.

Investigating Risk Factors and Health Care Costs Associated with Patients with Gout: Optimal Time to Initiate Urate-Lowering Therapy

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BACKGROUND: Effects of risk factors and time of initiating chronic urate-lowering agents on health care utilization and costs were not well understood.

OBJECTIVE: To evaluate the impact of time of initiation of chronic urate-lowering agents on gout-related health care costs and the risk factors associated with high costs.

METHODS: Eligibility and claims data from a large physician group were used to identify patients with primary gout meeting study criteria during the index period (January 2006 through December 2007). Selection criteria included (a) age ≥ 18, (b) at least 1 diagnosis of gout (ICD-9-CM codes 274.xx) or at least 1 pharmacy claim for chronic urate-lowering agents (allopurinol or probenecid), (c) 12 months continuous eligibility pre- and post- either the first gout diagnosis or first pharmacy claim (index date); and (d) no prior diagnosis or gout-related medication within 12 months before index date. Patients were stratified by time of initiating chronic agents: (a) at index date (whether or not diagnosis was available), or (b) after index date (therapy was initiated after diagnosis). Health care utilization and costs were compared for the 12-month follow-up period. High health care costs were defined as >75th percentile of total gout-related costs (approximately $200 in annual costs). Multivariable logistic regression predicted the risk factors associated with high health care costs.

RESULTS: 523 patients met study criteria. Compared with patients initiating chronic agents after index date (n = 188, mean time to initiate chronic agents = 99.2 days), patients initiating chronic agents at the index date (n = 335) had fewer outpatient visits (0.9 vs. 2.9; P < 0.001), lower outpatient costs ($55 vs. $175; P < 0.001), and lower total gout-related costs ($207 vs. $1066; P < 0.001). Statistically significant factors associated with high gout-related costs were as follows: time of initiating chronic therapy, after index versus at index (OR = 6.105, CI = 3.872-9.625); adherence to medication versus nonadherence (OR = 1.520-5.720); age <65 years versus >65 years (OR = 2.472, CI = 1.452-4.208); and any rheumatologist visit versus no visit (OR = 2.619, CI = 1.278-5.368).

CONCLUSIONS: Delaying chronic urate-lowering therapy is associated with higher gout-related health care costs and increased gout-related utilization of services.

SPONSORSHIP: This research was funded by Takeda Pharmaceuticals North America, Inc., Deerfield, IL.

Long-Term Consequences and Costs Associated with Venous Thromboembolism

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BACKGROUND: Patients with venous thromboembolism (VTE) are at increased risk of developing recurrent VTE and post-thrombotic syndrome (PTS), and it is important for health care systems and formulary/policy decision makers to understand the long-term costs associated with VTE.

OBJECTIVE: To quantify the long-term consequences and costs associated with the development of VTE.

METHODS: An analysis was conducted of health insurance claims between January 2004 and September 2008 from the Ingenix IMPACT database. Subjects aged ≥18 years as of the date of first VTE diagnosis (index deep vein thrombosis [DVT], pulmonary embolism [PE], or both) with ≥180 days of continuous insurance coverage prior to the index date were identified and matched 1:1 with controls without VTE (no VTE), based on exact matching factors and propensity scores. Patients' histories were analyzed for up to 1 year after the index VTE event. The proportion of patients with recurrent VTE requiring hospitalization and PTS events was calculated. PTS was defined as occurring ≥90 days after the index VTE event if the patient had both a venous imaging procedure and a claim for lower extremity pain, swelling, varicose veins, post-phlebitic syndrome, or other disorders of the circulatory system. Total incremental health care costs associated with VTE were calculated, as well as costs related to complications of VTE, including medical services for VTE, PTS, thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency.

RESULTS: The VTE and no-VTE cohorts (16,969 subjects in each group) were well matched with respect to age, gender, comorbidities, and VTE risk-factor distributions. The index VTE was DVT, PE, or both in 12,711, 2,473, and 1,785 patients, respectively. The risks of recurrent VTE requiring hospitalization and PTS during the 1-year follow-up period were 3.6% and 6.2%, respectively. VTE patients had significantly higher average yearly costs compared to the no-VTE group ($33,531 vs. $17,590, cost difference = $15,941, 95% CI = 14,819-17,012). The largest driver of cost difference was all-cause hospitalization ($10,659, 95% CI = 9,846-11,491). Costs related to VTE complications represented 18.3% of the overall cost difference ($20,13; 95% CI = 26,93-31,57).

CONCLUSIONS: In this large matched-cohort study, VTE was associated with a 3.6% risk of hospitalization due to VTE recurrence and a 6.2% risk of PTS at 1 year after index VTE. Costs related to VTE complications represented nearly one-fifth of the incremental costs associated with VTE.

SPONSORSHIP: This research was funded by Ortho-McNeil Janssen Scientific Affairs, LLC, Raritan, NJ.

Low Montelukast Persistence Regardless of Diagnosis: Utilization Management Opportunity

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BACKGROUND: Montelukast is FDA approved for asthma and allergic rhinitis. For asthma, first-line therapy is an inhaled corticosteroid (ICS) and for allergic rhinitis it is a nasal steroid. Patients who begin treatment with montelukast and subsequently stop may delay more effective therapy.
OBJECTIVE: To evaluate montelukast persistency based on members’ associated medical diagnoses.

METHODS: Members newly initiating montelukast during 2009 Q4 were identified from a 1.2 million member commercially insured population. New initiators were defined as no montelukast supply or first-line therapy in the 60 days prior to their first 2009 Q4 montelukast claim. Members were continuously enrolled from January 1, 2009, through April 30, 2010, and their therapy was followed for 120 days post their initial montelukast claim evaluating persistence and alternative agents at 30, 60, 90, and 120 days. Members’ medical claims from January 1, 2009, through April 30, 2010, were assessed hierarchically first for allergy agents and then for asthma then for allergic rhinitis.

RESULTS: Of 819,060 continuously enrolled members, 8,667 (1.1%) had a montelukast claim in 2009 Q4, and 907 (10.5%) were members with medical claim for allergies. Of 8,667 members, 1,566 (18.1%) members newly initiating montelukast monotherapy during 2009 Q4 were defined to have a montelukast only pattern (no other asthma therapy). Those who had 1 or more claims for other first-line therapy were classified as Montelukast + other asthma therapy. Follow-up Period 30 Days 60 Days 90 Days 120 Days

- Montelukast only: 566 (62.4%) 308 (34.0%) 282 (31.1%) 204 (22.5%)
- Montelukast + other asthma agents: 333 (36.7%) 142 (15.7%) 104 (11.5%) 76 (8.4%)
- ICS, other asthma agents: 2 (0.2%) 60 (6.6%) 50 (5.5%) 59 (6.5%)
- No asthma therapy: 6 (0.7%) 397 (43.8%) 471 (51.9%) 568 (62.6%)

CONCLUSIONS: Patients with advanced/metastatic RCC tended to be older and male, with site of metastases observed in liver, lung, and bone. The treatment duration decreased from first line to second line, likely reflecting disease progression. During 2009, the most common first-line treatments observed were temsirolimus and sunitinib, and the most common second-line treatment was everolimus, bevacizumab, and sunitinib.

SPONSORSHIP: This research was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Modeled Effect of Generic Docetaxel on Total Medical Cost of Care with Taxanes in Metastatic Breast Cancer

OBJECTIVE: To determine if discounting docetaxel cost based on the availability of the generic impacts total medical cost of care comparisons between the taxane chemotherapy agents.

METHODS: Paid medical claims from May 1, 2006, and April 30, 2009, were utilized. Based on ICD-9-CM codes and previous chemo, we identified 4,903 women with metastatic breast cancer receiving docetaxel (n = 2,990), paclitaxel (n = 1,643), or nab-paclitaxel (n = 261). Median per patient per month (PPPM) total medical costs were determined and adjusted for a variety of variables with multiple regression. We then imputed several discounted docetaxel costs into the model and repeated the total medical cost analysis.

RESULTS: Before discounting, the PPPM cost (95% CI) for docetaxel was $4,655 ($4,525-$4,810), for nab-paclitaxel $4,537 ($4,160-$4,947), and $4,537 ($4,160-$4,947), and...
for paclitaxel $3,784 ($3,599-$3,979). At a 95% reduction in docetaxel price, total medical costs became statistically significantly lower than those in the nab-paclitaxel group ($3,698 [3,574-$3,827]) vs. $4,230 [$3,841-$4,659]; see figure).

