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Reference

It seems that internationally acclaimed modern Impressionist David Lloyd Glover was destined to become an artist. Born in 1949 in the city of Victoria on Vancouver Island in British Columbia, Canada, he grew up on a 600-acre seaside estate known as Hatley Castle, formerly the Scottish baronial manor of James Dunsmuir, Lieutenant Governor. It had been converted in 1948 to the Royal Roads Military College, where his father served as an administrator. The estate's beautiful English, Japanese, and Italian gardens had an early influence on Glover and his artwork, and inspired his lifelong interest in man's relationship with nature. A couple of creative family members also influenced the budding young artist. His uncles, Guy Glover, a famous film producer, actor, and head of the National Film Board of Canada, and Norman McLaren, a world-renowned film artist, animator, and painter, both encouraged him in his artistic pursuits. Possessing remarkable talent for his age, Glover won a city-wide, juried painting exhibition in 1958 when he was only 9 years old. At 14, he was accepted as a student at the Vancouver School of Art despite its minimum age requirement of 18.

By his late teens, Glover had developed remarkable skills in pen and ink by studying the techniques of 19th-century English illustrators. His mastery of this style led to an editorial illustrator position at the Victoria Times newspaper. Within 3 years, the newspaper selected Glover to be its political cartoonist. His professional accomplishments also include graphic design, art direction, and the founding of an award-winning advertising agency, Truman/Glover Advertising, Ltd., in 1974.

After selling his interest in the company in 1977, Glover returned to his first love of fine art. He began with watercolors executed in the style of the British masters, and his paintings were met with instant success. Glover soon developed a strong following and became one of the best-selling artists at Vancouver's most respected gallery, Harrison Galleries.

In 1988, Glover's art dealer in Los Angeles encouraged him to come to Southern California to work as an artist in residence. "After a few months, California got under my skin in a big way and I decided to make it my home," he says. During the next few years, several art galleries in Los Angeles began exhibiting his paintings. Enthusiastic art collectors and Hollywood celebrities quickly snapped up Glover's original works and serigraph editions. Since then, he has exhibited his art at other noteworthy galleries in California, New York, Arizona, and Louisiana, as well as galleries in Canada, Mexico, and Japan, where he ranks among the country's most widely collected original artists.

Inspired by the great French Impressionists Monet, Renoir, and Cézanne, Glover began painting in oil in the early 1990s. He promptly mastered this medium, too. In an article that appeared in the December 2005 issue of American Art Collector magazine, Glover was described as a "sublime colorist," whether working in watercolor or oil. He also paints in acrylic, a very versatile medium.

The Art Brilliant gallery on Rodeo Drive in Beverly Hills held a special exhibition of Glover's art in June 2005. According to the biography on his website, davidlglover.com, "The show featured Glover's jazz portrait series of the great icons in American jazz. Images of the greats like Ella Fitzgerald, Louis Armstrong, John Coltrane, and Miles Davis were featured, along with portraits of some of the contemporary legends like Wayne Shorter and Herbie Hancock. Herbie also made a personal appearance at the show in honor of his friend David Lloyd Glover." Wayne Shorter happens to be a friend of the artist as well. Both Hancock and Shorter played in the Miles Davis quartet at one time. Davis, the iconic American trumpeter, bandleader, and composer, was at the forefront of several major developments in jazz music, including bebop, cool jazz, and jazz fusion. Glover says that he titled this issue's fabulous cover painting Sir Miles Davis because the musician was knighted by the French in 1991. He cropped the image to emphasize Davis' upper body and chose bright hues for his jacket to reflect his colorful music and persona.

In addition to Glover's jazz portraits, he has painted portraits of other pop stars such as John Wayne, Marlon Brando, Frank Sinatra, Elvis, and Michael Jackson. "Capturing the images of the icons of American popular culture has always been of great interest to me," he says. "I try to tell their story with colors alone." His vivid portraits are extraordinary—they truly convey the essence of each individual.

To see the list of galleries and websites that carry Glover's magnificent iconographic and landscape art, visit the "Dealers & Links" page on his website, davidlglover.com/9.html. His work is also available online through the Fine Art America website, fineartamerica.com—simply enter the name David Lloyd Glover in the search box.

Sheila Macho
Cover Editor
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Discontinuation Rates and Health Care Costs in Adult Patients Starting Generic Versus Brand SSRI or SNRI Antidepressants in Commercial Health Plans

Anna Vlahiotis, MA; Scott T. Devine, PhD; Jeff Eichholz, PharmD; and Adam Kautzner, PharmD

ABSTRACT

BACKGROUND: Generic antidepressants offer significant prescription drug cost savings compared with brand-name antidepressants, but critics of managed care interventions promoting generic medication use suggest that some generic antidepressants are not as safe or effective as the brand alternatives.

OBJECTIVE: To assess (a) rates of discontinuation of the initially dispensed medication and (b) disease-specific and total health care costs and pharmacy costs, comparing patients who initiated therapy with brand versus generic selective serotonin reuptake inhibitors (SSRI) or selective norepinephrine reuptake inhibitors (SNRI).

METHODS: Antidepressant users aged 18 to 64 years with no pharmacy claims for an SSRI/SNRI in the 180 days prior to the start of SSRI/SNRI therapy (baseline) were identified in the MarketScan database between July 1, 2005, and June 30, 2007, and were followed for 180 days (follow-up). All study patients met the following criteria: (a) continuously eligible from baseline through follow-up; (b) at least 1 medical claim with a primary or secondary diagnosis of major depressive disorder (ICD-9-CM codes 296.2 or 296.3) in either the baseline or follow-up period; and (c) no pharmacy claims for antipsychotic medications in the baseline period. For brand versus generic antidepressant initiators, logistic regression was used to determine the odds of 6-month therapy discontinuation, defined as no medication refills or absence of a refill for the initially dispensed medication within 1.5 times the days supply dispensed, adjusted for important covariates. Costs were measured as total plan allowed charges including member cost share. Adjusted mean (least squares means holding covariates) all-cause medical costs, disease-specific (claims with secondary diagnosis field) medical costs, all-cause pharmacy costs, and SSRI/SNRI antidepressant costs were compared for brand versus generic initiators using generalized linear regression models, also adjusted for baseline covariates.

RESULTS: Of 16,659 new SSRI/SNRI users, 47.8% (n = 7,955) initiated a brand-name medication and 52.2% (n = 8,704) initiated a generic product. Of the 7,955 who initiated a brand-name antidepressant, 46.8% (n = 3,723) discontinued the initially dispensed drug within 180 days, compared with 44.2% (n = 3,843) of the 8,704 who initiated a generic. The adjusted odds of discontinuation among generic and brand drug users did not significantly differ (odds ratio [OR] = 1.09, 95% CI = 0.98-1.22). Adjusted all-cause 6-month average health care costs in patients initiating therapy on a generic antidepressant were $3,660 (95% CI = $3,538-$3,787) compared with $4,587 (95% CI = $4,422-$4,757) for patients initiating on a brand-name antidepressant. Adjusted average 6-month SSRI/SNRI antidepressant costs were 43.7% lower in patients initiating on a generic drug ($174 vs. $309).

CONCLUSIONS: The likelihood of discontinuation was similar for patients who initiated therapy with brand or generic antidepressants, and short-term health care costs and pharmacy costs were lower in patients starting a generic SSRI/SNRI. The results suggest that the use of generic antidepressants as first-line agents in the treatment of major depressive disorder is associated with continuation rates similar to initiation with brand antidepressants but with lower health care costs.

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What is already known about this subject

• Evidence suggests that generic selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs) provide cost savings over brand-name medications. An observational study by Dunn et al. showed that a step-therapy edit requiring patients to use a generic antidepressant prior to use of a brand-name medication resulted in drug cost savings of $1,880,562 ($0.36 per member per month) in 2005 dollars in the first year of implementation of the program, but the authors did not look at the impact on health outcomes or medical costs.

• Despite evidence of cost savings, some case reports and bioequivalence studies suggest a disadvantage in efficacy and tolerability of generic medications compared with brand-name equivalents. Further, observational reports have provided mixed evidence of safety and efficacy among brand and generic SSRIs and SNRIs. These studies are of varying quality, adding lack of clarity to the debate.

What this study adds

• Comparing patients initiating antidepressant therapy with a brand versus generic medication, there was no significant difference in the likelihood of discontinuation of the initially dispensed medication during the first 180 days of SSRI or SNRI therapy. Health care costs were lower among patients starting a generic SSRI/SNRI, even after adjustment for measurable factors that may affect costs, such as age and comorbidity.

• The discontinuation rate within 180 days of initiating antidepressant drug therapy among patients starting on a generic medication was 44.2%, compared with 46.8% among patients initiating therapy on a brand medication (P=0.006). However, the adjusted odds of discontinuation among generic users did not significantly differ from those of brand drug users (OR = 1.09, 95% CI = 0.98-1.22).
Discontinuation Rates and Health Care Costs in Adult Patients Starting Generic Versus Brand SSRI or SNRI Antidepressants in Commercial Health Plans

What this study adds (continued)

- Total adjusted average 6-month health care costs in patients initiating therapy on a generic drug were $3,660 (95% CI = $3,538-$3,787), 20% less than the average $4,587 (95% CI = $4,422-$4,757) for patients initiating on a brand-name drug (P < 0.001). Average SSRI/SNRI antidepressant costs in patients initiating therapy on a generic drug were $174 (95% CI = $169-$180), 44% less than the average $309 (95% CI = $300-$319) for patients initiating on a brand-name medication (P < 0.001).

Brand-name selective serotonin reuptake inhibitors (SSRIs), such as Lexapro (escitalopram; Forest Laboratories) and Paxil CR (paroxetine controlled release; GlaxoSmithKline), and brand-name SNRIs, such as Cymbalta (duloxetine HCl; Lilly), are often prescribed as first-line medications by physicians for the treatment of some mental health disorders, such as major depressive disorder. Decisions to prescribe brand-name medications rather than generic therapeutic equivalents may be made on the basis of perceived clinical effectiveness or tolerability but also may be influenced by the marketing efforts of pharmaceutical companies. However, there is mixed evidence of treatment continuity and cost-effectiveness when comparing brand and generic antidepressant therapies.

Multiple meta-analyses of randomized controlled trials have found that treatment of adults with major depressive disorder with second-generation antidepressants is generally efficacious and safe, with more recent evidence suggesting greater efficacy for sertraline compared with other second-generation drugs. A 2009 multiple-treatments meta-analysis of 12 new-generation antidepressants, which included both single-source brand and generically available agents, concluded that clinically meaningful differences in efficacy and tolerance among the medications favored escitalopram and sertraline; the authors noted that sertraline had the most favorable balance between costs, benefits, and acceptability among patients. Nonetheless, a comparative effectiveness review sponsored by the Agency for Healthcare Research and Quality cautioned that such studies were not intended to test variation in individual responses to individual drugs, and case reports of symptom relapse following generic substitution have emerged in the literature. Investigations by the U.S. Food and Drug Administration into reports of this type, comparing brand versus generic bupropion, found minor differences in pharmacokinetics that did not fall outside of accepted boundaries for bioequivalence. A Carlat Psychiatry Report on the issue (2009) noted that the preponderance of evidence suggesting that generic drug substitutions result in failure was found in “single cases or very small case series, virtually all written by authors who are also paid consultants for pharmaceutical companies.” Still, concerns about generic substitution of antidepressants have persisted. Observational comparisons and bioequivalence studies of patients treated with brand versus generic second-generation antidepressants have produced mixed findings.

As part of containing the rising cost of health care in general, and prescription medications specifically, managed care organizations, employer groups, and other plan sponsors are increasingly adopting intervention programs that are designed to encourage efficient use of pharmaceuticals, including step therapy. Step-therapy programs work by requiring that patients attempt the use of first-line medications prior to receiving pharmacy benefit coverage for other prescription drugs in the same therapy class. The first-line medications are often lower-cost generic drugs that can offer the same health benefits as the more expensive brand-name drugs originally prescribed by physicians. Because the value of the brand-name SSRIs/SNRIs has not been unequivocally demonstrated, generic antidepressants may offer cost savings without an increase in adverse health outcomes, as is intended in step-therapy programs.

Studies have examined the impact of obligatory generic antidepressant step-therapy programs on pharmacy costs and utilization or have estimated the economic impact of cost control programs among patients with a single diagnosis, but no published research identified through a Medline search has evaluated multiple outcomes associated with the initial prescription of different generic SSRIs or SNRIs compared with brand medications in patients with major depressive disorder. Although the outcomes of a utilization management program requiring first-line use of a generic medication were not directly measured, the purpose of this study was to answer questions about potential treatment failure by assessing discontinuation rates and health care costs, comparing patients who initiated therapy with a generic versus a brand-name SSRI or SNRI. The study was conducted by a pharmacy benefits management (PBM) company.

Methods

Study Cohort and Data Source

A cohort study design was used to compare discontinuation rates and health care utilization costs among patients using brand versus generic SSRI or SNRI antidepressant therapy. Data from the MarketScan Commercial Claims and Encounters dataset (Thomson Reuters, New York, NY) for the period of January 1, 2005, to December 31, 2007, were used. These data include commercial (e.g., not Medicare or Medicaid) health insurance claims (inpatient and outpatient medical, and outpatient pharmacy) as well as enrollment data from large employers and health plans across the United States that provide private health care coverage for more than 45 million employees, their spouses, and dependents, all of whom are younger than age 65 years. This administrative
Inclusion criteria required that the patient: (a) had a pharmacy claim for an SSRI or SNRI during an identification period from July 1, 2005, through June 30, 2007, identified by mapping National Drug Code (NDC) numbers provided in the MarketScan dataset to generic product identifier (GPI, Medi-Span, Inc., Indianapolis, IN) codes beginning with 5816 or 5818; (b) was a new user of an SSRI or SNRI, defined as the absence of a pharmacy claim for an SSRI or SNRI in the 180 days prior to the date of the first observed SSRI/SNRI claim in the identification period (index date); (c) did not have pharmacy claims for antipsychotic medications (GPI codes beginning with 59) in the 180 days prior to the index SSRI/SNRI claim; (d) was aged 18 years or older as of the index pharmacy claim date; (e) was continuously enrolled in a prescription drug benefit plan for 180 days prior to the index pharmacy claim and 180 days after the index pharmacy claim; (f) did not have claims with a negative days supply, duplicate claims, or reversed claims with negative cost values in the 180 days prior to or after the index pharmacy claim; and (g) had at least 1 claim with a primary or secondary diagnosis of single-episode or recurrent major depressive disorder as indicated by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 296.2 and 296.3 in the 180 days prior to or after the index pharmacy claim, as these are patients who may require longer term therapy.19 Brand versus generic status for each SSRI/SNRI pharmacy claim was determined by mapping the NDC number in the MarketScan file to an internal PBM file that indicated brand or generic status.

Exposure and Covariates

The exposure of interest was the occurrence of a new pharmacy claim for a generic SSRI or SNRI. Pharmacy and medical claims were evaluated for the 6-month time periods before (baseline) and after (follow-up) the index date. Exposure could occur at any point on or after July 1, 2005.

Patient age category (in years: 18 to 25, 26 to 40, 41 to 55, 56 to 64) as of the date of the index pharmacy claim was included as a potential covariate because age may be associated with antidepressant treatment outcomes.20,21 Gender may also place patients at increased risk for developing certain types of psychiatric disorders such as depression,22 and differences in adverse effects and time-to-response to different therapies have been reported between male and female antidepressant users.23,24 Based upon the apparent differences in response to therapy, gender was also included as a potential confounder, with female gender as the reference group.

The risk for therapy discontinuation may also increase with some comorbidities.25 A Charlson Comorbidity Index (CCI) score based on the 180 days prior to and after the index pharmacy claim (baseline and follow-up) was calculated for all members of the sample. The CCI is a validated measure of the burden of chronic illnesses that has been adapted for use with ICD-9-CM codes found in administrative claims data over a 12-month period.26 The CCI was included as a potential confounder and measured as a categorical variable (scores of 0, 1 to 2, 3 to 5, and 6 or more). In addition, the medical costs incurred by patients with some mental health illnesses can be an indication of symptom severity.27 The summed all-cause medical costs (total plan allowed amounts for outpatient and inpatient hospital and for physician services, not including pharmacy costs) incurred by patients in the baseline period were also measured, and analyzed as a categorical variable based on quartiles ($1-$178, $179-$657, $658-$2,402, and $2,403 or more).