CONCLUSIONS: Only at a modeled 95% reduction from the branded price did the total medical cost associated with docetaxel become less expensive than nab-paclitaxel. This result may be affected by wide confidence intervals around the price of both drugs. Despite a higher acquisition cost for nab-paclitaxel compared with docetaxel, total medical costs will likely remain similar between the drugs once docetaxel becomes generically available.

SPONSORSHIP: This research was funded by Abraxis Bioscience, Bridgewater, NJ.

Multiple Sclerosis Medical and Pharmacy Cost Trends 2006 to 2009
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BACKGROUND: Biologic drugs used to treat multiple sclerosis (MS), such as the beta-interferons and glatiramer, have an average wholesale price (AWP) of over $30,000 a year. With the recent FDA approval of 2 new MS agents, dalfampridine (Ampyra) at over $15,000 AWP per year and fingolimod (Gilenya) at over $45,000 AWP per year, it is important insurers have a comprehensive understanding of the direct medical and pharmacy cost trends to forecast future MS expenditures.

OBJECTIVE: To describe MS pharmacy and medical cost trends.

METHODS: Medical and pharmacy claims for commercially insured members, continuously enrolled from 2006-2009 (4 years), were queried to identify those who met 1 or both of 2 criteria: (a) at least 1 medical claim with an MS-related ICD-9-CM diagnosis code of 340* in January 2006, and at least 1 MS medical claim in each of 2007, 2008, and 2009; (b) at least 1 MS medical claim in the first quarter of 2006 and a pharmacy claim for a MS biologic (beta-interferon or glatiramer) in January 2006. Costs were total allowed amounts (plan and member) for all medical and pharmacy claims.

RESULTS: Of 390,108 continuously enrolled members, 361 (0.09%) met study criteria. In 2006, per patient per year total costs were $29,652 with $17,117 (57.7%) coming from pharmacy. Total costs increased to $37,592 with $22,015 (58.6%) coming from pharmacy in 2009. These increases equate to a 2006 through 2009 total cost compound annual growth rate (CAGR) of 8.2%, pharmacy cost CAGR of 8.8%, and medical cost CAGR of 7.5%.

CONCLUSIONS: MS direct pharmacy and medical costs are increasing at a similar rate (CAGR 8.8% and 7.5%, respectively). Pharmacy costs were the majority of direct costs, at a relatively constant 57% to 59%. With the addition of 2 new drugs for MS treatment, of which dalfampridine can be used in combination with a traditional biologic agent at an approximate cost of $15,000 a year, pharmacy costs are projected to exceed 70% of total direct health costs.

SPONSORSHIP: This research was conducted by Prime Therapeutics, LLC, Eagan, MN, without external funding.

National Breakthrough Pain Survey: Assessment of Quality of Life, Functioning, Productivity, and Health Care Utilization
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BACKGROUND: Breakthrough pain (BTP) is a transitory exacerbation of pain on a background of otherwise controlled persistent pain in patients receiving long-term opioid therapy. Limited data exist on the functional impairment and health care utilization experienced by patients with BTP.

TABLE  Medical and Pharmacy Cost Trends 2006 to 2009 for 361 Commercially Insured Members with MS Followed for 4 Years

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Medical Expenditures</th>
<th>Total Pharmacy Expenditures</th>
<th>Pharmacy Expenditure Trend</th>
<th>Medical Expenditure Trend</th>
<th>Combined (Medical and Pharmacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nb</td>
<td>Total Paid</td>
<td>Nb</td>
<td>Total Paid</td>
<td>% Pharmacy</td>
</tr>
<tr>
<td>2006</td>
<td>361</td>
<td>$4,525,284</td>
<td>354</td>
<td>$6,179,083</td>
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</tr>
<tr>
<td>2007</td>
<td>360</td>
<td>$4,460,924</td>
<td>350</td>
<td>$6,218,874</td>
<td>58.2%</td>
</tr>
<tr>
<td>2008</td>
<td>361</td>
<td>$5,290,883</td>
<td>351</td>
<td>$6,998,839</td>
<td>56.9%</td>
</tr>
<tr>
<td>2009</td>
<td>360</td>
<td>$5,623,476</td>
<td>349</td>
<td>$7,947,356</td>
<td>58.6%</td>
</tr>
</tbody>
</table>

*Data are from a commercial midwestern health plan of approximately 1.4 million members. The analysis period was January 1, 2006, through September 30, 2010.

Nb is number of members with 1 or more medical or pharmacy claim(s) in the given analysis year. All PPPY calculations use 361 members, although not every member may have had medical or pharmacy claims in a given year.

CAGR = compound annual growth rate (all CAGRs in table are relative to 2006); MS = multiple sclerosis; NA = not applicable; PPPY = per patient per year.

The data presented in this poster abstract were reported in part in the November/December 2010 issue of JMCP. Schafer JA, Gunderson BW, Gleason PP. Price increases and new drugs drive increased expenditures for multiple sclerosis. J Manag Care Pharm. 2010;16(9):713-17. Available at: http://www.amcp.org/data/jmcp/713-717.pdf
OBJECTIVE: To describe the burden of illness associated with BTP, the National Breakthrough Pain Survey (NBTPS) evaluated a population of commercially insured patients from a large administrative claims database in the United States.

METHODS: Based on ICD-9-CM codes and opioid prescription claims data, patients were separated into 3 cohorts: a control cohort (no clinically significant pain), cancer-related chronic pain, and noncancer-related chronic pain. Patients were contacted by phone and, upon consent, responded to demographic and disease/treatment-related questions, a structured interview for BTP, and questionnaires to assess quality of life, functioning, and productivity (SF-12, BPI, Sheehan Disability Scale [SDS]). Claims data and survey data were then merged for the health care utilization and cost analysis.

RESULTS: As of July 30, 2010, > 2,300 patients were screened; 905 completed the survey (control = 367). For this interim analysis, the cancer and noncancer cohorts were combined (>95% noncancer). Of the 538 respondents with controlled persistent pain, 428 (79.6%) reported experiencing BTP. Responses to the BPI total interference were significantly worse for patients with BTP (mean [SD], 34.9 [16.0]) than with no BTP (25.0 [14.9]; P = 0.001) and the control cohort (5.0 [9.2]; P = 0.001). The SDS total was significantly worse for patients with BTP (5.2 [3.0]) than with no BTP (3.8 [3.0]; P = 0.001) and the control cohort (0.5 [1.2]; P < 0.001). The SF-12 Physical was significantly worse for patients with BTP (29.2 [9.1]) than with no BTP (34.3 [10.0]; P < 0.001) and the control cohort (53.4 [6.8]; P < 0.001). The SF-12 Mental for patients with BTP (47.2 [11.5]) was similar to patients with no BTP (48.8 [11.1]; P = 0.372), but significantly worse than the control cohort (54.7 [6.0]; P < 0.001).

CONCLUSIONS: This is the largest survey of BTP to date, and it will provide detailed information on the effect of BTP on quality of life and health care utilization on community-dwelling, insured patients. Based on interim results, patients with BTP reported substantial reductions in quality of life and functioning compared with patients with chronic pain and no BTP, as well as those with no clinically significant pain. The full survey results, including the utilization and cost analysis, will be presented.

SPONSORSHIP: This research was funded by Cephalon, Inc., Frazer, PA.

Optimum Time Post-Index Fill to Administer the Adherence Estimator: A Brief Proximal Screener for Patient Propensity to Adhere to Prescription Medications

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BACKGROUND: The Adherence Estimator (AE) is a 3-item survey designed for use by providers, including physicians, pharmacists, nurses, and case managers, to segment patients into low, medium, and high risk for nonadherence to prescription medications based on their medication beliefs.

OBJECTIVE: To identify the optimum time to administer the AE after patients obtain their first prescription fill for a new medication.