Depression has been successfully managed in the primary care setting,28 but therapy discontinuation may be more likely among patients who are receiving specialized psychiatric care, such as psychotherapy.22 Thus, receipt of inpatient or outpatient psychiatric medical care, indicated by Current Procedural Terminology (CPT) codes 90801-90829 (psychiatric interviews and psychotherapy) and 90862-90899 (other psychiatric services or procedures, such as pharmacologic management, electroconvulsive therapy, and hypnotherapy) in the baseline period, was examined as a potential confounder. Recent evidence also suggests that some SSRIs may be associated with an increased risk of bleeding,29 which could theoretically suggest that patients beginning anticoagulant therapy may be more likely to discontinue therapy. A binary variable indicating a pharmacy claim for an anticoagulant (GPI codes beginning 8310 [heparins], 8320 [coumarin anticoagulants, including warfarin], or 8333 [thrombin inhibitors]) in the baseline period was also measured.

Finally, primary or secondary diagnosis of a comorbid mood disorder during either the baseline or follow-up period, including anxiety state (ICD-9-CM codes 300.0x), bipolar disorder (ICD-9-CM codes 296.0, 296.4, 296.5, 296.6, 296.7, 296.8) or obsessive compulsive disorder (ICD-9-CM codes 300.3, 301.4) was also assessed. Each comorbid mood disorder was measured as a separate binary variable. Both time periods were included because diagnosis prior to the initiation of an SSRI or SNRI may have affected which medication was prescribed, and diagnosis after the initiation of therapy may have affected the decision to discontinue or augment therapy.

Outcomes

Two primary outcomes were measured during the follow-up period: discontinuation of the initial GPI-10 coded medication, including its brand or generic status, and health care costs. During the 180 days after initiation of therapy, patients could discontinue the initially dispensed therapy (i.e., either switch to a different antidepressant drug or terminate antidepressant therapy altogether) or continue on the index
medication. A 6-month follow-up time period was chosen for this study, which is consistent with the National Committee for Quality Assurance recommendations for effective management of major depressive disorder treated with antidepressant medication. A discontinuation date was considered as the date of the last pharmacy claim for the initial medication plus the days supply dispensed for the last pharmacy claim, and a study completion date was defined as the index pharmacy claim date plus 180 days. Patients were considered to have discontinued therapy if the index pharmacy claim was not refilled within 1.5 times the days supply dispensed (e.g., 45 days on a 30-day supply, 135 days on a 90-day supply). A switch from the initial medication to another medication with a different GPI-10 was considered a discontinuation, as was a switch between the brand and generic formulations of the same medication. Medication switches were counted as discontinuations to measure change to the initially prescribed medication, addressing the concern that the initial prescription of a generic medication is associated with greater proportions of patients who discontinue or otherwise fail therapy. Once a patient was defined as discontinued, re-initiation of the index medication was not considered.

Total health care costs included the plan allowed charges, including member cost share, for all inpatient and outpatient medical services claims and for all outpatient pharmacy claims in the 180-day follow-up period. Costs were further categorized as disease-specific (charges incurred for medical claims with an associated primary or secondary diagnosis of major depressive disorder as indicated by ICD-9-CM codes or pharmacy claims for any SSRI or SNRI) and all-cause (charges incurred for any claims—not dependent on ICD-9-CM diagnosis codes or therapeutic classes).

Older antidepressants, such as tricyclic antidepressants, are still used alone and in conjunction with newer SSRIs and SNRIs because some patients respond differently to different mechanisms of action. As response or nonresponse to other antidepressants may affect continuation of SSRIs or SNRIs, and as failure to respond to SSRIs or SNRIs may be reflected by new treatment with an older antidepressant, augmentation of therapy with a non-SSRI/SNRI antidepressant (GPI codes beginning 5812 [modified cyclics, including nefazodone and trazodone], 5820 [tricyclic antidepressants], and 5830 [miscellaneous antidepressants, including bupropion]) in the 180-day period after the index pharmacy claim was also considered as a secondary outcome.

Statistical Analysis
Each variable that could potentially affect the relationship between the exposure and discontinuation was entered into a logistic regression model. Variables with a P value of less than 0.1 in bivariate screening were entered into full models, and variables with a P value of less than 0.05 were retained in the final model. The variables used in specifying the logistic regression model included patient age category, gender, CCI category, baseline medical cost category, receipt of psychiatric medical care in the baseline period, indication of anticoagulant therapy in the baseline period, indication of a comorbid mood disorder diagnosis in either the baseline or follow-up period, and an indicator of which SSRI or SNRI was initially prescribed.

To assess the impact of augmentation of SSRI/SNRI therapy with a non-SSRI/SNRI antidepressant after initiation of therapy, a stratified analysis compared the relationship between the initial exposure to a generic or brand SSRI/SNRI and therapy discontinuation in a subsample of patients who filled a prescription for a non-SSRI/SNRI antidepressant in the follow-up period versus a subsample of patients who did not. The odds ratios of the final logistic regression models were compared in the subsamples.

Generalized linear models (GLM) were constructed to measure the relationship between exposure status and health care costs. Models were specified with a gamma distribution and log link function to satisfy the assumptions of homoskedasticity and a normal distribution. The summed all-cause total health care costs, disease-specific total health care costs, all-cause pharmacy costs, and SSRI or SNRI antidepressant costs measured in the follow-up period were each evaluated. The associations of health care costs and pharmacy costs with generic drug status were assessed, controlling for covariate effects with a P value of less than 0.1 in bivariate screening. Variables with a P value of less than 0.05 were retained in the final models.

Least squares mean costs holding covariates at their mean values were calculated for patients initiating brand-name versus generic medications. For each least squares mean, t-type 95% confidence intervals (CIs) were constructed using the SAS (SAS Institute Inc., Carey, NC) LSMEANS option in the GENMOD procedure. All variables were checked for missing data. Statistical analyses were performed using SAS version 9.2. The a priori alpha value was 0.05.

Results
There were 2,545,696 individual patients identified with a pharmacy claim for an SSRI or SNRI between July 1, 2005, and June 30, 2007 (Figure 1). From this sample, 951,605 were excluded because they were not new to SSRI/SNRI therapy; 148,600 were excluded because they had a pharmacy claim for an antipsychotic in the baseline period; 74,237 were excluded because they were younger than 18 years old; 742,271 were excluded for lack of continuous enrollment in the 180 days prior to and after the index pharmacy claim; 35,524 were excluded because of negative days supply of the index medication, single claims being counted multiple times, or negative cost values; and 576,800 were excluded because they did not have a primary diagnosis of major depressive disorder,
leaving 16,659 patients in the final sample. The decline in sample size resulting from excluding patients without a depression diagnosis has occurred in other observational studies using administrative claims databases. There were no missing data in the analytic sample.

**Therapy Discontinuation**

The demographic and clinical characteristics of the patients were stratified by whether or not they discontinued therapy (Table 1). Within 180 days of initiating therapy on a brand or generic SSRI/SNRI, 7,566 patients (45.4%) discontinued the initially dispensed therapy. Of these, 2,916 (38.5% of those discontinuing, 17.5% of the sample overall) did not refill the initial prescription and 2,423 (32.0% of those discontinuing, 14.5% of the sample overall) switched to a different antidepressant medication (data not shown). Among patients who discontinued therapy, the mean (median) time until discontinuation was 50.8 (30) days (range 1 to 158 days); 68.8% of patients who discontinued did so in the first 60 days of therapy; and 84.0% discontinued within the first 90 days after initiating therapy (data not shown).

Of 8,704 patients who started treatment with a generic SSRI/SNRI, 3,843 (44.2%) discontinued the initially dispensed therapy during follow-up. Of those, 1,509 (39.3% of those discontinuing, 17.3% of generic users overall) did not refill their initial prescription, and 1,199 (31.2% of those discontinuing, 13.8% of generic users overall) switched to a different antidepressant medication (data not shown). Among patients who discontinued therapy after initiating therapy with a generic SSRI or SNRI, the mean (median) time until discontinuation was 51.2 (30) days (range 1 to 157 days); 68.0% of patients who discontinued did so in the first 60 days after the index pharmacy claim, and 84.4% discontinued therapy within the first 90 days (data not shown).

Of 7,955 patients who initiated treatment with a brand SSRI/SNRI, 3,723 (46.8%) discontinued the initially dispensed therapy during follow-up. Of those, 1,407 (37.8% of those discontinuing, 17.7% of brand users overall) did not refill the initial prescription and 1,224 (32.9% of those discontinuing, 15.4% of brand users overall) switched to a different antidepressant medication (data not shown). Among patients who discontinued therapy after initiating therapy with a branded medication, the mean (median) time until discontinuation was 50.3 (30) days (range 1 to 158 days); 69.9% of patients who discontinued did so in the first 60 days after the index pharmacy claim; and 83.7% discontinued therapy within the first 90 days (data not shown).

Patients who discontinued therapy were slightly younger on average than patients who did not discontinue (mean ages 39.3 years vs. 41.9 years, respectively, P<0.001) and were more likely to have comorbid mood disorder diagnoses during the study period. Use of escitalopram or paroxetine HCl was more common among patients who discontinued therapy compared with those who did not discontinue (23.2% vs. 20.6%, respectively, and 11.2% vs. 7.9%, respectively, both P<0.001).

Patients who initiated therapy on a generic SSRI/SNRI had similar odds of discontinuing the initially dispensed drug in the first 180 days of therapy compared with patients who initiated

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**FIGURE 1 Patient Selection Flowchart**

![Patient Selection Flowchart](Image)

SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
analyses stratified by augmentation (i.e., in 2 subsample groups of patients who augmented therapy with a non-SSRI/SNRI antidepressant during follow-up vs. those who did not), patients who initiated therapy on a generic SSRI/SNRI were no more likely to discontinue therapy than patients who started a branded alternative (odds ratio [OR] = 1.09, 95% CI = 0.98-1.22; Table 2). Variables in the final model included generic status of the index pharmacy claim; age; gender; indicators for psychiatric medical treatment, comorbid anxiety disorder, and bipolar disorder; and specific SSRI/SNRI drug. In the

### TABLE 1

Profiles of 16,659 New SSRI/SNRI Users in the First 180 Days After Initiating Antidepressant Therapy in the 2005-2007 MarketScan Database

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Continued Initially Dispersed Therapy n (%)</th>
<th>Discontinued Initially Dispensed Therapy n (%)</th>
<th>P Value</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand index pharmacy claim</td>
<td>4,232 (46.5)</td>
<td>3,723 (49.2)</td>
<td>Referent Category</td>
<td></td>
</tr>
<tr>
<td>Generic index pharmacy claim</td>
<td>4,861 (53.5)</td>
<td>3,843 (50.8)</td>
<td>0.006</td>
<td>0.90 (0.85-0.96)</td>
</tr>
</tbody>
</table>

| Gender | | Referent Category |
| Female | 6,005 (66.0) | 4,880 (64.5) | 0.038 | 1.07 (1.00-1.14) |
| Male | 3,088 (34.0) | 2,686 (35.5) | |

| Age in years | | |
| 18 to 25 | 1,023 (11.3) | 1,248 (16.5) | Referent Category |
| 26 to 40 | 2,947 (32.4) | 2,773 (36.7) | 0.77 (0.70-0.85) |
| 41 to 55 | 3,822 (42.0) | 2,770 (36.6) | 0.59 (0.54-0.65) |
| 56 to 64 | 1,301 (14.3) | 775 (10.2) | <0.001 | 0.49 (0.43-0.55) |

| Charlson Comorbidity Index | | |
| 0 | 7,233 (79.5) | 6,011 (79.4) | Referent Category |
| 1 to 2 | 1,601 (17.6) | 1,334 (17.6) | 1.00 (0.93-1.08) |
| 3 to 5 | 179 (2.0) | 171 (2.3) | 1.15 (0.93-1.42) |
| 6 or more | 80 (0.9) | 50 (0.7) | 0.239 | 0.75 (0.53-1.07) |

| Medical costs in U.S. dollars | | |
| $1-$178 | 2,239 (24.6) | 1,928 (25.5) | Referent Category |
| $179-$657 | 2,316 (25.5) | 1,849 (24.4) | 0.93 (0.85-1.01) |
| $658-$2,402 | 2,336 (25.7) | 1,826 (24.1) | 0.91 (0.83-0.99) |
| $2,403+ | 2,202 (24.2) | 1,963 (25.9) | 0.008 | 1.04 (0.95-1.13) |

| Specific SSRI/SNRI drug | | |
| Fluoxetine | 1,964 (21.6) | 1,317 (17.4) | <0.001 | Referent Category |
| Citalopram | 1,459 (16.0) | 1,104 (14.6) | 0.010 | 0.89 (0.82-0.97) |
| Escitalopram | 1,873 (20.6) | 1,756 (23.2) | <0.001 | 1.17 (1.08-1.29) |
| Fluvoxamine | 19 (0.2) | 20 (0.3) | 0.461 | 1.27 (0.68-2.38) |
| Paroxetine HCl | 721 (7.9) | 844 (11.2) | <0.001 | 1.46 (1.31-1.62) |
| Paroxetine mesylate | 8 (0.1) | 9 (0.1) | 0.533 | 1.36 (0.52-3.51) |
| Sertraline | 1,829 (20.1) | 1,493 (19.7) | 0.594 | 0.98 (0.91-1.05) |
| Duloxetine | 541 (5.9) | 473 (6.3) | 0.417 | 1.05 (0.93-1.20) |
| Venlafaxine | 679 (7.5) | 550 (7.3) | 0.627 | 0.97 (0.86-1.09) |

*For categorical variables, P values were derived from Pearson chi-square tests. All tests compared patients who did versus those who did not discontinue therapy.

*Measured during a 12-month period including both the 180-day baseline and follow-up periods.

*Measured in the 180-day baseline period.

*Available in branded and generic formulations at given points between January 1, 2005, and December 31, 2007.

*Available only in a branded formulation between January 1, 2005, and December 31, 2007.

CI = confidence interval; HCl = hydrochloride; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
Discontinuation Rates and Health Care Costs in Adult Patients Starting Generic Versus Brand SSRI or SNRI Antidepressants in Commercial Health Plans

### TABLE 2

**Logistic Regression Analysis of Discontinuing the Initially Dispensed Antidepressant Therapy in 16,659 New SSRI/SNRI Users in the First 180 Days After Initiating Therapy in 2005-2007**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients (C = 0.582)</td>
<td>New Non-SSRI/SNRI (C = 0.638)</td>
<td>No New Non-SSRI/SNRI (C = 0.579)</td>
</tr>
<tr>
<td>Brand index pharmacy claim</td>
<td>Referent category</td>
<td>Referent category</td>
<td>Referent category</td>
</tr>
<tr>
<td>Generic index pharmacy claim</td>
<td>1.09 (0.98-1.22)</td>
<td>1.45 (0.89-2.34)</td>
<td>1.08 (0.96-1.21)</td>
</tr>
<tr>
<td>Male</td>
<td>1.08 (1.01-1.15)</td>
<td>1.16 (0.89-1.51)</td>
<td>1.07 (1.00-1.15)</td>
</tr>
<tr>
<td>Aged 18 to 25 years</td>
<td>Referent category</td>
<td>Referent category</td>
<td>Referent category</td>
</tr>
<tr>
<td>Aged 26 to 40 years</td>
<td>0.76 (0.69-0.84)</td>
<td>1.00 (0.69-1.45)</td>
<td>0.75 (0.67-0.83)</td>
</tr>
<tr>
<td>Aged 41 to 55 years</td>
<td>0.83 (0.53-0.64)</td>
<td>0.63 (0.44-0.90)</td>
<td>0.58 (0.52-0.64)</td>
</tr>
<tr>
<td>Aged 56 to 64 years</td>
<td>0.47 (0.42-0.53)</td>
<td>0.44 (0.26-0.75)</td>
<td>0.47 (0.42-0.54)</td>
</tr>
<tr>
<td>Anxiety disorderb</td>
<td>1.10 (1.01-1.20)</td>
<td>1.22 (0.88-1.69)</td>
<td>1.09 (0.99-1.19)</td>
</tr>
<tr>
<td>Bipolar disorderb</td>
<td>1.80 (1.33-2.45)</td>
<td>3.33 (0.94-11.73)</td>
<td>1.67 (1.22-2.30)</td>
</tr>
<tr>
<td>Medical costs $1-$178b</td>
<td>Referent category</td>
<td>Referent category</td>
<td>Referent category</td>
</tr>
<tr>
<td>Medical costs $179-$657b</td>
<td>0.94 (0.87-1.03)</td>
<td>0.82 (0.57-1.17)</td>
<td>0.95 (0.87-1.04)</td>
</tr>
<tr>
<td>Medical costs $658-$2,402b</td>
<td>0.95 (0.87-1.04)</td>
<td>0.70 (0.49-1.00)</td>
<td>0.97 (0.88-1.06)</td>
</tr>
<tr>
<td>Medical costs $2,403 or moreb</td>
<td>1.09 (0.99-1.20)</td>
<td>0.83 (0.58-1.20)</td>
<td>1.10 (1.01-1.21)</td>
</tr>
<tr>
<td>Psychiatric medical careb</td>
<td>1.06 (0.99-1.14)</td>
<td>0.92 (0.68-1.25)</td>
<td>1.06 (0.99-1.14)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Referent category</td>
<td>Referent category</td>
<td>Referent category</td>
</tr>
<tr>
<td>Citalopram</td>
<td>1.13 (1.01-1.25)</td>
<td>1.48 (1.00-2.20)</td>
<td>1.10 (0.99-1.23)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1.50 (1.29-1.74)</td>
<td>3.57 (1.93-6.61)</td>
<td>1.42 (1.22-1.66)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1.45 (0.77-2.75)</td>
<td>NA</td>
<td>1.31 (0.68-2.53)</td>
</tr>
<tr>
<td>Paroxetine HCl</td>
<td>1.79 (1.57-2.03)</td>
<td>2.67 (1.63-4.39)</td>
<td>1.74 (1.53-1.98)</td>
</tr>
<tr>
<td>Paroxetine mesylate</td>
<td>1.82 (0.69-4.79)</td>
<td>NA</td>
<td>1.40 (0.50-3.92)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1.24 (1.11-1.39)</td>
<td>2.52 (1.59-4.02)</td>
<td>1.19 (1.06-1.33)</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1.48 (1.24-1.78)</td>
<td>2.36 (1.11-5.04)</td>
<td>1.44 (1.19-1.73)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1.32 (1.11-1.57)</td>
<td>2.70 (1.34-5.46)</td>
<td>1.26 (1.05-1.50)</td>
</tr>
</tbody>
</table>

**a**MarketScan database; results stratified by whether patients initiated therapy on a non-SSRI/SNRI during the 180-day follow-up period.

**b**Comorbid anxiety disorder or bipolar disorder diagnosis measured in the 180-day baseline and follow-up periods; medical costs measured in the 180-day baseline period; psychiatric medical care measured in the 180-day baseline period.

**c**c-statistic (area under receiver operating characteristics curve); CI = confidence interval; HCl = hydrochloride; NA = not applicable; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

medication (Table 2). This finding suggests that while important, augmentation with a non SSRI/SNRI antidepressant does not affect the relationship between the generic status of the index pharmacy claim and discontinuation of therapy.

### Health Care Costs

After adjustment for other factors associated with health care costs in patients with major depressive disorder, patients who initiated therapy on a generic drug had lower health care costs during the first 180 days after the index SSRI/SNRI prescription compared with brand drug users (Table 3). The adjusted average total health care costs (least squares mean costs) in the first 180 days after the index pharmacy claim among patients who initiated therapy on a generic SSRI/SNRI were $3,660 (95% CI = $3,538-$3,787) versus $4,587 (95% CI = $4,422-$4,757) among patients who initiated therapy on a brand medication. Least squares mean disease-specific health care costs were also lower in patients who initiated therapy on a generic medication compared to a branded medication ($803, 95% CI = $771-$836 vs. $1,125, 95% CI = $1,077-$1,175). All-cause pharmacy costs and SSRI or SNRI antidepressant pharmacy costs each were significantly lower among patients who initiated therapy with a generic medication compared with patients who initiated therapy with a brand medication ($761, 95% CI = $738-$785 vs. $965, 95% CI = $934-$998, respectively, for all-cause pharmacy costs; $174, 95% CI = $169-$180 vs. $309, 95% CI = $300-$319, respectively, for SSRI or SNRI antidepressant pharmacy costs).

### Discussion

The principal objective of this study was to determine if there were differences in discontinuation rates and health care costs between patients who initiated antidepressant therapy on a generic SSRI or SNRI compared with patients who initiated therapy on a brand-name SSRI or SNRI medication. The adjusted comparison suggested there was no significant difference in the likelihood of discontinuation during the first 180 days of therapy, and the analysis of health care costs indicated
that costs were lower among patients starting a generic SSRI/ SNRI compared with patients starting a brand drug, even after adjustment for other factors that may affect those costs.

Recent proposed legislation in at least 1 state (Missouri) has called for a limitation on pharmacy utilization management programs—such as step therapy—which promote the use of generic medications as first-line therapy.²⁵ Although the explicit occurrence of a step-therapy edit at the point of service was not measured in the present study, most of the sample patients could have been prescribed generic antidepressants, even though some patients were prescribed brand-name drugs, as almost all of the SSRIs had generic alternatives during the study period.²⁶ One report estimated that in 2005, 80% of antidepressant pharmacy claims could have been filled with generic drugs; however, the generic dispensing ratio in that year was only 50%.²⁷ The present study provided an approximation of the conditions in which step-therapy programs are commonly applied to promote increased use of generic medications. The findings provide evidence that first-line use of generic SSRIs or SNRIs in the treatment of major depressive disorder is not associated with a greater likelihood of discontinuation and may contribute to lower total health care costs, most likely by lowering the cost of drug therapy. The initiation of antidepressant therapy with a generic SSRI or SNRI could reduce the pharmacy costs for health care payers by almost 50% in some cases, without leading to treatment failure or increased medical costs in the short term. The study findings, therefore, have specific implications for cost management strategies like step therapy, and are important for health care payers who have an investment in patient health.

Limitations

This study has several limitations. First, because of its observational design, the study demonstrates associations but does not establish causality. As in any observational research, the study analyses could control only for measured confounders, not for all factors potentially affecting the study outcomes. In particular, the study may have been confounded by the failure to adequately control for disease severity. Information about previous treatment or duration of disease outside of the 180 days prior to treatment initiation is not included in the MarketScan database, and no tests of mental health disease severity are captured in the database. Medical service utilization and the likelihood of discontinuing therapy may be related to disease severity or the presence of treatment-resistant disease. Adjustments in regression models for factors that may be related to disease severity, such as whether the patient received psychiatric medical care, and stratification by other factors that may be related to disease severity, such as therapeutic augmentation with other non-SSRI/SNRI antidepressants, were used to mitigate the potential impact of disease severity.

Second, drug-specific side-effect profiles were another potential confounder. Side effects are potentially influential in a patient’s decision to discontinue therapy, and may differentially disadvantage some drugs. Adjustment in regression models for the specific SSRI or SNRI medication potentially controlled for the impact of differential side effects on the risk of discontinuation and health care costs.

Third, the study results may be limited in generalizability because MarketScan data are restricted to populations of commercially insured beneficiaries less than 65 years old. It has been previously shown that depression and anxiety disorders

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### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Least Squares Mean All-Cause Health Care Costs</th>
<th>Adjusted Least Squares Mean Disease-Specific Health Care Costs</th>
<th>Adjusted Least Squares Mean All-Cause Pharmacy Costs</th>
<th>Adjusted Least Squares Mean SSRI/SNRI Antidepressant Pharmacy Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand index pharmacy claim</td>
<td>$4,387 ($4,422-$4,757)</td>
<td>$1,125 ($1,077-$1,175)</td>
<td>$965 ($934-$998)</td>
<td>$309 ($300-$319)</td>
</tr>
<tr>
<td>Generic index pharmacy claim</td>
<td>$3,660 ($3,538-$3,787)</td>
<td>$803 ($771-$836)</td>
<td>$761 ($738-$785)</td>
<td>$174 ($169-$180)</td>
</tr>
</tbody>
</table>

*Adjusted for age; gender; Charlson Comorbidity Index score measured in the 180-day baseline and follow-up periods; medical costs incurred in the 180-day baseline period; comorbid anxiety disorder or bipolar disorder in the 180-day baseline and/or follow-up periods; psychiatric medical care in the 180-day baseline period; and specific drug.

*Adjusted for age; gender; Charlson Comorbidity Index score measured in the 180-day baseline and follow-up periods; medical costs incurred in the 180-day baseline period; comorbid anxiety disorder or bipolar disorder diagnosis in the 180-day baseline and/or follow-up periods; psychiatric medical care in the 180-day baseline period; and specific drug.

*Adjusted for age; gender; Charlson Comorbidity Index score measured in the 180-day baseline and follow-up periods; medical costs incurred in the 180-day baseline period; comorbid anxiety disorder or bipolar disorder diagnosis in the 180-day baseline and/or follow-up periods; psychiatric medical care in the 180-day baseline period; and specific drug.

*Adjusted for age; gender; Charlson Comorbidity Index score measured in the 180-day baseline and follow-up periods; medical costs incurred in the 180-day baseline period; comorbid anxiety disorder, bipolar disorder or obsessive-compulsive disorder diagnosis in the 180-day baseline period; and specific drug.

CI = confidence interval; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
commonly affect elderly patients, and that prescription drugs may differentially affect these patients. In addition, patient location or access to a provider of mental health care are not available in the MarketScan data. The population may be restricted to those who have adequate geographic access to a provider of mental health care, and may not be generalizable to patients in all geographic locations.

Fourth, it is also possible that some patients taking a generic drug who appeared to have discontinued therapy actually began using a deeply discounted or low-cost generic program offered at local grocery stores and supermarkets during the study period. This problem potentially overestimated the discontinuation rate among patients who initiated therapy on a generic medication. In addition, patients who were receiving samples of brand medications or patients who had been treated for previous episodes of major depressive disorder prior to the initial pharmacy claim or baseline period may have been new users at the time of their initial pharmacy claim. New users were defined as patients without a pharmacy claim for an SSRI/SNRI in the 180 days prior to the index medication. Both the use of samples of brand medications and recurrences of previously treated depression have the potential to (a) underestimate true discontinuation among patients who had already experienced intolerance or lack of effect and (b) prevent discontinuation among patients who had already found the medication to be tolerable or effective. However, information about brand samples or previous history of SSRI/SNRI use prior to the study period was not available in the administrative claims data used for this study.

Fifth, our definition of therapy discontinuation did not differentiate patients who discontinued medication from patients who switched therapies. As the study objective was to evaluate the impact of the generic or brand status of the initial pharmacy claim only, which would most closely simulate the practice of a cost control program such as step therapy, any switches between SSRIs or SNRIs were intentionally labeled as discontinuations. Patients who switched therapy rather than refilling prescriptions for the index medication may have appeared to be discontinuing therapy entirely. This definition may have included patients who switched between the brand and generic formulations of the same medication. This decision represents a limitation especially for patients who initiated therapy on the branded formulation of sertraline because a generic version was made available in June of 2006 and may have prompted many patients to switch from the brand to generic formulation of sertraline. Although patients may have switched from a brand to a generic, which would presumably be beneficial and cost saving, a patient may have been just as likely to switch from a generic medication to a brand-name formulation, which would minimize any impact of differentially miscategorizing a switch as a discontinuation between the exposure groups.

Finally, we were not able to determine whether a patient was enrolled in a health plan with behavioral health carve-out. Such a benefit design may have affected the use of psychiatric medical care, and information about psychiatric medical care in health plans with a behavioral health carve-out may be incomplete if claims for such care were billed through another benefit. This information was not available in the administrative claims data used in the present study.

### Conclusions

Initiation of therapy on a generic SSRI or SNRI does not appear to be associated with a greater likelihood of therapy discontinuation and may be associated with decreased total health care costs in the first 180 days of therapy. The study’s results do not support the contention sometimes made by critics of pharmacy utilization management tools that generic antidepressants are less effective or safe than brand drugs.

### Authors

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### DISCLOSURES

No external funding supported this research. At the time this study was conducted, all authors were employees of Express Scripts, Inc., a pharmacy benefits management company, and held stock in Express Scripts as part of their employee benefits. Concept and design were performed by Devine and Vlahiotis. Data were collected by Vlahiotis and interpreted by all 4 authors. The manuscript was written and revised by Vlahiotis with the assistance of Devine, Eichholz, and Kautzner.

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### REFERENCES

Discontinuation Rates and Health Care Costs in Adult Patients Starting Generic Versus Brand SSRI or SNRI Antidepressants in Commercial Health Plans


INR Goal Attainment and Oral Anticoagulation Knowledge of Patients Enrolled in an Anticoagulation Clinic in a Veterans Affairs Medical Center

Jennifer W. Baker, PharmD, BCPS; Kristi L. Pierce, PharmD; and Casey A. Ryals, PharmD

ABSTRACT

BACKGROUND: In January 2009, the Joint Commission implemented a National Patient Safety Goal (NPSG) for ambulatory care, NPSG 3E, intended to reduce harm associated with the use of anticoagulation therapy. The 2011 NPSG 3E encompasses 8 elements of performance, including requirements that each organization (a) provide education regarding anticoagulation therapy to staff, patients, and families and (b) evaluate its safety practices and take appropriate action to improve its practices. The Alvin C. York (ACY) outpatient anticoagulation clinic provides education to new patients and their families at the initial clinic visit, with follow-up reinforcement of education as needed throughout their care.

OBJECTIVES: To (a) assess the knowledge level of patients receiving warfarin therapy in an anticoagulation clinic using the validated Anticoagulation Knowledge Assessment (AKA) questionnaire and (b) examine the relationship between patient anticoagulation knowledge and anticoagulation control as measured by the international normalized ratio (INR).

METHODS: All ACY Veterans Affairs (VA) anticoagulation clinic patients seen during their routine visit within an 8-week recruitment period from February 2010 to April 2010 were asked to complete the AKA questionnaire. Upon voluntary consent, the questionnaire was completed by the patient either during the clinic visit or returned later by mail. Demographic and clinical data were manually extracted from the computerized patient record system and included age, gender, indication for and duration of anticoagulation therapy, goal INR range, and the 10 INR values preceding the date of consent. A passing score was defined as at least 21 correct responses on the 29-item AKA questionnaire (72.4% correct). Statistical analyses included comparisons of demographic and clinical characteristics for patients with passing versus failing scores, assessed with Pearson chi-square and Fisher’s exact test, and bivariate analyses of INR control with anticoagulation knowledge, assessed with Spearman’s rho correlation. INR control was defined by 3 outcome measures: number of INRs within therapeutic range, time in therapeutic range (TTR), calculated using the Rosendaal method, and standard deviation (SD) of INR values. Anticoagulation knowledge was assessed with 2 measures: total AKA score and count of correct answers to a subset of 15 AKA items deemed by the investigators to be relevant to INR control.

RESULTS: Of 447 patients enrolled in the anticoagulation clinic, 260 consented to participate in the survey, of whom 185 patients completed the AKA instrument (n = 171 [92.4%] by mail) and were successfully matched to patient record system data. 178 (96.2%) respondents were male with a mean (SD) age of 68 (10.1) years. The majority of patients were undergoing anticoagulation treatment for atrial fibrillation (n = 113, 61.1%) or deep venous/pulmonary thromboembolism (n = 48, 25.9%). The majority of patients had been treated with warfarin for at least 1 year (n = 162, 87.6%). Most patients had goal INR ranges of 2.0 to 3.0 (n = 166, 89.7%). Of the 185 patients who completed the questionnaire, 137 (74.1%) achieved a passing score. The mean (SD) AKA questionnaire score was 78.1% (12.1%).

There were 8 questions that were answered correctly by less than 70% of patients and identified as potential deficiencies in patient education. For the 167 patients who had been on warfarin therapy for at least 6 months and had 10 previous INR values, there was no significant Spearman’s rho correlation between total number of correct questionnaire responses and INR control, defined as the count of the 10 previous INR values within goal range (rho = –0.022, P = 0.776), TTR (rho = 0.015, P = 0.848), and SD (rho = 0.047, P = 0.550). There was also no significant relationship between number of correct INR-relevant responses and INR control by any of the 3 outcome measures (count in range rho = 0.033, P = 0.676; TTR rho = 0.067, P = 0.388; and SD rho = –0.029, P = 0.708).

CONCLUSIONS: Although 74.1% of patients on long-term warfarin therapy achieved a passing score of at least 21 correct answers on the 29-question AKA instrument, there was no significant relationship between patient warfarin knowledge and INR control. Areas for improvement in patient education have been identified and procedures for educational modification are currently in development.

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What is already known about this subject

• Numerous factors complicate the clinical outcomes of warfarin therapy, such as concurrent disease states, drug regimens, diet and alcohol intake, physical illnesses, compliance, and patient knowledge of their responsibilities in therapy.