METHODS: The AE was part of a larger survey mailed to adults with prescription fill for 1 of 4 chronic diseases: asthma, type 2 diabetes, hypertension, and hyperlipidemia. Phase I of the survey was mailed to patients between 8 to 25 days post-index fill. Phase II surveys were mailed exactly 4 weeks later to patients who responded to phase I. The AE was included in both phases of the survey; thus, each respondent to phase I could potentially complete the AE twice. All complete responses to the AE (from phase I as well as phase II) were divided into 9 timing groups based on the time lag between index fill date and the date when the survey was signed by the respondent. Across different timing groups, the effectiveness of the AE in identifying patients most at risk for nonadherence was assessed by the following: (a) testing sensitivity of the AE (proportion of patients who were nonadherent according to pharmacy claims data that were accurately identified as medium/high risk by the AE) and (b) logistic regression models to test the ability of the AE to predict nonadherence as measured by pharmacy claims data for 3-months post-index fill. Patients were classified as nonadherent if the continuous, multiple-interval measure of medication gaps (CMG) for the index drug class exceeded 20.0%.

RESULTS: A total of 2,333 (1,466 phase I; 867 phase II) responses to the AE were available for analysis. The sensitivity of the AE was at its peak (67.4%) when it was completed between 6.5 to 7.5 weeks post-index fill. For this timing group, patients who were scored as medium/high risk by the AE had significantly higher odds (OR = 1.77; P = 0.040) of being nonadherent at month 3 as compared to those scored as low risk.

CONCLUSIONS: This study provides preliminary evidence that adherence screening instruments such as the Adherence Estimator may be most optimally administered about 7 weeks after patients obtain their first prescription fill for a new medication.

SPONSORSHIP: This research was funded by Merck & Co., Inc., Whitehouse Station, NJ.

Outcomes of a Retrospective Drug Utilization Review for High Risk Diabetics Not on Concurrent Hypertensive Therapy

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BACKGROUND: The HOPE (Heart Outcomes Prevention Evaluation) trial provides evidence that angiotensin-converting enzyme therapy can improve cardiovascular outcomes in high-risk patients, including those with diabetes. Furthermore, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in members with diabetes who also have high blood pressure is 1 of the measures the Centers for Medicare & Medicaid Services (CMS) has deemed important and has included in star rating measures. This is very important for the future of health plans in the Medicare market, since CMS will be using star ratings measures to determine bonus pay for Medicare Advantage plans starting in 2012.

OBJECTIVE: To increase the number of high risk diabetics (i.e., diabetics on a dyslipidemic agent or diabetics on a nitrate) utilizing either an ACE inhibitor or ARB. Medicare or Medicaid members enrolled in a large midwestern HMO plan that appear to be high-risk diabetics and are not taking an ACE inhibitor or ARB were identified.

METHODS: Through a retrospective drug utilization review (RetroDUR), eligible plan members who had a claim for an antidiabetic agent and either a nitrates or dyslipidemic agent during a 60-day review period were screened for an ACE inhibitor or ARB within the previous 6 months from the end of the review period. In the absence of a claim for an ACE inhibitor or ARB, a letter was sent to the member's last prescriber. The RetroDUR ran every 2 months; duplicate members were excluded within a 6-month time frame.

RESULTS: One year after the implementation of the program, of a possible eligible 220,000 members, 3,886 (1.8%) members had a claim for at least 1 antidiabetic agent and either a nitrates or dyslipidemic agent during a 60-day review period without a claim for an ACE inhibitor or ARB. Overall, there were 1,490 (38.3%) members deemed as successes (i.e., members who did not meet identification criteria 6 months later) with an annual cost avoidance of $300,000.

CONCLUSIONS: The RetroDUR may have been associated with a possible reduction in hospitalization costs due to increased number of diabetics
on ACE inhibitor or ARB therapy. Future goals of this program are to use health plan medical data to more accurately assess true cost avoidance.

SPONSORSHIP: This research was funded by MedImpact Healthcare Systems, Inc., San Diego, CA.

Outpatient Pharmacy Clinical Services (OPCS) Model to Improve Adherence and HEDIS Measures and Reduce Drug-Related Readmissions

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BACKGROUND: Outpatient pharmacists, through the Outpatient Pharmacy Clinical Services (OPCS) project, targeted nonadherent patients with diabetes and/or coronary artery disease (CAD) patients with a medication refill adherence ratio (MRAR) of <80% and hemoglobin A1c (A1c) and/or low density lipoprotein (LDL) above targets and addressed Barriers, Solutions, Motivation, Adherence tools, Relationships and Triage (BSMART methodology) to improve medication adherence and clinical outcomes. Pharmacists also targeted discharged patients with myocardial infarction, heart failure, and pneumonia to provide, in addition to a basic discharge consult, a post-discharge call after 3-5 days to these targeted patients in an effort to reduce medication-related readmissions.

OBJECTIVE: To assess the effects of the OPCS model on medication adherence, HEDIS measures, and drug-related readmissions.

METHODS: Outpatient pharmacists used algorithms to identify OPCS-eligible patients and consulted patients both in person (InReach) as patients visited the pharmacies, and over the phone (Outreach) for patients at home. Pharmacists identified adherence barriers to taking medications as prescribed and developed patient specific solutions to improve medication adherence. Pharmacists monitored the impact of the consultations on medication restarts, subsequent refills, lab values, and triaging to other services. Within the discharge group, pharmacists identified drug omissions, duplications, drug interactions, and communication with discharge providers. Pharmacists documented their interventions in the patients' electronic charts and maintained a log of time invested per intervention.

RESULTS: The OPCS project resulted in significant improvement in medication restarts (67%) and subsequent refill rate (46%). Consulted patients had an average 0.6 % decrease in A1c (from 9.2% to 8.6%) and an average 21.8 mg per dL decrease in LDL (from 131.6 mg per dL to 109.8 mg per dL). 74% of patients completed missing screening labs; 9% of patients were triaged to follow-up care. Forgetfulness, denial of conditions, lack of knowledge, and side effects accounted for the top 4 barriers for medication nonadherence, as reported by patients. InReach encounters averaged 10 minutes, while Outreach averaged 15 minutes.

CONCLUSIONS: OPCS is an important point of contact where outpatient pharmacists, as members of the health care team, are leveraging outpatient pharmacist expertise, partnership, and technology to impact medication adherence and compliance, improve clinical performance, and reduce drug-related readmissions.

SPONSORSHIP: This research was conducted by Kaiser Permanente, Harbor City, CA, without external funding.

Painful Diabetic Neuropathy Newly Prescribed Pregabalin or Gabapentin in Usual Care Settings

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BACKGROUND: Treatment of painful diabetic peripheral neuropathy (pDPN), 1 of the most important of the diabetic neuropathies due to its associated socioeconomic burden, is challenging. Although pregabalin and duloxetine are the only FDA-approved treatments, use of gabapentin is common in clinical practice. Studies have evaluated health care service use/costs among pDPN patients initiated on pregabalin or duloxetine; however, there is dearth of data on patients initiated on gabapentin.

OBJECTIVE: To characterize comorbidities, pain-related pharmacotherapy, and health care resource use among patients with pDPN newly prescribed pregabalin or gabapentin in clinical practice.

METHODS: Using the LifeLink Health Plan Claims Database, patients with pDPN (ICD-9-CM codes 357.2 or 250.6) newly prescribed (index event) gabapentin (n=1,178, 56.9±10.3 years old) were identified and propensity score-matched with patients initiated on pregabalin (n=1,178, 56.4±9.8 years old). Comorbidities, pain-related pharmacotherapy, and health care resource use/costs were examined during the 12-month pre-index and follow-up periods.

RESULTS: Both cohorts were characterized by multiple comorbidities and substantial use of pain-related and adjunctive medications. In the pregabalin cohort, the use of tricyclic antidepressants significantly decreased (16.0% vs. 13.2%) and nonsteroidal anti-inflammatory drugs (NSAIDs, 30.8% vs. 34.8%), muscle relaxants (19.2% vs. 22.9%), anticonvulsants (14.4% vs. 18.1%), benzodiazepines (22.3% vs. 25.0%), and topical agents (7.0% vs. 9.8%) increased (P<0.05) in the follow-up period. In the gabapentin cohort, there were significant increases (P<0.05) in the use of short- (55.4% vs. 61.2%) and long-acting (9.4% to 12.8%) opioids, SNRIs (14.2% vs. 16.7%), anticonvulsants (7.1% vs. 19.2%), benzodiazepines (19.1% vs. 24.3%), sedative/hypnotics (14.9% vs. 18.0%), and tramadol (13.3% vs. 16.8%). There were significant increases (P<0.05) in pharmacy, outpatient, and total costs in both cohorts and in costs of physician office visits in the gabapentin cohort. There was no difference in post-index median total costs between the pregabalin and gabapentin cohorts ($16,137 vs. $15,766).