• In a study of patients aged 80 years or older treated with warfarin, Kagansky et al. (2004) found that insufficient education as perceived by the patient or caregiver was associated with a higher rate of major bleeding events (5.2 per 1,000 patient-months) compared with no education (1.1 per 1,000 patient-months) and education that was patient-rated as sufficient (0.5 per 1,000 patient-months; P < 0.001).

• Tang et al. (2003) found a slightly positive Pearson correlation (r) between knowledge about warfarin and the number of international normalized ratio (INR) values within target range (r = 0.2, P = 0.024), indicating that 4% of variance in INR could be explained by the patient’s warfarin knowledge.

• To date, 2 questionnaires measuring patient knowledge of anticoagulation therapy have been validated: the Oral Anticoagulation Knowledge (OAK) test, created and validated by Zeolla et al. (2006), and the Anticoagulation Knowledge Assessment (AKA) questionnaire, designed and validated by Briggs et al. (2005). No analysis of the relationship between patient knowledge of warfarin therapy and therapeutic goal achievement has used a validated instrument.
anticoagulation with warfarin is a well-established and crucial intervention for the prevention and treatment of thromboembolic events.1,2 Numerous factors can affect the clinical response to anticoagulants, particularly warfarin, such as a patient’s concurrent disease states, drug regimens, diet and alcohol consumption, physical illnesses, compliance, and overall knowledge of therapy.1,4 For this reason, patients require a skillful health care provider in addition to a systematic approach to ensure proper patient follow-up during the initiation and continuation of warfarin therapy.

Reflecting these needs, in 2009 the Joint Commission created a National Patient Safety Goal (NPSG) 03.05.01 (or 3E) for ambulatory care to “reduce the likelihood of patient harm associated with the use of anticoagulation therapy.”5,6 The 2011 NPSG 3E guidelines describe patient education as “a vital component” of a warfarin therapy program, stating that providers should make sure patients understand risks involved with therapy, precautions to take, and the need for close follow-up (Figure 1). Element number 7 of NPSG 3E requires that the organization provide education regarding anticoagulation therapy to staff, patients, and families. Element number 8 requires that “the organization evaluate anticoagulation safety practices, take appropriate action to improve practices, and measure the effectiveness of those actions.”6,7

To date, a few studies have shown an association between the outcomes of anticoagulation therapy and health literacy, patient education, or knowledge of warfarin therapy; however, results are mixed.8-12 In a sample of 122 patients attending a warfarin clinic, Tang et al. (2003) discovered a positive Pearson correlation (r) between patient knowledge about warfarin therapy and the percentage of international normalized ratio (INR) values within therapeutic goal range (r = 0.20, P = 0.024).10 Additionally, in a study of patients aged 80 years or older, Kagansky et al. (2004) found that insufficient education on oral anticoagulation therapy (as perceived by the patient or caregiver) was a significant predictive factor for major bleeding events (5.2 per 1,000 patient-months) compared with no education (1.1 per 1,000 patient-months) and education that was patient-rated as sufficient (0.5 per 1,000 patient-months, P < 0.001). The percentage of INRs within the therapeutic range was highest among patients with perceived satisfactory education (45.1%) compared with those who perceived their education as insufficient (34.9%) or received no education (20.0%, P < 0.001).11

However, not all studies have found a positive correlation between patient knowledge and outcomes of warfarin therapy. Davis et al. (2005) found that adherence to therapy with warfarin was significantly associated with anticoagulation control, defined as the number of blood tests in appropriate therapeutic range divided by the number of blood tests performed during the 60-day period; however, knowledge of warfarin therapy, assessed with an 18-question multiple-choice test, was not associated with anticoagulation control.12 Only 14% of patients in the study by Davis et al. achieved good anticoagulation control, defined as more than 70% of INR values within therapeutic range.12

The major limitation of all of the aforementioned studies, regardless of their results, was the use of a nonvalidated questionnaire or survey to evaluate patient knowledge. Validation indicates that the questionnaire has been thoroughly tested for content validity, measures of question difficulty, readability, and item/person reliability. To date, 2 questionnaires measuring patient knowledge of warfarin therapy have been validated: the Oral Anticoagulation Knowledge (OAK) test, created and validated by Zeolla et al. (2006),13 and the Anticoagulation Knowledge Assessment (AKA) questionnaire, designed and validated by Briggs et al. (2005).14

Evaluation of current patient knowledge is the first step to improving the quality of anticoagulation therapy and patient care. Deficiencies in patient knowledge can be identified and addressed, creating an ongoing system of quality improvement for anticoagulation monitoring and patient safety. The present study assessed the current knowledge level of patients receiving warfarin therapy in the outpatient anticoagulation clinic at the Alvin C. York (ACY) campus of the Veterans Affairs (VA) Tennessee Valley Healthcare System (TVHS). Study investigators conducted this research to determine if corrective actions were needed to improve patient knowledge in accordance with the standards of NPSG 3E element number 8. Additionally, to date no published studies have used a validated instrument to assess the association of patient anticoagulation knowledge with INR control. Therefore, the present study assessed
Study Design and Setting
This was a single-center cross-sectional analysis of all current patients in the VA TVHS ACY anticoagulation clinic. This study was approved by the Institutional Review Board and Research and Development committees within TVHS. The outpatient anticoagulation clinic at the ACY campus of the VA TVHS was established in 2007 and is currently staffed with a doctor of pharmacy and a licensed practical nurse. Since initiation of the ACY anticoagulation clinic, patients and/or their primary caregivers are educated by the clinical pharmacy specialist at their first visit regardless of length of warfarin therapy prior to their initial clinic visit. At the time of this study, there were 447 patients enrolled in the anticoagulation clinic.

Study Sample
All 447 ACY clinic patients seen during their routine visits within an 8-week recruitment period from February 2010 to April 2010 were asked by the clinical pharmacy specialist to complete the AKA questionnaire. Patients were excluded if they refused participation, could not voice understanding after reading the informed consent, or if the study investigators felt in their best clinical judgment that the patient did not understand consent. Patients without at least 10 INR readings from the ACY clinic prior to the consent date and patients who had been enrolled in the clinic less than 6 months were eligible to complete the AKA questionnaire but were not included in the data analysis of the relationship between INR control and warfarin knowledge.

Study Procedures
Once consent was received, the AKA instrument was given to the patient. Patients were instructed to complete the questionnaire independently and without assistance. The patient could either fill out the questionnaire while in the office or take it home and mail it back to the clinic. If the patient requested to complete the survey at home, a postage-paid self-addressed envelope was provided for the return of the completed survey. Surveys were coded sequentially upon order of consent and paired with patient identifiers. This step was performed so that demographic data and the patient’s 10 INR measurements could be extracted manually from the computerized patient record system (CPRS) at a later date. Missing answers in survey responses were scored as incorrect answers. Results of the AKA instrument as completed by the enrolled patients were
Definitions of Study Variables

The primary outcome was the level of knowledge as determined by the score on the AKA questionnaire. The AKA questionnaire is made up of 29 multiple choice questions. Each question was worth 3.45 points. Correctly answering 21 questions (72.4%) or more was needed for determination of adequate knowledge of anticoagulation therapy (passing score). The secondary outcome was INR control, defined using 3 different methods: (a) the count of the 10 most recent INR values within therapeutic goal range (0, 1, 2, 3, etc.), (b) TTR calculated using the Rosendaal Method,15 and (c) anticoagulation stability measured as the SD of INR values. These measures have been used in previous studies of INR control.8,10,16,17 The 10 INR values obtained prior to the date of patient consent were assessed for evaluation of a patient’s recent INR control at the time of assessment of warfarin knowledge using the AKA instrument.

Two different scoring methods for the AKA instrument were used to assess correlation of warfarin knowledge with INR control. The first was the total count of correct answers for the instrument, with a maximum of 29. The second scoring method eliminated questions that were deemed by the investigators to be of limited relevance to INR control, for a total maximum score of 15 (Appendix).

Statistical Analysis

Associations between the independent variables and passing versus failing score, measured as a binomial, were assessed using Fisher’s exact test or Pearson chi-square test for categorical variables. Because the data were not normally distributed, Spearman’s rho correlation analysis was used instead of a Pearson correlation to assess the relationships between each of the 3 measures of INR control and both measures of anticoagulation knowledge. Analyses were performed with an a priori alpha value of 0.05 using SPSS version 17.0 (SPSS Inc., Chicago, IL) and the GraphPad InStat statistical package (GraphPad Software Inc., La Jolla, CA).

Results

Of the 260 anticoagulation clinic patients who consented during the 8-week enrollment period, 186 (71.5%) returned a completed questionnaire (Figure 2). One patient was lost due...
with 178 male patients (96.2%). The majority of patients were 68 (10.1) years for data analysis. Demographic and clinical characteristics of patients included in the correlation analyses are shown in Table 1. Comparing subgroups categorized by passing versus failing AKA score, no statistically significant between-group differences were found.

Spearman’s rho correlation (rho) analyses (Table 4) showed no significant correlations between total number of correct AKA answers and any of the 3 measures of INR control, whether defined as the count of the 10 previous INR values within goal range (rho = –0.022, P = 0.776), TTR (rho = 0.015, P = 0.848), or SD (rho = 0.047, P = 0.550). In sensitivity analyses limited to 15 AKA items deemed by the study investigators to be relevant to INR control (Appendix), there were no significant relationships between number of correct INR-relevant responses and INR control (rho = –0.033, P = 0.676; rho = 0.067, P = 0.388; rho = –0.029, P = 0.708).

### Discussion

Currently 2 anticoagulation knowledge questionnaires have been validated for content validity, construct validity, and reliability. The AKA questionnaire used a review of published literature and anticoagulation clinic protocols, as well as interviews with anticoagulation pharmacists for content validity. AKA investigators created a 29-item instrument covering 9 content areas, including medication, medication administration, medication interactions, activity, diet, side effects, informing health
TABLE 3

Demographics and Clinical Characteristics of Patients (n = 167) in Spearman’s Rho Correlation Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with Passing Scorea</th>
<th>Patients with Failing Scorea</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – mean [SD] in years</td>
<td>68.0 [9.9]</td>
<td>70.6 [10.9]</td>
<td>1.000</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Male</td>
<td>119 (96.0)</td>
<td>42 (97.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Female</td>
<td>5 (4.0)</td>
<td>1 (2.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>INR Goal Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>112 (90.3)</td>
<td>37 (86.0)</td>
<td>0.408</td>
</tr>
<tr>
<td>2.5–3.5</td>
<td>9 (7.3)</td>
<td>5 (11.6)</td>
<td>0.356</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.4)</td>
<td>1 (2.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>79 (63.7)</td>
<td>27 (62.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>31 (25.0)</td>
<td>11 (25.6)</td>
<td>0.843</td>
</tr>
<tr>
<td>Valve replacement</td>
<td>12 (9.7)</td>
<td>5 (11.6)</td>
<td>0.770</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>8 (6.5)</td>
<td>2 (4.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Other</td>
<td>6 (4.8)</td>
<td>1 (2.3)</td>
<td>0.681</td>
</tr>
<tr>
<td>Duration of warfarin therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months to 1 year</td>
<td>9 (7.3)</td>
<td>1 (2.3)</td>
<td>0.456</td>
</tr>
<tr>
<td>1 to 3 years</td>
<td>36 (29.0)</td>
<td>17 (39.5)</td>
<td>0.254</td>
</tr>
<tr>
<td>3 to 5 years</td>
<td>30 (24.2)</td>
<td>6 (14.0)</td>
<td>0.199</td>
</tr>
<tr>
<td>Greater than 5 years</td>
<td>49 (39.5)</td>
<td>19 (44.2)</td>
<td>0.595</td>
</tr>
</tbody>
</table>

aPassing score was defined as at least 21 questions answered correctly or an AKA questionnaire score of 72.4%.
bAssociations between variables were assessed using Fisher’s exact test or Pearson’s chi-square test.

TABLE 4

Spearman’s Rho Correlation Analysis of Anticoagulation Knowledge with INR Control

<table>
<thead>
<tr>
<th></th>
<th>Number in Rangea</th>
<th>Time in Therapeutic Rangea</th>
<th>Standard Deviationa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AKA score</td>
<td>Spearman’s Rho</td>
<td>Spearman’s Rho</td>
<td>Spearman’s Rho</td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>(P)</td>
<td>(P)</td>
</tr>
<tr>
<td>INR-relevant AKA itemsb</td>
<td>0.033 (0.676)</td>
<td>0.067 (0.388)</td>
<td>–0.029 (0.708)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aNumber in range is the count of INR values in therapeutic range, with a maximum of 10, measured prior to the consent date for participation in the study. Standard deviation was calculated for the same 10 INR values. Time in therapeutic range was calculated using the Rosenthal method.15, 16

bCount of correct answers in a subset of AKA items deemed by the investigators to be relevant to INR control (Appendix). AKA = Anticoagulation Knowledge Assessment questionnaire; INR = international normalized ratio.

Evaluation of anticoagulation knowledge has yielded undesirable pass rates in previous literature. Using a novel survey containing 7 open-ended questions, Tang et al. found that only 18% of patients achieved a passing score of at least 70%.18 Davis et al. found that 37% of patients achieved a passing score of at least 70% on a novel 18-question multiple-choice test.12 Using a previously created 20-question true-or-false questionnaire, Hu et al. (2006) found a 39% pass rate, defined as a score of at least 80%.18 In using the AKA questionnaire in the ACY VA TVHS anticoagulation clinic and defining a passing score as at least 72.4% (21 of 29) of questions answered correctly, we found that 74.1% of our patients achieved a passing score. However, patient education methods and study methodology for the previous studies varied among anticoagulation clinics and patient samples, making direct comparison of study results difficult.

Eight questions were answered correctly by less than 70% of patients. Four frequently missed questions covered dietary modifications; 2 addressed medication information; 1 addressed side effects; and 1 addressed informing health care providers. The 4 most frequently missed questions were evaluated for possible causes of patients’ incorrect answers. Question 5 addressed dietary modifications, and 59 (31.9%) patients picked the answer indicating that green leafy vegetables should be avoided completely instead of the choice for dietary consistency from week to week. Question 16 also addressed dietary concerns with 63 (34.1%) patients choosing orange juice instead of nutritional supplement as the agent that can decrease effectiveness of warfarin. This problem could have been due to confusion over discussion in the clinic regarding other juices, such as cranberry and grapefruit, which can increase the anticoagulant effect of warfarin. On question 25, another dietary evaluation, 44 (23.8%) and 73 (39.5%) patients, respectively, answered celery and green beans instead of cole slaw for having the most effect on their warfarin therapy. Finally, the outcomes for question 26 reflected a conflict in the teaching styles of the ACY clinic staff and the investigators who created the AKA questionnaire. The question asked patients what they should do if they had both brand and generic warfarin at home. The correct answer was to take one or the other but not both. However, another answer stated not to take either until speaking with their health care professional. Patients in the ACY clinic are taught to call the clinic with any questions they may have.

care providers, procedures, and lab monitoring. For content validity they used the Marzano’s Taxonomy. For reliability and overall analysis of their instrument, they used the Rasch dichotomous model.14 The AKA questionnaire was employed in our study because of its range of topics important in warfarin education. Patient responses provide objective data about different aspects of practice that are taught in patient education. Thus, the instrument served as a good quality control measure of patient counseling effectiveness.
have or changes in medications/diet. Therefore, both answers could be considered correct.

These frequently missed questions indicate potential areas for improvement in patient education, including reinforcement of dietary guidelines for warfarin therapy as well as when it is appropriate to contact the clinic for questions. Both areas represent potential starting points for re-education of current patients and primary education for new patients seen in the clinic. At this point, re-evaluation of the current educational techniques is indicated for identification of areas where improvements may be made.

There were no statistically significant differences in demographic or clinical characteristics between pass and fail groups, including duration of treatment or indication of therapy, age, or gender. Data from the Spearman's rho analyses revealed no statistically significant correlations between warfarin knowledge and INR control. These results add to the existing literature that has found mixed results when assessing the relationship between patient warfarin knowledge and INR control. Tang et al. did find a small positive correlation between anticoagulation knowledge and the number of INR values within target range, showing that 4% of variance in INR could be explained by anticoagulation knowledge.\(^\text{10}\) However, Davis et al. showed no significant association between knowledge or education and the proportion of INRs within the therapeutic range.\(^\text{12}\) Our study revealed a higher pass rate of 74.1% as compared with pass rates reported previously in the literature, but it is possible that the AKA questionnaire was not sufficiently sensitive in detecting warfarin knowledge that is clinically important in the 3 measures of INR control.

Limitations
First, the collection of survey data from patients was not standardized. Patients could complete the knowledge test in the clinic, take it home and return it by mail, or return it at their next scheduled appointment. Fifteen patients (8.1%) completed the questionnaire at the facility; the other 171 patients (92.4%) completed the questionnaire outside of the facility. Although patients were expected to complete the questionnaire independently regardless of the site of completion, there was no way to prevent patients from eliciting assistance from various resources to help them complete the questionnaire. This problem may have contributed to an inflated pass rate in this study. Second, 66 respondents (35.7%) left at least 1 question unanswered. Of the 66 respondents with incomplete questionnaires, 12 left more than 4 unanswered questions, 3 missed entire pages, and 2 failed to complete the questionnaire. Because unanswered questions were considered incorrect answers, the latter 5 patients received a failing score. This decision may have contributed to cases that were judged as knowledge failures who would have achieved pass scores if all of the questions had been answered. If a similar study is conducted in the future, it would be beneficial for patients to complete the questionnaire in a standardized, monitored environment and have completion of the entire questionnaire verified before submission to prevent these limitations from recurring. Third, of 447 patients treated in the clinic, 260 consented, but not all 187 non-consenting patients refused participation. Some were excluded by the investigators because of inability to voice understanding of the project or because the investigators determined, using their best clinical judgment, that the patient would be unable to understand consent. These exclusion factors are related to mental capacity, a potential confounding factor in this study’s results; however, counts of patients excluded for these reasons were not tracked during sample selection, and we are unable to report them. Fourth, the limited patient population available within the VA anticoagulation clinic setting of this study presents a significant limitation; the study sample consisted of veterans, most of whom are older males.

Conclusions
The present study assessed anticoagulation knowledge of patients receiving warfarin therapy in a VA outpatient anticoagulation clinic using a validated instrument and found a pass rate of 74.1%, much higher than reported previously in the literature. We found no statistically significant relationships between 3 measures of INR control and anticoagulation knowledge. However, this is the first report of the relationship between INR control and anticoagulation knowledge as assessed by the AKA questionnaire, and it is possible that this assessment instrument, although previously validated, was not sufficiently sensitive in detecting clinically important warfarin knowledge. The frequently missed questions indicate potential areas for improvement in patient education. Re-evaluation of the current educational techniques is underway for identification of areas where improvements may be made.

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REFERENCES


1. Which of these medications is recommended if you are taking Coumadin (warfarin) and want relief from a headache?
   a. Advil
   b. Motrin
   c. Aspirin
   d. Tylenol

2. Which of the following food items would interfere with your Coumadin (warfarin) medication?
   a. Bacon
   b. Broccoli
   c. Bananas
   d. Peeled cucumbers

3. While on Coumadin (warfarin) medication, in which of the following would you go directly to the emergency room?
   a. Small bruises
   b. Your appetite dramatically increases
   c. No change which will not stop bleeds
   d. Gums which bleed for a few seconds after brushing teeth

4. You just remembered that you forgot to take your evening Coumadin (warfarin) medication dose last night. You would—
   a. skip the dose of Coumadin (warfarin) you missed
   b. take the missed Coumadin (warfarin) dose right now
   c. wait and take 2 doses of Coumadin (warfarin) this evening
   d. take one-half of the missed dose of Coumadin (warfarin) right now

5. While on Coumadin (warfarin) you—
   a. should not eat spinach
   b. can eat spinach one time a month
   c. can eat as much spinach as you would like whenever you would like
   d. can eat spinach but need to eat the same amount regularly every week

6. While out with friends for dinner, you have just finished your third glass of wine. This amount of alcohol consumed in a single evening will—
   a. cause a decrease in your INR
   b. cause an increase in your INR
   c. not affect you or your Coumadin (warfarin) in any way
   d. make you sick when taking Coumadin (warfarin) medication

7. While in your pharmacy, you notice multivitamins are on sale. After some thought, you decide that you may need a multivitamin. You would—
   a. purchase the multivitamin and begin taking it regularly
   b. not take a multivitamin because it will cause a blood clot while taking Coumadin (warfarin)
   c. start taking it and bring the multivitamin to your next Coumadin Clinic visit to show the pharmacist
   d. purchase the multivitamin but do not start taking it until you talked with the pharmacist at your Coumadin Clinic

8. If you ran out of your prescription for your Coumadin (warfarin) you would—
   a. borrow Coumadin (warfarin) from a friend, as long as it is the same dose as yours
   b. call and ask for refills for that day so you do not miss a dose of Coumadin (warfarin)
   c. wait until your next appointment that is just a few days away to get a new prescription
   d. do nothing because you have taken Coumadin (warfarin) long enough, otherwise there would be more refills on your prescription

9. Which of the following is an effect of Coumadin (warfarin) medication that will most likely be experienced?
   a. Stroke
   b. Leg Clot
   c. Nosebleed which will not stop bleeding
   d. Blood in the urine

10. You have a cold, which includes a runny nose and cough. You—
    a. could safely take Nyquil to help get rid of the runny nose and cough
    b. take your friend’s medication that he/she uses for a bad cold because he/she is also on Coumadin (warfarin) medication
    c. would call the Coumadin Clinic and tell him/her you are on Coumadin (warfarin) medication and ask what you can take for your cold
    d. decide it is safer to suffer through the cold because most cold medications will interact with your Coumadin (warfarin) medication

11. When making a dental appointment while taking Coumadin (warfarin) medication, you need to remember you—
    a. cannot have procedures done on your teeth while taking Coumadin (warfarin)
    b. must tell your dentist you are taking Coumadin (warfarin) well in advance of having any procedure done
    c. can have procedures done and there is not a need to tell the dentist about the Coumadin (warfarin)
    d. can have the dental procedure done if when you arrive at your dental appointment you tell the dentist you are taking Coumadin (warfarin)

12. When the need arises to take an antibiotic (to get rid of an infection) while taking Coumadin (warfarin), you need to—
    a. take half of the prescribed length of therapy, and then call the Coumadin clinic
    b. refuse to take any new medication because you are taking Coumadin (warfarin)
    c. wait until your next Coumadin clinic visit and then tell the pharmacist about the antibiotic
    d. call the Coumadin Clinic right away and let them know you are starting a new medication

13. Coumadin (warfarin) works—
    a. in my liver to make my blood thicker
    b. in my liver to make my blood thinner
    c. in my kidneys to make my blood thicker
    d. in my kidneys to make my blood thinner

14. The best time of day for me to take my Coumadin (warfarin) is—
    a. at lunchtime
    b. in the evening
    c. in the morning before breakfast
    d. any time of day when I remember

15. Which of the following is an effect of my Coumadin (warfarin) medication that I will most likely experience if my INR is too high?
    a. A clot in the leg
    b. Minor bleeding
    c. Clot in the lung
    d. Bleeding in the brain
### APPENDIX

#### Anticoagulation Knowledge Assessment (AKA) Questionnaire

**INR Goal Attainment and Oral Anticoagulation Knowledge of Patients Enrolled in an Anticoagulation Clinic in a Veterans Affairs Medical Center**

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
</table>
| 16. Which of the following drinks can decrease the effectiveness of your Coumadin (warfarin)? | a. Deans 2% low-fat milk  
|                                                                           | b. Hershey’s chocolate shake  
|                                                                           | c. Tropicana orange juice  
|                                                                           | d. Ensure nutritional supplement |
Pharmaceutical Step-Therapy Interventions: A Critical Review of the Literature

Brenda R. Motheral, RPh, MBA, PhD

ABSTRACT

BACKGROUND: Adoption of step therapy (ST) is quickly outpacing the market's understanding of its clinical, humanistic, and economic outcomes. The broad scope of previous reviews of drug management programs has prohibited an in-depth discussion of the ST literature specifically.

OBJECTIVE: To conduct a critical review of ST program evaluations, discuss their policy implications, and provide recommendations for future research.

METHODS: PubMed was searched for relevant English-language articles, and references of relevant articles were examined. The ST policy under evaluation had to require use of a first-line agent prior to coverage of a second-line agent.

RESULTS: Fourteen evaluations of ST programs have been published, 7 in commercial populations and 7 in Medicaid. Twelve of the studies empirically examined claims data; 1 was a model; and 1 was limited to patient surveys. Five therapy classes, including antidepressants, antipsychotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors (PPIs), have been evaluated. The research has consistently found statistically significant drug cost savings with the exception of antipsychotics, where rebates have frequently been excluded. Savings result from greater use of first-line medications and from reduced medication initiation, with the magnitude of noninitiation varying across therapy classes. Three studies have examined medication adherence, producing mixed results. Five studies have empirically examined the effect of ST on hospitalization and emergency room utilization and costs, with none finding statistically significantly higher disease-related utilization or spend, outside of higher outpatient expenditures but not higher outpatient utilization in 1 study.

CONCLUSIONS: The research demonstrates that ST programs for therapy classes other than antipsychotics can provide significant drug savings through the greater use of lower-cost alternatives and, to a lesser extent, reduced drug utilization. The drug savings and clinical impact of ST for antipsychotics are unclear given the research conducted to date, but ST programs for NSAIDs and PPIs can provide significant drug savings without increasing use of other medical services. The research on ST shows gaps in the breadth of evaluation and methodological quality as well as possible study bias. Further research on ST is needed for other therapy classes and for the Medicare Part D population. Recommendations for other areas of research, needed methodological improvements, and reducing the potential for study bias are provided.

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What is already known about this subject

• Nearly 60% of commercial payers reported having 1 or more step-therapy (ST) programs in 2010, making it one of the most popular pharmacy benefit management tools. However, adoption of ST is quickly outpacing understanding of its clinical, humanistic, and economic outcomes.

• Previous reviews of drug cost management tools have reported drug cost savings from ST, highlighted higher discontinuation rates, and identified gaps in the literature related to inclusion of quality of care metrics. Prior critical reviews have focused primarily on the lack of inclusion of a broad range of relevant outcomes rather than on study quality, particularly internal validity.

What this study adds

• The research on ST shows gaps in the breadth of evaluation and methodological quality as well as potential study bias.

• Further research on ST is needed for numerous therapy classes where ST is common and for the Medicare Part D population. Research is also needed to better understand the impact of ST on treatment discontinuities, appropriateness of use, other medical costs, and member/provider satisfaction as well as the effect of alternative designs.

• Needed methodological improvements include (a) use of appropriate comparator groups, (b) examination of disease-related medical spending, (c) adjustment for multiple statistical tests, and (d) better causal linkage between program and outcomes.

• To help reduce the potential for study bias, independently funded evaluations and mandatory study registration prior to initiation should be considered.

With the growing availability of generic and lower-cost brand alternatives, step therapy (ST) has grown rapidly in popularity in commercial, Medicare, and Medicaid settings as a means to create better value from rising pharmaceutical spend. ST requires a member to try 1 of the first-line medications, often a generic alternative, prior to receiving coverage for a second-line agent, usually a branded product. Nearly 60% of commercial payers reported having 1 or more ST programs in 2010, now making it one of the most popular management tools.1 In a 2007 report on Medicare drug benefits, 7 of the top 10 largest Part D plans had 1 or more ST
programs, with the average being 6 programs.\textsuperscript{2} However, adoption of ST is quickly outpacing decision makers’ understanding of the clinical, humanistic, and economic value of these programs. Such knowledge is needed to avoid potential unintended consequences, such as medication noncompliance.\textsuperscript{3,4} Conversely, concerns over unintended consequences can prevent plan sponsors from adopting programs that evidence later shows to be robust, resulting in wasted dollars with no incremental health benefit. While systematic reviews of drug cost management programs have been conducted previously, the broad scope of these reviews has prohibited an in-depth discussion of the ST literature specifically.\textsuperscript{5-7} Accordingly, the purpose of this paper is to conduct a critical review of ST program evaluations and to provide recommendations for future research.

\section*{Methods}

To identify potential studies for inclusion, PubMed was searched for relevant English-language articles using these subject terms: step therapy, prior authorization (PA), drug policy, and pharmaceutical policy. The reference lists of known studies and review articles were examined to find articles as well. To be considered eligible for review, the policy under evaluation had to be implemented in the United States and require use of a first-line agent prior to coverage of a second-line agent, a hallmark characteristic of ST that distinguishes it from traditional PA. However, ST programs typically allow patients to seek coverage for the second-line agent without having used a first-line medication, utilizing a medical exception process; thus, ST and PA programs overlap in their designs. Three studies that examined policy changes across multiple Medicaid programs but did not separate ST from PA programs in the results were excluded from the review.\textsuperscript{8,10}

\section*{Results}

Fourteen evaluations of ST programs have been published to date.\textsuperscript{11-24} Seven of the studies were conducted in commercial populations (Table 1), while 7 assessed Medicaid ST programs (Table 2). An analysis by Panzer et al. (2005)\textsuperscript{12} was an economic model of an antidepressant ST program for patients with anxiety,\textsuperscript{13} and Cox et al. (2004) surveyed members with an ST edit/reject to assess their responses to the edit.\textsuperscript{14} The remaining 12 studies were retrospective, claim-based analyses, 7 of which examined drug expenditures only, and 5 of which examined drug and medical expenditures. Therapy classes examined include antidepressants, antihypertensives, antipsychotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors (PPIs).

Antipsychotic ST in Medicaid has been the most heavily studied subject. Researchers at Harvard published a series of closely related papers examining the effect of ST programs for antipsychotics in Maine.\textsuperscript{18-20} Although the titles of these 3 studies referred to them as PA programs, they actually met the criteria for ST outlined previously.\textsuperscript{18} For patients new to therapy with selected second-generation antipsychotics, prescribers had to provide evidence that a patient had not been adequately controlled by preferred agents. Anticonvulsants were placed on PA. Lu et al. (2010)\textsuperscript{20} found that drug treatment initiation for bipolar illness decreased by 32\% after implementation of the ST and PA programs in Maine, primarily due to a reduction in the use of nonpreferred agents without a corresponding increase in the use of preferred agents. Zhang et al. (2009)\textsuperscript{18} found that the same program resulted in an average $27 reduction per patient in pharmacy reimbursement for bipolar disorder during the 8-month policy period.\textsuperscript{20} However, the hazard rate of treatment discontinuation was 2.28 times as high in the post-policy period than in the pre-policy period, suggesting that the savings resulted from treatment discontinuation rather than switching to lower-cost alternatives. Soumerai et al. (2008)\textsuperscript{18} examined the impact of the same policy on antipsychotic users with a diagnosis of schizophrenia.\textsuperscript{20} Patients initiating atypical antipsychotics during the ST program had a 29\% greater risk of treatment discontinuity (i.e., gap, switch, or augmentation) than patients initiating before the ST program, whereas no change was observed in the comparison group over the same time period. The authors did not observe antipsychotic drug savings but acknowledged that they could not account for increased rebates from pharmaceutical manufacturers. Law et al. (2008)\textsuperscript{20} also examined the effect of an ST program for selected second-generation antipsychotic agents in Texas and West Virginia.\textsuperscript{21} Both states grandfathered prior users and required a trial with a preferred agent before coverage of a nonpreferred agent. Both states observed reductions in the market share of nonpreferred antipsychotics but neither state demonstrated significant savings in pharmacy spend, not factoring in manufacturer rebates.