CONCLUSIONS: Patients with pDPN prescribed pregabalin and gabapentin had a substantial comorbidity and pain medication burden. Although health care costs increased in both groups, the increase in pain medication burden was higher in the gabapentin group relative to the pregabalin group. Direct medical costs were similar for both groups.

SPONSORSHIP: This research was funded by Pfizer Inc., New York, NY.

Participant Characteristics Associated with Medication Adherence

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BACKGROUND: Medication adherence is a serious problem and an important health care challenge. Despite evidence indicating benefit, many patients do not take prescribed medications. To increase understanding within a large, integrated health system, we studied patient characteristics associated with medication adherence.

OBJECTIVE: To use automated pharmacy records to assess patient characteristics associated with adherence across 8 diseases.

METHODS: We identified all members older than 18 years with at least 2 prescription fills for greater than a 28 days supply from January 2007 through March 2009. The integrated health system covers approximately 750,000 members. Medications (n=128) to treat the following diseases were identified: depression, hypertension, hyperlipidemia, diabetes, asthma/COPD, multiple sclerosis, cancer, or osteoporosis. Diagnoses were identified by ICD-9-CM codes and merged with pharmacy claims. We examined differences by age, sex, race, comorbidity, and geo-code. Patients with 1 condition and 1 prescribed medication (n=15,334)
were analyzed. Analyses were repeated on patients with any number of conditions and medications among those specified (n = 31,636 patients). Adherence was calculated by the medication possession ratio at a threshold of 80%.

RESULTS: Adherence differed significantly by patient characteristics. Males were more adherent than females. Males, Caucasians, older patients, and patients living in areas having a higher proportion of residents with a high school education, lower poverty, and higher family income were associated with increased adherence. Among patients with any number of conditions, adherence increased with lower Charlson score and fewer conditions and medications. Substantial variation in adherence was found by condition. Specifically, multiple sclerosis, hypertension, hyperlipidemia, osteoporosis, and cancer had a high percentage of adherent patients (75%+). Adherence rates for depression, diabetes, and asthma/COPD were 62%, 51%, and 33%, respectively.

CONCLUSIONS: We expected adherence to be less significant within an integrated health system because pharmacy is a covered benefit, and members have enhanced medication access. However, significant differences were found by patient characteristics. Great room for improvement remains, specifically for diabetes and asthma. Patient-specific targeted efforts might be considered to improve adherence.

SPONSORSHIP: This research was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Patient Compliance with Metastatic Renal Cell Carcinoma Treatments

Hess GP,* Chen C, Liu Z, Gesme DH, Agarwala SS, SDI Health, 1 SDI Dr., Plymouth Meeting, PA 19462, gbess@sidihealth.com, 610.834.0800

BACKGROUND: Immunotherapy, tyrosine kinase inhibitors, and monoclonal antibodies directed at vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) are among the primary treatments for metastatic renal cell carcinoma (mRCC).

OBJECTIVE: To assess differences in compliance among common mRCC regimens in first-line and second-line therapy.

METHODS: A retrospective study was conducted utilizing medical and pharmacy claims covering January 1, 2008, to May 31, 2010, from SDI Health. Adult mRCC patients were identified by (a) a diagnosis of RCC and a secondary (i.e., metastatic) neoplasm (n = 336) or (b) RCC and treatment with IL-2, IFN, sunitinib, sorafenib, temsirolimus, everolimus, bevacizumab, or pazopanib (n = 744). Using a look-back period of at least 90 days, patients were indexed to the first therapy post-mRCC diagnosis. A subsequent 90-day gap, drug addition, or switch defined the end of therapy. Compliance was measured by medication possession ratio (MPR).

RESULTS: Compliance with mRCC treatments is generally high among the majority of patients, with significant variations surrounding the average MPR. Within first-line therapy, compliance was higher with oral versus infused treatment. Within common second-line treatments, sunitinib, everolimus, and IFN were observed to be associated with higher compliance.

SPONSORSHIP: This research was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Patterns of Atypical Antipsychotic Therapy Use in Adults with Bipolar I Disorder


BACKGROUND: Bipolar disorder is a chronic condition that can be effectively treated over the long term. It is best controlled when the treatment is continuous. Atypical antipsychotics are increasingly prominent in treating bipolar disorder.

OBJECTIVE: To describe the utilization patterns of atypical antipsychotics (AAs) across a wide spectrum of insured patients with bipolar I disorder.

METHODS: Adults diagnosed with bipolar I disorder with at least 1 prescription claim for an oral AA medication and 24 months continuous enrollment were identified in Thomson Reuters MarketScan Databases between 2002-2008 (commercial, Medicare, and Medicaid). Patients were stratified into new initiator cohort (no claims for an AA therapy during 12 months prior to index AA) and existing user cohort (evidence of AA therapy during 12 months prior to index AA). Utilization patterns in adherence (defined as medication possession ratio [MPR] ≥ 80%), persistence (gaps of at least 15 days between refills and an absence of 30 days or more of continuous concomitant nondexAA use), and discontinuation (at least 30 days with no AA and no evidence of switch or augmentation) were analyzed for 12 months post-index AA.

RESULTS: A total of 38,938 patients were analyzed: mean age 44.8 years, 66.6% female, 43% new initiators. The 4 most commonly used index AAs were olanzapine (31.4%), quetiapine (28.3%), risperidone (22.0%), and aripiprazole (6.4%). Adherence to the index AA was low in new initiators (8.3%; mean MPR = 0.2) and existing users (24.3%; mean MPR = 0.5). Persistence was also low (10.5% in new users; 32.1% in existing users). The index AA was discontinued in 63.4% of new users and 34.1% of existing users, with an average time to discontinuation of 66 days and 93 days, respectively. Most (69.5%) of the discontinued new users did not resume any antipsychotic therapy. Results were similar across all AAs and insurance types.

CONCLUSIONS: Generally low adherence to AA treatment was observed in this contemporary cohort of insured adults with bipolar I disorder. Most patients discontinued the initial therapy within 3 months and did not restart any antipsychotic treatment. These data suggest an unmet need and room for improvement in the current management of bipolar I disorder patients.

SPONSORSHIP: This research was funded by Merck & Co., Inc., Whitehouse Station, NJ.

Patterns of Osteoporosis Treatment Change in a Medicare Advantage Prescription Drug Plan

Xu Y,* Viswanathan HN, Ward M, Adams JL, Stolshek BS, Kallich JD, Saag KG, Humana, Inc., 315 W. Market St., 5th Fl., Louisville, KY 40202, yxy@humana.com, 502.580.8620

BACKGROUND: Among persons newly initiated on osteoporosis treatment for metastatic renal cell carcinoma (mRCC).

RESULTS: Adherence differed significantly by patient characteristics. Males were more adherent than females. Males, Caucasians, older patients, and patients living in areas having a higher proportion of residents with a high school education, lower poverty, and higher family income were associated with increased adherence. Among patients with any number of conditions, adherence increased with lower Charlson score and fewer conditions and medications. Substantial variation in adherence was found by condition. Specifically, multiple sclerosis, hypertension, hyperlipidemia, osteoporosis, and cancer had a high percentage of adherent patients (75%+). Adherence rates for depression, diabetes, and asthma/COPD were 62%, 51%, and 33%, respectively.

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METHODS: Adults diagnosed with bipolar I disorder with at least 1 prescription claim for an oral AA medication and 24 months continuous enrollment were identified in Thomson Reuters MarketScan Databases between 2002-2008 (commercial, Medicare, and Medicaid). Patients were stratified into new initiator cohort (no claims for an AA therapy during 12 months prior to index AA) and existing user cohort (evidence of AA therapy during 12 months prior to index AA). Utilization patterns in adherence (defined as medication possession ratio [MPR] ≥ 80%), persistence (gaps of at least 15 days between refills and an absence of 30 days or more of continuous concomitant nondexAA use), and discontinuation (at least 30 days with no AA and no evidence of switch or augmentation) were analyzed for 12 months post-index AA.

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BACKGROUND: Among persons newly initiated on osteoporosis
the limited evidence exists on the epidemiology of treatment change and associated factors.

OBJECTIVE: To examine patterns of osteoporosis treatment change, treatment discontinuation, and factors associated with treatment change among Medicare Advantage drug plan (MA-PD) members newly initiated on an osteoporosis therapy in a large national health plan.

METHODS: A retrospective cohort study was conducted in members newly initiated on an osteoporosis medication between January 1, 2006, and December 31, 2008 (intake period). Members were ≥50 years of age with continuous eligibility for 12 months prior to and following the date of the first osteoporosis medication claim (index date). Members were excluded if they had an osteoporosis medication claim in the pre-index period, Paget's disease, or neoplasms, and/or patients with evidence of any VTE event 90 days prior to the index surgery were excluded.

RESULTS: Of 9,167 eligible patients (42.5% male; median age 60.4 years), 3,109 had THR and 6,058 had TKR. In the pre-index period, patients had a mean 3.0 unique medications and 8.7 dispersions; 13.0% used anti-thrombotic medications. During hospitalization, 8,994 patients (98.1%) received VTE prophylaxis, including warfarin + a mechanical prophylaxis device (MPD) (23.4%), enoxaparin + MPD (22.4%), fondaparinux + MPD (5.7%), warfarin + enoxaparin + MPD (5.8%), enoxaparin (13.7%), warfarin (12.9%), or other anti-thrombotic agent (14.6%). Slightly more THR than TKR patients received enoxaparin (14.8% vs. 13.2%, respectively; P = 0.03). Patients given warfarin, enoxaparin, and MPD had the highest mean comorbidity score (0.70). Post-discharge, only 26.4% of all patients received any form of thromboprophylaxis: 17.6% received warfarin, 5.5% enoxaparin, and 5.3% other therapeutic. Patients who received either warfarin or enoxaparin as inpatients were more likely to receive the same medications after discharge. There was no difference in post-discharge prophylaxis distribution by surgery type except for MPD use. However, MPD use following hospitalization was quite low for both THR and TKR patient groups (0.2% and 1.2%, respectively).

CONCLUSIONS: Nearly all THR/TKR patients received thromboprophylaxis during hospitalization, but only about 1 in 4 received anticoagulation post-discharge. During their inpatient stay, more than half of the patients received an MPD along with a pharmacologic anticoagulant. On average, patients given warfarin, enoxaparin, and MPD (e.g., as a bridging regimen) had the highest comorbid risk profiles. Post-discharge thromboprophylaxis patterns did not vary significantly by surgery type.

SPONSORSHIP: This research was funded by Johnson and Johnson Pharmaceutical Research and Development, Titusville, NJ.

Patterns of Thromboprophylaxis Use in Patients Undergoing Total Hip and Knee Replacement Surgery in a Large U.S. Health Plan

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BACKGROUND: Risk of venous thromboembolism (VTE, deep vein thrombosis and/or pulmonary embolism) following total hip or knee replacement (THR/TKR) is high, yet guideline-recommended prophylaxis may not be routinely practiced.

OBJECTIVE: To examine use of thromboprophylaxis during hospitalization and through 90 days post-discharge among patients undergoing THR or TKR surgery.

METHODS: The study cohort was identified from 2004-2009 medical claims data of a large U.S. managed care plan linked to Premier's Perspective hospitalization data. Use of thromboprophylaxis for inpatient stay and through the following 90-day post-discharge period was assessed. Aspirin use during inpatient stay and prescription aspirin in follow-up were evaluated as well. Patients with evidence of any VTE event 90 days prior to the index surgery were excluded.

RESULTS: Of 9,167 eligible patients (42.5% male; median age 60.4 years), 3,109 had THR and 6,058 had TKR. In the pre-index period, patients had a mean 3.0 unique medications and 8.7 dispersions; 13.0% used anti-thrombotic medications. During hospitalization, 8,994 patients (98.1%) received VTE prophylaxis, including warfarin + a mechanical prophylaxis device (MPD) (23.4%), enoxaparin + MPD (22.4%), fondaparinux + MPD (5.7%), warfarin + enoxaparin + MPD (5.8%), enoxaparin (13.7%), warfarin (12.9%), or other anti-thrombotic agent (14.6%). Slightly more THR than TKR patients received enoxaparin (14.8% vs. 13.2%, respectively; P = 0.03). Patients given warfarin, enoxaparin, and MPD had the highest mean comorbidity score (0.70). Post-discharge, only 26.4% of all patients received any form of thromboprophylaxis: 17.6% received warfarin, 5.5% enoxaparin, and 5.3% other therapeutic. Patients who received either warfarin or enoxaparin as inpatients were more likely to receive the same medications after discharge. There was no difference in post-discharge prophylaxis distribution by surgery type except for MPD use. However, MPD use following hospitalization was quite low for both THR and TKR patient groups (0.2% and 1.2%, respectively).

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SPONSORSHIP: This research was funded by Johnson and Johnson Pharmaceutical Research and Development, Titusville, NJ.
baseline health care expenditures explained the most variance in 1-year and 2-year COST (adjusted R2 = 27.9%, 31.1%); the updated CCI was the best predictor of 1-year and 2-year HOS (AIC = 8,581, 13,821); and the number of distinct medications was superior in predicting 1- and 2-year ED (AIC = 16,969, 25,059). In the logistic regressions, the number of distinct medications was the best predictor of 1-year and 2-year emergency department use (c = 0.653, 0.654), but the baseline health care expenditures performed the best in predicting 1-year and 2-year hospitalizations (c = 0.682, 0.672) and high health care expenditures (c = 0.822, 0.834).

CONCLUSIONS: In a diabetic population under age 65, baseline health care expenditures appeared to be a better predictor of future health care expenditures and individuals who incurred high expenditures. The number of distinct medications seemed to be superior in predicting emergency department use, while the updated CCI seemed to be superior in predicting the number of hospitalizations.

SPONSORSHIP: This research was conducted by the University of Texas at Austin, College of Pharmacy, Austin, TX, without external funding.

Pharmacoeconomic Evaluation of Romiplostim for the Treatment of Primary Adult Chronic Immune Thrombocytopenia

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BACKGROUND: Romiplostim is indicated for the treatment of chronic immune thrombocytopenia (ITP), a disease characterized by low platelet counts and increased risk of bleeding.

OBJECTIVE: To assess the treatment costs relative to response, from a health plan perspective, of romiplostim compared to “Watch & Rescue” (i.e., physicians monitor patients until a bleeding-related episode occurs and rescue therapy is administered) as a therapy for the treatment of adult chronic ITP.

METHODS: The model was based on the 6-month romiplostim randomized studies and includes 2010 Medicare costs for treatment, administration costs, ongoing patient management costs, side effects and, bleeding-related episode costs (including use of intravenous immunoglobulin [IVIg] rescue therapy). Costs were compared to the post-hoc analysis of durable platelet response (platelets ≥50,000 for at least 6 weeks during the last 8 weeks on study) regardless of whether rescue therapies were administered at any time during the study for each treatment option observed in clinical trials (romiplostim and Watch & Rescue). Using a trial-based simulation, romiplostim costs consider an average dose of 388 mcg per administration for splenectomized patients and 242 mcg per administration for nonsplenectomized patients.

RESULTS: For splenectomized patients, the expected cost of treating a patient with romiplostim over a 6-month period (trial period) is $49,765, for a durable response of 45%, or a cost per patient with a durable response of $110,589 ($49,765 divided by 45%; table). Comparatively, the expected 6-month cost of treating the same patient with a Watch & Rescue approach is $16,266, for a durable response of 5%, or a cost per patient with a durable response of $325,320 ($16,266 divided by 5%). For nonsplenectomized patients, the expected 6-month cost of treating a patient with romiplostim is $38,675, for a durable response of 66%, or a cost per patient with a durable response of $58,598 ($38,675 divided by 66%). Comparatively the expected 6-month cost for the Watch & Rescue approach is $12,528, for a durable response of 14%, or a cost by response of $89,486 ($12,528 divided by 14%).