In contrast, Farley et al. (2008)\textsuperscript{20} found about $7 million in drug cost savings for Georgia Medicaid after implementing ST for atypical antipsychotic medications compared with a state Medicaid program without ST. Georgia Medicaid required patients to try 2 typical antipsychotics before receiving coverage for an atypical antipsychotic. The study by Farley et al. is the only analysis of medical expenditures following an antipsychotic ST program.\textsuperscript{22} The authors did not find increases in disease-related inpatient or long-term care expenditures but did find an increase in disease-related outpatient medical expenditures ($32 per member per month [PMPM]). To further understand the outpatient cost finding, the authors examined disease-related outpatient utilization and found no significant increase in the ST group compared with the non-ST group.\textsuperscript{22}

For other therapy classes, research has found that ST produces drug savings. Three studies have examined antidepressant ST.\textsuperscript{11,14,15} Dunn et al. (2006)\textsuperscript{11} found a 9.0\% lower drug cost per day ($0.36 PMPM) for patients in an antidepressant ST
### TABLE 1 Published Evaluations of Step-Therapy Programs in Commercial Populations

<table>
<thead>
<tr>
<th>Authors/Source/Intervention</th>
<th>Study Groups</th>
<th>Design and Outcomes</th>
<th>Key Findings and Limitations</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
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</tr>
<tr>
<td>Mark et al. (2010)¹¹</td>
<td>Antidepressant users in employer plans, younger than 65 years of age and 3.75 years of continuous eligibility</td>
<td>Pre/Post with comparison group of employers with no ST</td>
<td>• 23.6% greater generic use and ~18% lower brand use by fifth quarter after implementation</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Thomson Reuters</td>
<td></td>
<td>Pre/Post with comparison group of employers with no ST</td>
<td>• No difference in antidepressant days supply or number of prescriptions after 4 quarters</td>
<td></td>
</tr>
<tr>
<td>Generic antidepressant required before coverage of brand (no other details provided)</td>
<td></td>
<td>Primary outcomes: antidepressant prescription use and all-cause medical utilization and spending</td>
<td>• Antidepressant Rx savings not assessed</td>
<td></td>
</tr>
<tr>
<td>Prior users were grandfathered</td>
<td></td>
<td></td>
<td>• Increase in all-cause outpatient office, inpatient, and ER visits and spending</td>
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<td></td>
<td></td>
<td></td>
<td>• No difference in mental health-related utilization</td>
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<td></td>
<td></td>
<td>The key limitations include:</td>
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<td></td>
<td></td>
<td></td>
<td>• Lack of reporting of baseline antidepressant utilization or all-cause spending for the 2 groups</td>
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<td></td>
<td></td>
<td></td>
<td>• Reporting of nonsignificant differences in mental health-related utilization as significant in the abstract</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• No examination of mental health-related expenditures</td>
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<tr>
<td>Dunn et al. (2006)¹²</td>
<td>Antidepressant users in a 440,000-member HMO compared with PBM without ST</td>
<td>Pre/Post with comparison, compared 12 months before and after</td>
<td>• Generic dispensing was 12.6 percentage points greater in year following implementation</td>
<td>No external funding</td>
</tr>
<tr>
<td>Intermountain Healthcare</td>
<td></td>
<td>Pre/Post with comparison, compared 12 months before and after</td>
<td>• No difference in days of therapy between intervention and comparison group</td>
<td></td>
</tr>
<tr>
<td>Generic antidepressant (excluding TCAs) required before coverage of brand; waiver of first generic copayment ($5–$10)</td>
<td></td>
<td>Primary outcomes: antidepressant generic dispensing, utilization, and spending</td>
<td>• Antidepressant drug cost per day was 9.0% lower or $0.36 PMPM for intervention group</td>
<td></td>
</tr>
<tr>
<td>Prior users were grandfathered</td>
<td></td>
<td></td>
<td>The key limitations include:</td>
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<td></td>
<td></td>
<td></td>
<td>• Exclusive focus on drug utilization and savings</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Implementation of a dose-optimization program during the study may have overestimated savings</td>
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<tr>
<td>Panzer et al. (2005)¹³</td>
<td>Commercial health plan members using antidepressants for anxiety</td>
<td>Markov Model Primary outcomes: length of therapy, change in therapy, antidepressant drug cost, and all-cause medical spending</td>
<td>• 4.5% greater frequency of therapy change in ST</td>
<td>Glaxo-SmithKline</td>
</tr>
<tr>
<td>Blue Cross Blue Shield of Delaware</td>
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<td></td>
<td>• 4.5% lower frequency of continuous therapy for at least 6 months</td>
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<tr>
<td>Generic SSRI required before coverage of brand SSRI for patients with anxiety</td>
<td></td>
<td></td>
<td>• Antidepressant drug savings of $0.26 PMPM</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• All-cause medical costs increased $0.32 PMPM</td>
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<td></td>
<td></td>
<td></td>
<td>The key limitations include:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Use of a cross-sectional study of compliance and medical costs as a model input to make causal conclusions about ST</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• No reporting of baseline antidepressant utilization or all-cause spending for the 2 groups</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Lack of reporting of baseline antihypertensive utilization or all-cause spending</td>
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<td></td>
<td></td>
<td></td>
<td>• Reporting of nonsignificant differences in mental health-related expenditures as significant in the abstract</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• No examination of mental health-related expenditures</td>
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<tr>
<td>ARBs/ACE Inhibitors</td>
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<tr>
<td>Mark et al. (2009)¹²</td>
<td>ARB/ACE inhibitor users in employer plans, younger than 65 years of age and 3.75 years of continuous eligibility</td>
<td>Pre/Post with comparison</td>
<td>• No difference in days supply or number of prescriptions after 5 quarters</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Thomson Reuters</td>
<td></td>
<td>Pre/Post with comparison</td>
<td>• Higher discontinuation rate (13% vs. 10% unadjusted)</td>
<td></td>
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<tr>
<td>130-day trial with preferred ACE inhibitor or ARB before coverage of nonpreferred ACE inhibitor or ARB</td>
<td></td>
<td>Primary outcomes: antihypertensive prescription use and all-cause medical utilization and spending</td>
<td>• Higher all-cause inpatient, ER and outpatient visits and spending</td>
<td></td>
</tr>
<tr>
<td>Prior users were grandfathered</td>
<td></td>
<td></td>
<td>• Did not report baseline antihypertensive utilization or all-cause spending for the groups</td>
<td></td>
</tr>
<tr>
<td>Yokoyama et al. (2007)¹³</td>
<td>ARB/ACE inhibitor users in 3 health plans with 15 months continuous eligibility</td>
<td>Pre/Post with comparison</td>
<td>• Attempted ARB initiation was 19.2% for intervention and 26% for comparison group</td>
<td>Novartis</td>
</tr>
<tr>
<td>Wellpoint NexRx</td>
<td></td>
<td>Pre/Post with comparison</td>
<td>• Of those with ARB reject, 45% received ARB, 49% received other Rx, 7% received no medication</td>
<td></td>
</tr>
<tr>
<td>Coverage of ARB if claim for ACE inhibitor, ACE inhibitor/ HCTZ, ARB, or ARB/HCTZ in prior 3 months</td>
<td></td>
<td>Primary outcomes: initiation of drug, edit response, and switching</td>
<td>• 24.0% of patients in the intervention group who applied for an ARB but were given ACE inhibitor monotherapy switched to or added an ARB within 12 months, compared with 6.1% of those started initially on ACE inhibitor</td>
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<tr>
<td>Prior users were grandfathered</td>
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<td></td>
<td>• Savings of 16.9% or $0.03 PMPM</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>The key limitations include:</td>
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<td></td>
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<td></td>
<td>• Questionable comparability of the control group, which may have led to underestimation of the sentinel effect and, correspondingly, drug savings</td>
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<td></td>
<td></td>
<td></td>
<td>• Exclusive focus on drug utilization and savings</td>
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</tbody>
</table>
program versus a comparison group, and Panzer et al.’s model simulated drug savings of $0.26 PMPM for antidepressant ST. Also looking at antidepressants, Mark et al. (2010) reported an initial savings of 1.7% across total prescription drug costs (not just antidepressant spend) but found that the savings diminished over time. The authors did not report expenditures for antidepressant medications.

Two evaluations of antihypertensive ST have been published. Yokoyama et al. (2007) found a 12.8% lower cost per day for patients in an angiotensin II receptor blockers (ARB) ST program versus a comparison group. An accompanying editorial in JMCP questioned whether Yokoyama et al. underestimated the drug savings from the sentinel effect, since the rate of initiation of other angiotensin-converting enzyme (ACE) inhibitor or ARB therapy was 2.4 times higher in the comparison group. Mark et al. (2009) examined total prescription drug expenditures for antihypertensive users (i.e., not just antihypertensive spend) and reported that overall prescription drug spending initially declined 3.1% after program implementation, but the savings did diminish somewhat over time. The authors did not report changes in antihypertensive drug spending.

Motheral et al. (2004) found drug savings of $0.93 PMPM following implementation of an ST program for PPIs, NSAIDs, and selective serotonin reuptake inhibitors (SSRIs). Within the Georgia Medicaid population, Delate et al. (2005) found a $1.70 PMPM, or nearly 50%, decrease in antisecretory expenditures from implementing ST without grandfathering for PPIs. Smalley et al. (1995) found a decrease of 53% in expenditures for NSAIDs after implementation of ST for brand NSAIDs without grandfathering in Tennessee Medicaid. Accordingly, other than studies of antipsychotics within Medicaid populations, the only studies that have not found sustained drug savings from ST are those that examined total prescription drug costs for patients enrolled in ST rather than disease-specific drug costs.

Research shows that drug cost savings result from greater use of first-line medications and also from less medication use as evidenced in the claims data. Using patient self-report, Motheral et al. found that 17% of patients received no medication after the ST edit, and 16% paid full price for the brand medication. Using similar methodology for PPI and NSAID users, Cox et al. found that 11% of patients received no medication, 8% purchased an over-the-counter (OTC) alternative, and 11% received a sample for the brand drug from their physicians. In both studies, the percentage of patients receiving no medication was highest for PPIs. Yokoyama et al. found that 7% of patients did not have an antihypertensive claim in the 12 months following the ST edit. Delate et al. found that 22% of Medicaid patients with an ST edit for a PPI did not have any

<table>
<thead>
<tr>
<th>Authors/Source/Intervention</th>
<th>Study Groups</th>
<th>Design and Outcomes</th>
<th>Key Findings and Limitations</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Therapy Classes</td>
<td></td>
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</tr>
<tr>
<td>Motheral et al. (2004)</td>
<td>1 employer group compared with random sample of users from PBM without ST</td>
<td>Pre/Post with comparison group for claims analysis</td>
<td>• Savings of $0.93 PMPM across the 3 classes</td>
<td>No external funding</td>
</tr>
<tr>
<td>Delate et al. (2005)</td>
<td>1 HMO with ST edit for PPIs or NSAIDs</td>
<td>Descriptive Initial survey sent to those with edits and follow-up survey sent to nonutilizers</td>
<td>• 44% received different drug than prescribed, 13% received PA for brand, 11% received no medication, 11% paid full price for brand, 8% purchased OTC, and 11% had other responses</td>
<td>No external funding</td>
</tr>
<tr>
<td>Smalley et al. (1995)</td>
<td>Members from 1 HMO with ST edit for PPIs or NSAIDs</td>
<td>Response to the edit and reasons for non-utilization</td>
<td>• Patient satisfaction lower for nonusers and those paying full price</td>
<td>No external funding</td>
</tr>
<tr>
<td>Yokoyama et al. (2007)</td>
<td>Prior users were grandfathered</td>
<td>Initial survey sent to those with edits and follow-up survey sent to nonutilizers</td>
<td>• Rate of initiation of either ACE inhibitor or ARB therapy was 2.4 times higher</td>
<td>No external funding</td>
</tr>
<tr>
<td>Mark et al. (2010)</td>
<td>H2-blocker use before coverage of a PPI, 2 trials of generic NSAIDs before coverage of brand NSAID; fluoxetine or fluvoxamine maleate use before coverage of brand SSRI</td>
<td>Primary outcomes: drug savings for PPIs, antidepressants, and NSAIDs, response to the edit, and patient satisfaction</td>
<td>• 29% switched to generic; 23% had a PA for the brand, 16% paid full price for the brand, 17% received no medication, and 15% had other responses</td>
<td>No external funding</td>
</tr>
<tr>
<td>Mark et al. (2009)</td>
<td>H2-blocker use before coverage of a PPI, 2 trials of generic NSAIDs before coverage of COX-2 inhibitor</td>
<td>• 33% response rate to survey with small sample sizes</td>
<td>• Only 1 employer represented in treatment arm</td>
<td>No external funding</td>
</tr>
<tr>
<td>Delate et al. (2005)</td>
<td>Prior users were grandfathered</td>
<td>• No examination of clinical and other economic outcomes</td>
<td>• No examination of clinical and other economic outcomes</td>
<td>No external funding</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; COX = cyclooxygenase; ER = emergency room; H2-blocker = histamine-2-receptor antagonist; HCTZ = hydrochlorothiazide; HMO = health maintenance organization; NSAID = nonsteroidal anti-inflammatory drug; OTC = over-the-counter; PA = prior authorization; PBM = pharmacy benefits management company; PMPM = per member per month; PPI = proton pump inhibitor; Rx = prescription; SSRI = selective serotonin reuptake inhibitor; ST = step therapy; TCA = tricyclic antidepressant.
## TABLE 2
Published Evaluations of Step-Therapy Programs in Medicaid Populations

<table>
<thead>
<tr>
<th>Authors/Source/Intervention</th>
<th>Study Groups</th>
<th>Design and Outcomes</th>
<th>Key Findings</th>
<th>Sponsor</th>
</tr>
</thead>
</table>
| **Antipsychotics (and Anticonvulsants for Selected Studies)**<br>Lu et al. (2010)<sup>20</sup> Harvard Medical School<br>Coverage of nonpreferred drug (olanzapine or aripiprazole) after trial of risperidone and subsequent trial of either ziprasidone or quetiapine used at full dose for 2 weeks<br>Nonpreferred anticonvulsants (lamotrigine, topiramate, gabapentin, brand carbamazepine, brand valproic acid, oxcarbazepine, levetiracetam) required a PA<br>Prior users were grandfathered<br>Harvard Medical School<br>Farley et al. (2008)<sup>21</sup> University of North Carolina<br>Nonresponse to 2 typical antipsychotics before coverage of an atypical antipsychotic<br>Georgia and Mississippi (control)<br>Medicaid members who were not dual-eligible and subset of continuously enrolled schizophrenia patients<br>Pre/Post with comparison state with no ST<br>Primary outcomes: antipsychotic utilization and spend<br>• Decrease in Rx initiation of 32% by 4 months after ST implementation, representing 50 fewer initiations per 10,000 patients per month<br>• Reduction in initiation of nonpreferred agents but no corresponding increase in use of preferred agents<br>• No difference in switching pre- and post-change or between treatment and comparison groups<br>The key limitations include:<br>• No examination of clinical and economic outcomes (due to short policy duration)<br>• Significant overlap with Zhang et al.—unclear why it was published as a second manuscript<br>Robert Wood Johnson<br>Law et al. (2008)<sup>22</sup> Harvard Medical School<br>Same policy intervention as Lu et al. (2010)<br>Maine and New Jersey (comparison)<br>Medicaid members aged 18 years or older and continuously enrolled from 2001 to 2004 with bipolar disorder<br>Pre/Post with comparison state with no ST<br>Primary outcomes: bipolar Rx (antipsychotics and anticonvulsants) initiation and switching<br>• 8 percentage point reduction in use of nonpreferred agents over 8-month policy period<br>• No increase in use of preferred agents<br>• No increase in rates of switching<br>• Hazard ratio of treatment discontinuation was 2.28 times as high after the ST implementation, adjusting for comparison group trends<br>• Drug savings of $27 per patient over 8 months resulted from treatment discontinuations rather than switches to preferred agents for bipolar patients<br>The key limitations include:<br>• Lack of inclusion of rebates in drug savings<br>• No examination of clinical and economic outcomes (due to short policy duration)<br>Robert Wood Johnson and others<br>Soumerai et al. (2008)<sup>23</sup> Harvard Medical School<br>Same policy intervention as Lu et al. (2010)<br>Maine and New Jersey (comparison)<br>Medicaid members aged 18-63 years and continuously enrolled from 2001 to 2004 with schizophrenia<br>Pre/Post with comparison state with no ST<br>Primary outcomes: schizophrenia Rx (antipsychotics) spending and discontinuities<br>• Maine antipsychotic users with schizophrenia had a 29% greater risk of a gap, switch, or augmentation in therapy, in post-change period (more than two-thirds were gaps)<br>• No change in drug use observed, relative to comparison group, without factoring in rebates<br>The key limitations include:<br>• Lack of inclusion of rebates in drug savings<br>• No examination of clinical and economic outcomes (due to short policy duration)<br>AHRQ and others<br>Law et al. (2008)<sup>24</sup> Harvard Medical School<br>14-day trial of preferred agent before coverage of aripiprazole, brand clozapine, fluoxetine-olanzapine, or olanzapine (West Virginia)<br>Trials of preferred agent before coverage of brand clozapine, fluoxetine-olanzapine, or olanzapine (Texas)<br>West Virginia and Texas Medicaid comparison population, and 38 other state Medicaid programs<br>Pre/Post with comparison to states with no ST<br>Primary outcomes: antipsychotic utilization and spend<br>• Market share of nonpreferred antipsychotics decreased 3.5% immediately and 13.9% after 2 years in West Virginia. No statistically significant difference was observed for Texas or the comparison states<br>• Neither state showed a significant decrease in overall antipsychotic drug spend, without including rebates, relative to the comparison groups<br>The key limitations include:<br>• Lack of inclusion of rebates in drug savings<br>• No examination of clinical and economic outcomes<br>Multiple<br>Zhang et al. (2009)<sup>25</sup> Harvard Medical School<br>Same policy intervention as<br>Primary outcomes: schizophrenia Rx (antipsychotics and anticonvulsants) initiation and switching<br>• Drug savings of $27 per patient over 8 months resulted from treatment discontinuations rather than switches to preferred agents for bipolar patients<br>The key limitations include:<br>• No examination of clinical and economic outcomes (due to short policy duration)<br>• Significant overlap with Zhang et al.—unclear why it was published as a second manuscript<br>Robert Wood Johnson<br>Harvard Medical School<br>Same policy intervention as Lu et al. (2010)<br>Primary outcomes: schizophrenia Rx (antipsychotics and anticonvulsants) initiation and switching<br>• Drug savings of $27 per patient over 8 months resulted from treatment discontinuations rather than switches to preferred agents for bipolar patients<br>The key limitations include:<br>• Lack of inclusion of rebates in drug savings<br>• No examination of clinical and economic outcomes (due to short policy duration)<br>Robert Wood Johnson and others<br>Harvard Medical School<br>Same policy intervention as<br>Primary outcomes: schizophrenia Rx (antipsychotics and anticonvulsants) initiation and switching<br>• Drug savings of $27 per patient over 8 months resulted from treatment discontinuations rather than switches to preferred agents for bipolar patients<br>The key limitations include:<br>• Lack of inclusion of rebates in drug savings<br>• No examination of clinical and economic outcomes (due to short policy duration)<br>Robert Wood Johnson and others<br>Harvard Medical School<br>Same policy intervention as<br>Primary outcomes: schizophrenia Rx (antipsychotics and anticonvulsants) initiation and switching<br>• Drug savings of $27 per patient over 8 months resulted from treatment discontinuations rather than switches to preferred agents for bipolar patients<br>The key limitations include:<br>• Lack of inclusion of rebates in drug savings<br>• No examination of clinical and economic outcomes (due to short policy duration)<br>Robert Wood Johnson and others
subsequent antisecretory claim. In both studies, the extent to which the patients received samples/OTCs or paid full price for the second-line brand medication is unknown.