CONCLUSIONS: The result in chronic adult ITP shows that romiplostim represents an efficient use of health care resources, enabling better health outcomes at a significantly lower cost per treatment success than that of standard treatment.

SPONSORSHIP: This research was funded by Amgen Inc., Thousand Oaks, CA.

Pharmacoeconomic Evaluation of Romiplostim for the Treatment of Primary Adult Chronic Immune Thrombocytopenia (ITP)

<table>
<thead>
<tr>
<th>Cost by Response (in 2010 $) Per Patient for a U.S. Health Plan</th>
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<tbody>
<tr>
<td><strong>Splenectomized Patients</strong></td>
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<tr>
<td>Total 6-month cost per patient</td>
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<tr>
<td>Rate of durable response&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Cost per patient with a durable response</td>
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<tr>
<td>Difference (romiplostim–Watch &amp; Rescue)</td>
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<tr>
<td><strong>Nonsplenectomized Patients</strong></td>
</tr>
<tr>
<td>Total 6-month cost per patient</td>
</tr>
<tr>
<td>Rate of durable response&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Cost per patient with a durable response</td>
</tr>
<tr>
<td>Difference (romiplostim–Watch &amp; Rescue)</td>
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</tbody>
</table>


Predictors of Inappropriate Antibiotics Prescribing for Adults with Nasopharyngitis, Acute Bronchitis, and Acute Respiratory Tract Infections

Chopra P, Agrawal RN,* Shah J, Aparasu R, University of Houston, College of Pharmacy, 1441 Moorsund St., Houston, TX 77030; ruchika.ag87@gmail.com, 317.445.3560

BACKGROUND: Nasopharyngitis, acute bronchitis, and acute upper respiratory tract infections (ARTIs) are viral infections for which antibiotics should not be prescribed as per the American Academy of Family Physicians. In 1996, 56% of patients with these conditions in the United States were inappropriately prescribed antibiotics. Such inappropriate prescribing may lead to the emergence of resistant bacteria, increased health care utilization, and an increased economic burden.

OBJECTIVE: To assess the predictors of inappropriate antibiotic prescribing for adults with nasopharyngitis, acute bronchitis, and ARTIs in ambulatory care settings in the United States.

METHODS: The 2007 National Ambulatory Medical Care Survey was used to evaluate inappropriate antibiotic prescribing rates. Adults 18 years or older with nasopharyngitis, ARTIs, or bronchitis were identified using ICD-9-CM codes for this retrospective cross-sectional analysis. Descriptive analyses were conducted to evaluate antibiotic prescribing patterns. The predictors of antibiotic use were modeled as a function of patient, physician, and practice characteristics using logistic regression.

RESULTS: In 2007, 16.3 million office visits (95% CI = 13.4 million-19.1 million) resulted in a diagnosis of nasopharyngitis (0.48 million visits, 3%), ARTI (0.4 million visits, 3%), or acute bronchitis (0.47 million visits, 4%), and inappropriate antibiotic prescribing rates for these conditions were 2.7%, 49.2%, and 57.0%, respectively. Logistic regression analysis showed that patients who received care from general and family practice physicians (odds ratio [OR] = 4.44, 95% CI = 1.58-12.477, P = 0.004) and from internal medicine physicians (OR = 3.437, 95% CI = 1.226-9.636, P = 0.019) were more likely to be prescribed antibiotics inappropriately when compared to patients of other physicians. Patients from the South (OR = 3.117, 95% CI = 1.244-7.810, P = 0.015) were more likely to be prescribed antibiotics compared to patients from the Northeast.

CONCLUSIONS: Inappropriate antibiotic prescribing is common and exhibits variation across physician specialties and geographical region. There is a need to optimize antibiotic prescription rates especially for acute respiratory tract infections and acute bronchitis by focusing...
intervention efforts on general and pharmacy practice physicians, internal medicine physicians, and physicians from the South, especially in managed care settings.

SPONSORSHIP: This research was conducted by the University of Houston, College of Pharmacy, Houston, TX, without external funding.

Preliminary Evaluation of Extended-Release Naltrexone in Michigan and Missouri Drug Courts

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BACKGROUND: Drug courts are designed for offenders who commit crimes under the influence of drugs or alcohol.

OBJECTIVE: This pilot study examined the feasibility and effectiveness of treatment with extended-release naltrexone (XR-NTX) in the drug court setting.

METHODS: Data were collected on alcohol-dependent clients treated with XR-NTX and a similar number of matched controls (i.e., no XR-NTX) from 2 courts in Michigan and 1 in Missouri. Treatment with XR-NTX was open-label, voluntary, and combined with psychosocial treatment. Referrals came from judges, probation officers, court coordinators, and treatment providers. All of the clients were considered by the courts to be the most difficult cases. The principal outcome was re-arrest rate.

RESULTS: 64 clients were treated with XR-NTX (n = 32; 32 mean prior convictions) or standard care (control group n = 32; 24 mean prior convictions). Treatment with XR-NTX (vs. control) was associated with (a) a relative reduction in risk (RRR) of missing a drug court session (RRR = 57%; P = NS); (b) a reduction in the rate of positive drug and alcohol tests per month (RRR = 35%; P = NS); (c) a reduction in the proportion of individuals with >25% positive alcohol or drug tests (RRR = 33%; P = NS); and (d) a reduction in the number of new arrests while under drug court supervision (XR-NTX: 8% vs. Control: 26% per year; RRR = 69%; P = 0.05).

CONCLUSIONS: The current pilot sample was difficult to obtain, suggesting why effectiveness research in this setting is so rare. Nonetheless, treatment with XR-NTX appeared to be feasible and was associated with a consistently large treatment effect across multiple outcomes relevant to the drug court setting.

SPONSORSHIP: This research was funded by Alkermes, Inc., under a contract with Northwest Professional Consortium (NPC) Research. Research design, data collection, data analyses, and report writing were performed primarily by NPC Research. Extended-release injectable naltrexone was developed with support from National Institute on Drug Abuse Grant R43DA013531 and National Institute on Alcohol Abuse and Alcoholism Grant N43AA001002. Funding for the purchase of extended-release naltrexone for clients of Missouri Drug and DUI Courts was provided through an allocation by the Missouri Department of Corrections to the Division of Alcohol and Drug Abuse and an allocation from the Department of Mental Health Medication Assisted Treatment Fund for Uninsured.

Real-World Clinical Outcomes and Costs in Atrial Fibrillation/Flutter Patients on Combined Warfarin and Antiarrhythmic Drug Therapy

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BACKGROUND: Antiarrhythmic drugs and warfarin (W) are often co-administered for atrial fibrillation/flutter (AF/AFL). Amiodarone (A) shows multiple drug interactions and potentiates the anticoagulant effect of W, affecting bleeding risk and stroke prevention outcomes.

OBJECTIVE: To assess rates of de novo stroke, hemorrhage, and arterial embolism in AF/AFL patients receiving W + A or W + another Class I/III antiarrhythmic drug (AAD).

METHODS: This retrospective cohort study identified AF/AFL patients aged 18 years or older with concurrent pharmacy claims (at least 60 days supply over 90 days) for W and A or AAD from the Ingenix IMPACT database (1997-2009). Patients had to have at least 1 claim with an AF/AFL diagnosis ≤ 6 months before starting concomitant W + A or W + AAD (index date) and continuous pre- (≥ 6 months) and post-index (≥ 12 months) enrollment. Events were measured over the post-index period until first occurrence, drug discontinuation, or end of eligibility/data availability. Health care resource use and costs (US$2009) were measured over 12 months post-index. Multivariate regression analysis was used to adjust for demographic/clinical differences between cohorts.

RESULTS: 4,238 patients (mean age 66.5 years; 70% male; mean Charlson Comorbidity Index [CCI] = 1.76) received W + A, and 6,332 patients (mean age 61.9 years; 65% male; mean CCI = 0.89) received W + AAD. After excluding patients with prior hemorrhagic/embolic events, clinical outcomes data were obtained for 3,919 (92.5%) and 6,028 (95.2%) patients, respectively. The W + A cohort had a higher combined incidence of stroke, hemorrhage, or arterial embolism than the W + AAD cohort (see table). The W + A cohort had higher incidences of all-cause (incidence rate ratio [IRR] = 1.11, P < 0.001) and cardiovascular-related (IRR = 1.35, P < 0.001) health care resource use than the W + AAD cohort. Over 12 months, the W + A cohort incurred incremental total health care costs of $4,114, which largely comprised incremental inpatient ($2,397) and outpatient ($1,171) costs.

CONCLUSIONS: In real-world practice, AF/AFL patients tend to be at higher risk of embolic/hemorrhagic events and to have higher health care (especially inpatient) costs with W + A than with W + AAD.

SPONSORSHIP: This research was funded by sanofi-aventis, Bridgewater, NJ.

Real-World Evaluation of the Cost-Effectiveness of Prophylactic Treatment in the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer: Dalteparin Versus Enoxaparin

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BACKGROUND: Patients with cancer are at increased risk of venous thromboembolism (VTE) and recurrent VTE.

OBJECTIVE: To evaluate the cost-effectiveness of prophylactic treatment for VTE with dalteparin and enoxaparin in cancer patients.

TABLE: Clinical Outcomes in Atrial Fibrillation/Flutter Patients on Combined Warfarin and Antiarrhythmic Drug Therapy

<table>
<thead>
<tr>
<th></th>
<th>Warfarin + Amiodarone</th>
<th>Warfarin + AAD</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, hemorrhage, or arterial embolism (% patients)</td>
<td>10.4%</td>
<td>6.2%</td>
<td>1.20 (1.02-1.40)</td>
<td>0.024</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.6%</td>
<td>4.2%</td>
<td>1.12 (0.93-1.36)</td>
<td>0.230</td>
</tr>
<tr>
<td>Hemorrhage/bleeding</td>
<td>0.8%</td>
<td>0.6%</td>
<td>0.86 (0.50-1.47)</td>
<td>0.578</td>
</tr>
<tr>
<td>Arterial embolism</td>
<td>2.4%</td>
<td>1.3%</td>
<td>1.39 (0.98-1.97)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

AAD = another antiarrhythmic drug; CI = confidence interval.
METHODS: Commercial claims data from January 1, 2004, to December 31, 2008, were used in this retrospective analysis. The study population was identified as follows: cancer patients (ICD-9-CM codes 140.xx-239.xx) with a diagnosis of VTE including deep vein thrombosis (deep vein thrombosis [DVT]; ICD-9-CM codes 451.xx-453.xx or 997.2x) and/or pulmonary embolism (pulmonary embolism [PE];ICD-9-CM codes 415.1x) and at least 18 months of continuous enrollment. An index VTE was identified as the earliest diagnosis, inpatient or outpatient, of VTE. Inpatient admissions with a primary or secondary diagnosis of VTE following the index event were recurrent events. Statistical comparisons of rates were conducted. Bootstrap sampling with replacement was applied to generate mean cost-effectiveness results on 100 random samples 1,000 times.

RESULTS: 12,059 cancer patients were identified with a previous VTE event, 396 treated with dalteparin and 11,663 treated with enoxaparin. Both gender and age were similar between treatment cohorts: 50.5% and 50.0% in the dalteparin and enoxaparin groups (P=0.83), with the greatest proportion of patients between the ages of 55 and 64 years (27.3% and 27.2%; P=0.98). Cancer tumor sites were also similar: 2.8% and 3.7% of dalteparin and enoxaparin patients had a recurrent VTE while on study medication (P≤0.01). Bleeding rates were similar: 3.03% and 2.14% (P=0.23). The total annual cost of a recurrent VTE per person was $19,589.06 (95% CI = $19,083.64 - $20,094.46), while the mean cost of bleeding associated with the use of anticoagulants was $1,341.25. Applying event rates to the costs of VTE and bleeding rates for dalteparin and enoxaparin yields expected costs per treated patient of $548.49 and $753.50, respectively. The total comparative costs of $589.13 and $753.50, respectively. 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care costs for patients with VTE and major bleeding were significantly higher for those with the event versus those without the event ($52,157 vs. $24,164, P<0.001 for VTE; $33,656 vs. $24,765, P<0.001 for major bleeding).

CONCLUSIONS: An inappropriately low proportion of medically ill patients in the United States receive thromboprophylaxis. VTE event rates were lower for patients who received prophylaxis versus those who did not receive it.

SPONSORSHIP: This research was funded by Johnson and Johnson Health Care Companies, New Brunswick, NJ.

### Time Between Infusions During First 18 Months of Infliximab Treatment in Patients with Rheumatoid Arthritis

**Bolge SC,* Schmeichel Mueller C, Bailey RA, Carter C, Ingham M, Centocor Ortho Biotech Services, LLC, 800 Ridgeview Dr., Horsham, PA 19044; bolge@its.jnj.com, 215.325.4859**

**BACKGROUND:** Infliximab is approved by the FDA for administration at weeks 0, 2, 6, and then every 8 weeks with potential to increase frequency to every 4 weeks based on clinical response in patients with rheumatoid arthritis (RA).

**OBJECTIVE:** To evaluate the time intervals between infliximab infusions during the first 18 months of treatment in RA patients across multiple large U.S. claims databases.

**METHODS:** Data were obtained from 3 retrospective claims databases (HealthCore Integrated Research Database [infliximab initiation July 2004 through October 2008], IMS LifeLink Health Plan Claims Database [January 2004 through December 2007], Wolters Kluwer Pharma Solutions [WKPS] databases [January 2004 through December 2007]) and 1 hospital database (Premier Perspective Database [July 2007 through March 2008]). Patients included in the analyses were aged ≥18 years, diagnosed with RA (ICD-9-CM codes 714.xx), naïve to therapy (6-12 months without biologic therapy prior to infliximab in claims data and no previous infliximab use in hospital data), and had no other select inflammatory condition. The induction period included the first through third doses, and the maintenance period included the fourth through twelfth doses, representing the first 18 months of therapy.

**RESULTS:** Observed intervals between infliximab infusions are consistent across databases. Within individual databases, mean days between infusions in the maintenance period ranged from a low to high of 56.1-63.5 in HealthCore, 53.1-60.3 in IMS LifeLink, 54.1-59.4 in Premier Perspective, and 52.8-55.0 in the WKPS database.

**CONCLUSIONS:** Real-world data across multiple large databases observed that average days between infliximab infusions in the first 18 months of treatment are consistent with U.S. prescribing information for RA. When examining biologic dosing frequency patterns, it may be important to consider multiple data sources.

**SPONSORSHIP:** This research was funded by Centocor Ortho Biotech Services, LLC, Horsham, PA, without external funding.

## Table

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Mean [SD] Days Between Infliximab Infusions During First 18 Months of Treatment Across 4 Databases</th>
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<tbody>
<tr>
<td></td>
<td>HealthCore</td>
</tr>
<tr>
<td>Infliximab users, n</td>
<td>938</td>
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<tr>
<td>1st-2nd infusion</td>
<td>27.8 [49.8]</td>
</tr>
<tr>
<td>2nd-3rd</td>
<td>39.5 [28.4]</td>
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<td>3rd-4th</td>
<td>63.5 [65.5]</td>
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<td>4th-5th</td>
<td>59.7 [44.9]</td>
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<td>5th-6th</td>
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<td>6th-7th</td>
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<td>8th-9th</td>
<td>56.5 [30.2]</td>
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<tr>
<td>9th-10th</td>
<td>54.2 [20.3]</td>
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<tr>
<td>10th-11th</td>
<td>56.1 [35.9]</td>
</tr>
<tr>
<td>11th-12th</td>
<td>53.3 [23.0]</td>
</tr>
</tbody>
</table>

WKPS = Wolters Kluwer Pharma Solutions database.

## Background

Nearly 225,000 patients are diagnosed with lung cancer each year. The death rate from lung cancer exceeds that from breast,
prostate, and colon cancers combined with about 160,000 fatalities annually in the United States. Non-small cell lung cancer (NSCLC) is the most common form of lung cancer. The costs of treatment vary widely, and long-term efficacy is limited in patients with advanced NSCLC.