Other than studies of the atypical antipsychotics, only 3 studies have empirically assessed the impact of ST on longer-term medication adherence. Mark et al. found a 3 percentage point higher rate of antihypertensive medication discontinuation in an ST group (13%) versus a comparison group (10%). Among antihypertensive users, days supply of antihypertensives was 7.9% lower for the ST group than the comparison group immediately after ST implementation, but this difference disappeared by 5 quarters after implementation. Interestingly, the same pattern occurred for total number of prescriptions per antihypertensive user. For antidepressants, Mark et al. found 3.9% lower days supply immediately following ST implementation, but by 4 quarters after implementation, the antidepressant days supply was higher in the ST group than in the comparison plans without ST for antidepressants. Dunn et al. also found no significant differences in days supply of antidepressants following implementation of ST.

In terms of switching or augmentation, Yokoyama et al. found that 24.0% of patients in the intervention group who applied for an ARB but were given ACE inhibitor monotherapy switched to or added an ARB within 12 months, a higher switch percentage than was observed for patients initially started on an ACE inhibitor in the comparison group (7.2%). However, for all the intervention group patients who initiated an ACE inhibitor, the 12-month rate of switching or augmentation with an ARB was 6.1%, similar to that of the comparison group.

Other than studies of antipsychotics, 4 studies have empirically examined the effect of ST on inpatient, emergency room (ER), and outpatient measures. Mark et al. reported higher all-cause inpatient, ER, and outpatient expenditures after implementation of an ST program for antidepressants, adjusting for baseline differences in costs and demographics. However, the authors failed to report baseline medical utilization or spending to allow for assessment of the comparability of the 2 groups. Calculation of unadjusted average all-cause medical and pharmacy costs showed an average $1,967 annual cost per patient for ST plans in the year after implementation of ST (2006), 6.9% lower than the average for the comparison plans without ST for antidepressants. The authors also reported nonsignificant increases as meaningful differences for mental health-related utilization. Specifically, mental health-related inpatient admissions had a generalized estimating equation (GEE) coefficient of 0.184 and P value of 0.15, and mental health-related ER visits had a GEE coefficient of 0.185 and P value of 0.13 (Table 4 in the study report), but the abstract reported that “overall and mental health-specific inpatient and ER utilization and costs increased.” As to costs, despite the mention of increased mental health costs in the study abstract, no multivariate model of mental health-related medical expenditures was found in the article, only a model for all-cause expenditures (Table 5 and Figure 1 in the study report). Finally, during the time period of the study by Mark et al., many employers and health plans...
were actively adopting new strategies to improve Health Plan Employer Data and Information Set (HEDIS) scores for depression treatment, including initiation of antidepressant therapy. The authors did not indicate whether the treatment or comparison group had such programs in place during this time period that could have affected the study results.

In a study with similar design for antihypertensive ST, Mark et al. did not find differences in all-cause inpatient or outpatient expenditures but did find higher all-cause inpatient, outpatient, and ER utilization. The authors did not examine either disease-related (cardiovascular) utilization or expenditures in this earlier study.

In Georgia Medicaid, Delate et al. found that enrollees who received a histamine-2 receptor antagonist (H2RA) or no antisecretory drug following an ST edit were no more likely to incur greater gastrointestinal (GI)-related or total medical care expenditures than were enrollees who received a PPI. Nonusers following a PPI PA edit were less likely than patients who received a second-line PPI medication to have any GI diagnosis (48% vs. 81%, respectively, P < 0.001), suggesting at least some channeling of patients to the appropriate alternative. Smalley et al. found no increase in musculoskeletal-related Medicaid expenditures for nondrug services following implementation of an ST program for brand NSAIDs. Neither study had an external control group, but both used within-group comparators to account for underlying market trends.

Panza et al. used a model to simulate medical costs for antidepressant ST for patients with anxiety, with or without depression. The probability that each patient would experience continuous treatment for 180 days or longer, discontinue treatment early, or have a therapy change (defined as either a switch or augmentation) was determined from previous descriptive literature (which the authors could not access for review—one study being published in a magazine not Medline-indexed and the other as an abstract only). Drug use was then assigned to each patient based on a previous study, with patients having less than 180 days of therapy being assigned $5,223 in medical costs, those with 180 days or more being assigned $4,102 in costs, and those with a therapy change being assigned $6,741 in medical costs.

The model simulated a net $0.06 PMPM increase in all-cause total medical costs. The key limitation of this model is the choice of study used for the medical cost assumptions, which was a cross-sectional examination of the association between drug use patterns for antidepressants and medical costs. Results from such cross-sectional studies cannot be translated into causal conclusions about interventions due to the presence of the healthy adherer effect, the tendency of people who are adherent to their medications to also engage in other healthy behaviors, such as exercising regularly and eating a healthy diet. The presence of the healthy adherer effect leads to cross-sectional studies showing that higher rates of medication adherence are associated with better outcomes and lower health care costs with effect sizes far beyond what evidence from randomized controlled trials (RCTs) would suggest. Thus, the attempt to make causal inferences about ST from a cross-sectional study of compliance and medical costs is a fatal flaw and prohibits making any conclusions from the model by Panza et al.

Finally, the number of studies of humanistic outcomes, such as patient satisfaction, is also quite limited. Across PPIs, SSRIs, and NSAIDs, Motheral et al. found that compared with receipt of a generic, paying out of pocket for the brand drug (odds ratio of 0.25; P < 0.05) and receiving no medication (odds ratio of 0.12; P < 0.01) were associated with significantly lower satisfaction with the pharmacy benefit. Cox et al. did not find a statistically significant relationship between outcome of the ST edit and pharmacy benefit satisfaction but did find that patients who received a covered medication other than the brand were less satisfied with medication than those who received the brand drug (P < 0.001).

Discussion

The research demonstrates that ST programs for therapy classes other than antipsychotics can provide significant drug savings through the greater use of lower-cost alternatives and to a lesser extent, reduced drug utilization. As expected, programs that do not grandfather have shown the largest savings, but elimination of grandfathering will not be appropriate for all therapy classes and will risk increased member and provider dissatisfaction. While substitution with lower-cost alternatives is the primary objective of an ST program, reduced drug utilization is not an intended goal, the exception being those therapy classes where appropriate OTC substitutes are available. Depending on the therapy class, research has found that between 7% and 22% of patients have no prescription claim submitted to their insurance provider following an ST edit. Some nonutilization in the prescription claims actually reflects OTC purchases or other responses that may be clinically appropriate. However, survey research has shown that a small percentage of nonutilization remains even after accounting for these other behaviors, at least for the therapy classes studied to date, including NSAIDs, PPIs, and antidepressants. In the first 2 classes, nonutilization may have little if any clinical impact on the patient given the less severe indications for which these drugs are sometimes used, and the extent of true nonutilization has not been examined for therapy classes, the exception being antipsychotics, where the potential clinical impact may be more significant.

At least 1 pharmacy benefit management company (PBM) has developed a program to reduce the likelihood of nonuse after ST intervention. This program identifies patients who have not filled a prescription claim within 2 days following their ST edit and then notifies the patient and provider...
about the ST program, explaining medication alternatives and the steps for obtaining a PA. Based on unpublished RCTs, the addition of a follow-up letter has improved medication initiation rates, increased use of generics, and reduced PAs for brand medications. Notably, the Centers for Medicare and Medicaid Services (CMS) requires a similar notice to be mailed within 3 business days to each Medicare Part D beneficiary who receives a 1-time transition fill for a drug subject to ST, PA, or nonformulary edits. Greater adoption of this type of tool, for patients with and without transition fills, would likely help to improve appropriate utilization associated with ST programs and increase member satisfaction.

For antipsychotics, the inconsistent findings for drug savings across studies likely reflects the different program designs and the lack of accounting for rebates where relevant. Georgia Medicaid found significant savings for a program that required use of 2 typical antipsychotics, which are available in generics and are far less expensive than atypicals. The other studies all had 1 or more atypical antipsychotic on the preferred drug list, reducing the potential savings, particularly when savings from rebates are not included. In addition, unlike other antipsychotic programs evaluated, Georgia Medicaid did not grandfather prior users, which also would have contributed to the greater observed savings. Antipsychotic ST in Medicaid enrollees with bipolar disorder or schizophrenia has been associated with reductions in treatment initiation and continuation, unintended consequences that may have contributed to the withdrawal of these policies in Maine and Georgia. In these studies, risperidone was the preferred atypical antipsychotic, except for Georgia which had no atypical on the preferred list. Each atypical medication's efficacy and side effect profile may or may not make it a good choice for initial therapy in any one patient, perhaps contributing to the reduced initiation observed in Maine. However, the extent to which the observed treatment discontinuities result in increased use of other medical services is unclear, since Farley et al. found no increase in inpatient expenditures, ER expenditures, or outpatient utilization for an ST program that considered typicals as first-line and appeared not to grandfather prior users. Furthermore, in the Vermont Medicaid program, rescission of a PA exemption for new users of antipsychotics, antidepressants, and anxiolytics/sedatives was not followed by decreased utilization of medications on the PA list, and mental health-related hospitalizations declined following removal of the PA exemption. As none of the studies that found increased treatment discontinuities examined other medical utilization or clinical outcomes, it is unclear whether the potentially inconsistent findings are due to differences in program design or a lack of short-term link between decreased medication use and use of other medical services. If the latter, are the observed treatment discontinuities leading to negative effects on important clinical outcomes that do not necessarily manifest in claims-based measures of utilization?

Given the conflicting findings to date, future research should assess whether ST for antipsychotics creates unintended adverse clinical consequences by increasing therapy discontinuities early in treatment, examining variations across specific disease populations and program designs. No direct implications can be drawn from this research for the use of ST to address the broader use of antipsychotics in the commercially insured population given that rates of off-label use are high, and commercially insured patients may be less vulnerable to the administration requirements of ST. As part of its comparative effectiveness research program, the Agency for Healthcare Research and Quality (AHRQ) concluded in 2007 that there was “insufficient high-grade evidence to reach conclusions about the efficacy of atypical antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) for off-label uses such as behavioral problems in dementia, depression, obsessive-compulsive disorder, postraumatic stress disorder, and personality disorders.

For PPIs and NSAIDs, the research indicates that ST, even without grandfathering, can reduce drug expenditures without increasing use of other related medical services, making these therapy classes low-hanging fruit for increased management for plan sponsors who have yet to implement ST. Beyond these limited comments, no other definitive conclusions can be made about ST programs related to quality of care, humanistic outcomes, or medical expenditure offsets due to the lack of data on key outcomes and the critical limitations of some of the published work. Recommendations for future research fall into 3 areas: (a) research topics, (b) methodological considerations, and (c) publication bias.

**Research Topics**

ST research published to date has examined only a small portion of the therapy classes, outcome domains, and populations that warrant evaluation (Table 3). Specifically, there is a need for further research on ST programs in each of the following areas:

**Evaluation of ST programs in other populations and therapy classes**, such as antihyperlipidemics, antiasthmatics, antidiabetics, and multiple specialty therapy classes. ST programs now exist for dozens of therapy classes with adoption continuing to grow. For example, in 2010, nearly 40% of employers had implemented ST for antihyperlipidemics, yet no evaluations of this therapy class have been published. Research in the Medicare population is also needed as price sensitivity and indications for use can vary.

**Improved understanding of the prescription drug savings from step therapy**, including an examination of the net savings of ST after program fees and rebates (when applicable), an understanding of how the savings change over time as
Physicians become familiar with the program (i.e., sentinel effect), and the extent to which savings are driven by greater use of generics versus OTC use or nonutilization.

**Evaluations of the effect of step therapy on treatment discontinuities**, including medication switching and adherence in clinically relevant therapy categories. To date, treatment discontinuities have been examined in a minority of studies, producing mixed results. Are patients who switch to the first-line agent more likely to prematurely discontinue therapy or to switch to an alternative medication? If so, are these discontinuities driven by real or perceived differences in effectiveness? Alternatively, do lower copayments for generic drugs lead to higher medication adherence in ST?

**Examination of the effect of step-therapy programs on the appropriateness of use.** The extent to which patients are being channeled to the appropriate alternative has received little attention outside of the work of Delate et al.\(^{23}\) For statins, are patients at higher risk for cardiovascular events more likely to receive a PA for a higher dose brand medication and less likely to not initiate therapy? The definition of appropriate use will vary by therapy class and could include comparisons of use by indication, severity, and/or based on clinical guidelines.

**Evaluations of the effect of step-therapy programs on clinical outcomes and use of other medical services**, including hospitalizations and ER visits. The current research on other medical utilization is limited in quantity and plagued by questionable methodology. This research should also include relevant safety-related hospitalizations, since research in Canada found that more restrictive ST for cyclooxygenase (COX)-2 inhibitors was associated with a lower rate of hospital admission due to GI bleed.\(^{36}\) While ST evaluations have often been conducted by PBMs that may lack medical data, health plans routinely have access to the medical data. In the future, examination of clinical outcomes beyond those obtained by claims...
data will be important as research expands into conditions where claims-based measures may not exist and/or lack the sensitivity to detect clinically meaningful changes in selected conditions, such as rheumatoid arthritis.

Insights into patients’ and physicians’ understanding and satisfaction with step therapy. Early research found that commercially insured patients perceived ST edits to be the same as PAs and were not aware that lower cost therapeutic alternatives existed, leading to unnecessarily high rates of PA and nonutilization.29 Such misperceptions may be even greater among Medicaid and Medicare populations, which only serves to reduce program performance and increase dissatisfaction among beneficiaries. Given that concerns over member disruption and dissatisfaction are perhaps the biggest barriers to adoption of ST programs and that research is very limited, this is a valuable area for further research.

Examination of alternative step-therapy designs. ST programs can vary in terms of their extent of coverage and approval process. Two coverage variations that warrant evaluation are (a) programs that do not grandfather prior users of the second-line alternative, a feature that may grow for selected therapy classes where clinically questionable use is rampant, and (b) programs that cover OTC alternatives when available. Such design variations have the potential to significantly affect not only drug savings, as research in Medicaid has already shown, but also treatment discontinuities, patient satisfaction, and administrative burden for patients and providers. As Curtiss previously highlighted, the restrictiveness of the PA process can also vary based on the PA exception criteria and the approval process (e.g., phone versus fax), and more research is needed to understand how these variations affect program outcomes.29 Even the most common criterion, prior use of a first-line agent, may not always be automated in the claims data,30 but evaluations of nonautomated interventions have been limited to Medicaid populations.