**OBJECTIVE:** To (a) determine the per-patient-month (PPPM) total medical cost associated with various regimens in advanced NSCLC, (b) compare these costs per median survival time, and (c) examine the costs of ancillary medications (colony-stimulating factors [CSFs], anti-emetics, and erythropoietins [EPOs]) associated with chemotherapy for NSCLC.

**METHODS:** Paid medical claims from 2 large data sets were combined and analyzed. Date of service was from March 31, 2004, to April 30, 2009. An inception cohort with NSCLC was identified with ICD-9-CM codes and chemotherapy regimens. Total medical costs were aggregated from the date of first chemotherapy until the patient’s data ended. PPPM costs were then multiplied by estimated median survival duration (obtained from clinical trials) and the regimens compared.

**RESULTS:** Four regimens in 5,124 patients represented 87% of the observed platinum-based chemotherapy. The cost model was robust ($R^2=0.54$). The adjusted median PPPM total medical costs and cost per median survival are shown in the table. Compared with patients receiving carboplatin-paclitaxel (CP), those receiving carboplatin-docetaxel (CD) and carboplatin-paclitaxel-bevacizumab (CPB) had $3,803 and $6,809-$8,051 more CSF cost, respectively. Carboplatin-gemcitabine (CG) was not different from CP. Patients on CD and CG had more erythropoiesis-stimulating agent (ESA) cost than those on CP. CG patients had the lowest anti-emetic costs.

**CONCLUSIONS:** Total medical costs were lowest for carboplatin + paclitaxel and highest for carboplatin + paclitaxel + bevacizumab. Significant differences existed in the utilization of ancillary medications. These results indicate opportunities exist for health plans to manage costs related to NSCLC.

**SPONSORSHIP:** This research was funded by Abraxis Bioscience, Bridgewater, NJ.

### Use of Antidepressants and Atypical Antipsychotics in Patients with Pseudobulbar Affect

**Formella A,* Work S, Colamonico J, Kaye R, Avanir Pharmaceuticals, 101 Enterprise, Ste. 300, Aliso Viejo, CA 92656; aformella@avanir.com, 949.389.6754**

**BACKGROUND:** Pseudobulbar affect (PBA) is a disorder of involuntary emotional expression occurring secondary to neurologic disease or injury that results in sudden, uncontrollable, outbursts of laughter or crying that are incongruent or out of proportion with underlying emotional state. Prevalence estimates vary with underlying disorder, with highest prevalence in persons with stroke and amyotrophic lateral sclerosis (ALS, up to 50%-60%). PBA episodes are a source of embarrassment for patients and caregivers, often leading to social withdrawal and reduced quality of life (QOL). Tricyclic antidepressants (TCAs), serotonin or norepinephrine reuptake inhibitors (SSRIs/SNRIs), and atypical antipsychotics (AAs) have been used off-label to treat PBA.

**OBJECTIVE:** To determine the prevalence of TCA, SSRI, SNRI, and AA use in patients screening positive for PBA symptoms and evaluate the symptom severity in patients who use these medications versus those who do not.

**METHODS:** Patients with amyotrophic lateral sclerosis, multiple sclerosis, Parkinson’s disease, Alzheimer’s disease, stroke, or traumatic brain injury and PBA symptoms of inappropriate laughing or crying as indicated by a score ≥ 13 on the Center for Neurologic Studies-Lability Scale (CNS-LS) participated in an online burden of illness survey. Ratings were completed by patients or their caregivers. Respondents were questioned about the patient’s use of antidepressant and/or antipsychotic medications. The severity of PBA symptoms in patients with a CNS-LS score ≥ 13, was compared in patients who were taking and those not taking these medications.

**RESULTS:** A total of 404 of the 1,061 (38%) survey respondents had a CNS-LS score ≥ 13. Among these patients, 57% were taking SSRIs, SNRIs, TCAs, or AAs. The disease group with the highest percentage of patients with PBA symptoms taking these medications was ALS (75%), while corresponding percentages for the other conditions were between 38% and 60% of patients. The most commonly used medication was sertraline (18% of patients with PBA symptoms). In patients with PBA symptoms the mean CNS-LS score was 19.7 for those taking medications versus 17.7 those not taking medications. Mean CNS-LS score was 19.5 for PBA patients taking SSRIs/SNRIs, 20.6 for TCAs, and 20.7 for AAs.

**CONCLUSIONS:** These survey results suggest that PBA symptoms remain problematic for many patients despite treatment with off-label medications and that there remains a need for new PBA treatments.

**SPONSORSHIP:** This research was funded by Avanir Pharmaceuticals, Aliso Viejo, CA.

### Utilization of Atypical Antipsychotic Treatment Among Adults with Schizophrenia

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**BACKGROUND:** Atypical antipsychotics (AA) are generally first-line treatments for schizophrenia, however, nonadherence is common and may be associated with poor treatment outcomes.

**OBJECTIVE:** To evaluate utilization patterns of AA in a contemporary cohort of insured adults with schizophrenia.

**METHODS:** Claims data from 3 Thomson Reuters MarketScan Research databases (Commercial, Medicare, Medicaid) were used to identify a cohort of adults aged 18 years or older with a schizophrenia diagnosis (ICD-9-CM codes 295.xx) and evidence of at least 1 oral AA pharmacy claim between January 2002 and September (Commercial/Medicare) or December 2008 (Medicaid). All participants were enrolled for at least 24 months (a 12-month baseline period preceding and an additional 12 months following the index AA pharmacy claim). Patients were classified as new users (no AA claims during the baseline period) or existing...
Cost-Effectiveness of Oral Fingolimod and Intramuscular Interferon-Beta 1a for Relapsing Remitting Multiple Sclerosis (RRMS): Results Based on Efficacy Inputs from a Head-to-Head Study

Agashivala NV,* Dastani HB, Carlton R, Sarnes E, Novartis Pharmaceuticals Corporation, One Health Plaza, 405-4026A, East Hanover, NJ 07936; neetu.agashivala@novartis.com, 862.778.0019

BACKGROUND: Multiple sclerosis (MS) carries a substantial economic burden that impacts managed care plans. Members with MS accumulate medical costs greater than 2- to 3-times those of all enrollees. The number of relapses experienced by a MS patient is a significant predictor of the total costs of care. In a 12-month, head-to-head, double-blind, double-dummy, Phase 3 study (TRANSFORMS; N = 1,292) oral fingolimod 0.5 mg once daily was shown to significantly reduce relapse frequency and severity compared with a first-line disease-modifying therapy (DMT), weekly intramuscular (IM) interferon-beta (IFNβ-1a).

OBJECTIVE: To estimate the cost per relapse avoided with oral fingolimod 0.5 mg compared with IM IFNβ-1a in a hypothetical managed care plan from a U.S. commercial payer perspective.

METHODS: This Microsoft Excel-based model estimated the cost-effectiveness of fingolimod based on the number of incident and prevalent patients with relapsing remitting multiple sclerosis (RRMS) receiving fingolimod 0.5 mg once-daily and IM IFNβ-1a 30 mcg in a U.S. health plan. The analysis calculated the cost per relapse avoided for both drugs over 1 year (including drug acquisition costs, direct costs of managing relapses of variable severity, and monitoring costs) divided by the number of relapses avoided. The annualized relapse rates for fingolimod and IM IFNβ-1a were derived from the TRANSFORMS clinical trial (0.16 and 0.33, respectively), as was the frequency of relapse severity. The number of relapses experienced by a patient before treatment (0.77 per year) was derived from an observational real-world study. Cost data were derived from published sources (inflated to US$2010) and were modifiable to reflect a plan’s actual costs.

RESULTS: The cost per relapse avoided was $82,016 for fingolimod 0.5 mg compared with $86,296 for IM IFNβ-1a 30 mcg. Results of a univariate sensitivity analysis of the cost per relapse avoided for fingolimod showed the results were most sensitive to the drug acquisition cost of fingolimod and the number of relapses in untreated patients.

CONCLUSIONS: In this cost-effectiveness analysis using efficacy results from the head-to-head, randomized controlled trial of fingolimod versus IM IFNβ-1a, fingolimod had a lower cost per relapse avoided than IM IFNβ-1a. Fingolimod had lower cost per relapse avoided due to its efficacy in reducing relapses in the TRANSFORMS clinical trial.

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* Corresponding author.

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