In addition, at least 1 PBM has reported use of “smart edits” for ST that link to the patient’s medical history to check for diagnoses in PA criteria.38 This process allows for automatic coverage of second-line medications for patients with clinical indications that meet the PA criteria, such as automated coverage of a statin for patients with evidence of a previous myocardial infarction in the claims data,39 or automated coverage of an antipsychotic for patients with a previous diagnosis of schizophrenia or bipolar disorder. An understanding of the incremental cost, savings, and quality of care from an integrated program is an important area of inquiry. Lastly, as physician adoption of e-prescribing and electronic medical records (EMRs) grows—allowing for instant awareness of and response to an ST edit—evaluations of real-time ST will be needed. To date, research has found that health information technology, such as EMRs, does not always live up to the high expectations placed on it, creating additional administrative burden and having questionable impact on quality of care.40,41 Whether physicians will view these automated tools and edits for ST as a timely and efficient addition to their practices to support provision of high quality and cost-effective care or, alternatively, distort the system by learning and reporting the clinical criteria that produce an approval is an open question.

Methodological Improvements
The suggestions for methodological improvements are not unique to ST evaluations nor do they represent an exhaustive list of good research practices. Rather, the recommendations highlight important areas for improvement based on the ST evaluations published to date.

Inclusion of appropriate comparator groups. Given that the effect of an ST program on drug costs or medical expenditure is likely to be small as a percentage of total expenditure (i.e., small effect size), it is critical to use comparison groups that are similar at baseline on the key outcomes, key drivers of utilization and expense (e.g., age), and benefit design (e.g., copayment amounts). In both studies by Mark et al., baseline comparisons on key variables, such as drug spending and disease-related medical expenditures, were not reported.11,12 Although the authors controlled for baseline measures in the statistical analyses, statistical controls are not always sufficient as noted by Fairman and Curtiss (2008), and baseline differences in known measures may signal differences in unknown factors.42

Examination of disease-related drug and medical spend. Mark et al.’s (2009, 2010) use of all-cause drug or medical spend as an outcome measure is a concerning methodological approach because examination of all-cause expenditures creates greater risk for spurious findings and confounding due to other variables. This concern is magnified by the lack of reporting of relevant baseline utilization and spending. It is critical to examine disease-related medical spending when assessing medical expenditure offsets to establish a logical causal pathway between ST implementation and medical outcomes.53 While sensitivity analysis can examine all-cause medical spend because of uncertainties in diagnostic coding, the primary endpoint should be disease-related drug and medical spending.

Adjustment for multiple statistical tests. ST evaluations have historically conducted dozens of statistical comparisons, increasing the risk of a significant finding merely due to chance. This problem is compounded by the large sample sizes, which can make the most trivial of differences statistically significant. Accordingly, it is appropriate to adjust for the multiple statistical tests by modifying the alpha required for statistical significance,44,45 which generally has not been done in published ST evaluations.

Better causal linkage between program and outcomes. In
the few studies that examined medical spending, the research has been challenged by the lack of linkage between medical expenditures and medication use patterns. One would hypothesize that other medical expenditures would increase the most among noncompliers and, in particular, noncompliers with a diagnosis indicating greater severity or need (e.g., users of antidepressants for major depression versus nonspecific pain), yet prior research has not been conducted at that level of specificity. Given the quasi-experimental and sometimes observational nature of these evaluations and the multitude of potential confounders, such specificity is necessary to establish the causal linkage between the program and outcomes observed.

Study Bias
Study bias can take many forms, including publication bias (i.e., selective publication of research findings, depending on the nature and direction of the results), multiple publication bias, or outcomes reporting bias.66 Outcomes reporting bias occurs when outcomes are selectively reported, when negative results are reported in a positive manner, and when conclusions are not supported by the results.

Examples of outcome reporting bias are widespread in health care. One study of RCTs found that primary outcomes data had been newly introduced, omitted, or changed in more than 60% of comparisons between publications and study protocols.47 As ST evaluations do not require registration, inferences must be drawn from examination of the published studies. In the case of the 2 pharmaceutical industry-sponsored studies by Mark et al., it is unclear why the authors chose all-cause medical utilization and expenditures as the exclusive endpoints in one study and the primary endpoints in another.11,12 The inclusion of total prescription drug spending rather than disease-related drug spending as the primary measure of program savings is equally puzzling, since there is no compelling explanation for why ST would affect drug expenditures that are unrelated to the disease.

Another potential indication of outcome reporting bias is that in their analysis of an ST for antidepressant drugs, Mark et al. reported that mental health-related inpatient admissions and ER visits were higher in the ST group relative to the comparison group following implementation, but they failed to mention that these results were not statistically significant.11 In fact, the results did not even approach statistical significance despite the large sample size. Against this backdrop, 2 recommendations are provided to reduce the potential for bias in ST evaluations.

Independently funded evaluations. While studies of Medicaid populations have received significant public funding, commercial program studies examining medical spending have been funded exclusively by pharmaceutical manufacturers. Bias in studies funded by pharmaceutical manufacturers has been reported for clinical trial efficacy and cost-effectiveness assessments and has been suggested for studies of prescription cost-sharing.48–50 While pharmaceutical funding does not necessarily indicate bias, it is important to conduct independently funded assessments of commercial ST programs. Of course, the potential for bias is not limited to pharmaceutical manufacturers. PBMs and health plans could be biased to demonstrate that these programs save money without affecting quality of care. However, no research has formally assessed the presence of bias among these health care stakeholders.

Study registration prior to initiation and mandatory publication. Registration of study protocols prior to study initiation and mandatory publication of full study results after study completion can help mitigate the potential for reporting bias. This idea was discussed for decades with regard to clinical trials, and in 2005, the International Committee of Medical Journal Editors implemented a requirement for clinical trial registration before patient enrollment. While the policy was criticized as burdensome and stifling of competition, the number of registered trials at ClinicalTrials.gov, the largest trial registry at that time, grew from 13,153 before the policy to include 67,000 trials as of January 2009.51 Currently, observational studies, such as ST evaluations, do not require registration. While this approach is not without its challenges, mandatory study registration is beginning to receive serious consideration for the broader set of observational research.52

Limitations
First, this study was limited to ST evaluations published in the United States. Second, while every attempt was made to identify ST evaluations even if they were identified as PA programs in the title, relevant research could have been missed. Similarly, ST and PA are not entirely distinct benefit tools, and while this study made every attempt to include only those programs that were primarily designed as ST, programs could have been misclassified. Third, the study did not use formal or quantitative approaches to assess publication bias; rather, conclusions reflect inferences made by the study author.

Conclusions
The popularity of step therapy among commercial, Medicaid, and Medicare plans is no doubt due to the wide availability of generic alternatives that offer significant savings, the strong clinical evidence that typically underlies these programs, and their ability to affect only new users, thereby minimizing member disruption. However, evaluations of ST programs have not kept pace with their growing use in the public and private sectors. An expanded research agenda is needed to better understand the economic, clinical, and humanistic outcomes of ST programs. In parallel, improved methodological approaches and greater use of established strategies for reducing study bias are warranted.
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29. Comments based on the author’s experience in conducting a randomized controlled evaluation of the program that has not been published.


What Do We Really Know About VBID? Quality of the Evidence and Ethical Considerations for Health Plan Sponsors

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As health care proposals are debated and specific reforms are implemented, there will be a vital need for solid, credible, actionable information about the impact of current policies. To meet the needs of health care reform, research will need to be significantly more responsive to demands for findings that are timely and actionable.

In March 2009, the Agency for Healthcare Research and Quality (AHRQ) convened a meeting of “policymakers, researchers, and producers of health care data” to “begin developing a strategy to optimize the availability of information and data for enactment and implementation of health care reform.” The needs described by participants were as expected: timely information about “the likely concrete effects of unique, specific policy proposals,” provided with an eye to “the specific levers available to policymakers,” developed with a “clear and transparent” methodology, and assessing “the impact on the public sector and consumer.” It is telling that the need for “solid data” was emphasized by “veterans of past health care reform efforts,” who also observed that current data needs “are much broader.”

Data Promulgated Versus Data Used: Is There a Credibility Gap?
The AHRQ’s envisioned role for accurate and transparent data in developing and monitoring a redesigned health care system represents an optimal scenario—if health care research “builds it,” policymakers “will come.” Yet, the ways in which health plan sponsors actually obtain and use information in making benefit design decisions may not match this expectation. A Diamond Management/Willis North America survey of large and small employers in a variety of industry sectors, conducted after passage of the Patient Protection and Affordable Care Act (PPACA) using an unreported sampling methodology, found that a slight majority (736 of 1,400, 52.6%) of respondents cited “in-house personnel” as their primary source of information about “the health care reform statute or regulations.” Insurance brokers and carriers were cited as a primary information source by 25.1% and 6.6%, respectively. Only 5.2% said that their primary information source was “free resources and tools as published by government agencies.”

Slow Uptake of VBID: Information Gap or Sensible Decision Making by Plan Sponsors?
The Rx Outcomes Adviser, a recently launched blog intended to provide health plan sponsors with actionable and evidence-based information about pharmacy benefits, highlighted in an early posting the costs and benefits of value-based insurance design (VBID), the lowering or waiving of copayments for “high-value” medications in an effort to increase their use. Because the blog’s purpose is to help decision makers navigate the challenge of reviewing and applying health outcomes research to make well-informed policy decisions, a focus on the cost-effectiveness of VBID is particularly appropriate.
Section 2713(a) of the PPACA calls for the creation of guidelines to “permit a group health plan and a health insurance issuer offering group or individual health insurance coverage to utilize [VBID],” suggesting that whether to adopt a VBID for the drug benefit may become an increasingly important question for payers.

Yet, despite being launched more than 9 years ago as “a concept that stands on science and equity” and sustained by financial support from the pharmaceutical industry and enthusiastic popular press coverage, VBID (initially termed “benefit-based copay”) has not caught on among the majority of health plan sponsors. Recent VBID use rates are estimated at approximately 20%, and plan deductibles over the past few years have generally trended higher, not lower. For example, when 507 employers with at least 1,000 employees were asked in the 2010 National Business Group on Health/Towers Watson (NBGH/TW) survey to indicate benefit design strategies that they had used during 2010, reductions in “pharmacy copays or coinsurance for those with chronic conditions” were cited by 19% of employers. Of 37 strategies mentioned in the 2010 survey, only 2 were used less often than copayment reductions: increasing the use of selective provider networks and providing incentives to use personal health records. In contrast, 23% of employers reported having “significantly increased” pharmacy copays, deductibles or coinsurance in 2010; 54% reported offering a consumer-directed (high-deductible) health plan (CDHP); and the percentage of CDHPs covering “preventive prescription drugs” at 100% (i.e., no patient cost-sharing) was just 20%. When asked about their plans for 2011, 28% of employers reported planning to significantly increase pharmacy cost-sharing requirements, and total estimated CDHP availability was expected to grow to 61%. Although reluctance to expend funds on health care in a declining economy was no doubt partly responsible for these trends, it is notable that employers were willing to make investments in other areas. For example, the percentages offering programs for lifestyle behavioral change, health coaching, and smoking cessation were 50%, 56%, and 76%, respectively.

Another indication of lukewarm interest in VBID is the less-than-enthusiastic treatment it receives from most large pharmacy benefits management (PBM) companies. This phenomenon is curious and worthy of attention because PBMs can be exceptionally customer-focused and would presumably embrace customer demands that are popular in the marketplace, since they typically do not bear financial risk (e.g., capitation) for the cost of pharmacy benefits. Yet, instead of pharmacy copayment reduction intended to improve medication adherence, PBMs focus more attention on alternative strategies that include dispensing medication in 90-day supplies, increasing direct contact between pharmacists and patients, providing targeted refill reminders to nonadherent patients, and implementing or enhancing clinical disease management programs (DMPs). The annual drug trend reports (DTRs) of PBMs, which reflect their marketplace strategies and benefit design recommendations, suggest a recognition that nonadherence is a multifaceted phenomenon encompassing negative perceptions about medications and side effects, patient characteristics (e.g., low literacy, forgetfulness), and therapeutic complexity requiring pharmacist intervention.

However, the topic of VBID has not been avoided altogether by PBMs. A few PBMs have reported observational investigations of the association between out-of-pocket cost and medication use or between medication adherence and all-cause health care costs. In a balanced approach to VBID, a health plan-owned PBM advises against zero-dollar copayments because “even as little as $5 per prescription gives the benefit more perceived value to members;” suggests that plan sponsors “carefully consider whether value-based pharmacy benefits are a good fit” for members with adherence of less than 80% for medications to treat diabetes, high blood pressure, or dyslipidemia; and recommends that to improve cost-effectiveness, sponsors consider copayment reductions for generic drugs only. These observations, and the advice of most PBMs to use a variety of tools and messaging strategies to improve adherence, are consistent with behavioral economics research suggesting that consumer purchasing behavior is neither entirely rational nor based solely on price.

Peer-reviewed evidence about the reasons for payers’ reluctance to adopt copayment reduction strategies is currently unavailable. However, popular press and industry reports suggest that major factors in the slow uptake for VBID include (a) the “potential for short-term increase in utilization and cost” with “uncertain” health benefits, (b) the possibility of “unintended incentives” that could reduce generic drug utilization if brand drug copayments are reduced too much, and (c) synergies between business interests and the use of alternative adherence promotion strategies.

**Payer Perspectives on High Cost and Uncertain Evidence for VBID**

A PBM medical officer interviewed for an October 2009 report on novel business models in the PBM industry cited a focus on improving medication adherence as an important market niche. Although noting that medication nonadherence represents a “tremendous opportunity...to lower medical costs, like [emergency room] visits for asthmatics,” the PBM executive argued against using copayment waivers to promote adherence, largely because of the high cost of VBID relative to other strategies that the PBM advocates as more effective: “Benefit designs that eliminate copays increase compliance by 1 to 5 percent, but a company takes on a huge additional expense by absorbing the copay. We found that moving patients to [mail order pharmacy] is the single most important thing you can
do to improve adherence.”23 The DTR of a health plan-owned PBM similarly acknowledges that “quantifying the [return-on-investment] for [VBID] is challenging” because “medical costs avoided, improved quality of life, reduced absenteeism and other positive outcomes are often cited but can be lost when incentives are applied too broadly.”28

Popular press interviews with benefit design consultants reported in May 2009 also suggested that cost relative to uncertain benefit is an important consideration for employers in making decisions about VBID, with one consultant noting that because of the economic downturn “it’s a little bit harder to get approval for reducing copays, especially when results are a little bit squishy” and another suggesting that growth in the copayment waiver trend is limited because “there’s not a ton of data” about the effects of VBID on overall medical cost.21 Nonetheless, a November 2010 press report on adopters of VBID suggested that the estimated 18% of employers with a chronic medication copayment waiver or reduction in place as of 2009 “are convinced this [approach] works, despite an absence of rigorous research to back them up.”20

Still, lack of reliable evidence about VBID may not be the only reason for tepid response to it by most PBMs. First, PBMs that own mail order pharmacies have an interest in using copayment incentives to encourage use of mail order by refill customers and might be expected for business reasons to recommend 90-day supplies, although some PBMs recommend 90-day dispensing for community pharmacies as well as mail order.28 Second, PBMs may be reluctant to recommend copayment reductions for brand medications for reasons that include client preference and higher profit margins on generic than brand drugs because of “spread” pricing.23

Notably, however, research evidence suggests that both of these PBM business interests are congruent with the needs of health care consumers. That is, consistent with PBM recommendations, mail order use is cost-effective for plan sponsors34 and positively associated with adherence to chronic medication therapy.35,36 although randomized trials of the effects of mail order pharmacy use on patient outcomes are clearly needed.37 Also supporting PBM recommendations are the findings of AHRQ-funded comparative effectiveness analyses suggesting that generic medications for high-prevalence chronic conditions, such as hypertension and diabetes,38,39 on average provide equivalent therapeutic effect at equivalent or better safety—a remarkable bargain for patients considering that 90-day supplies of generic drugs to treat high-prevalence chronic conditions are commonly available for $10-$12 in large community pharmacies.40

Proposal to Offset VBID Costs: Higher Cost Sharing for “Low-Value” Services

VBID proponents rightly point out that the net total cost of a VBID program consisting only of copayment reductions “critically depends on whether the incremental spending on the targeted services, such as hypertension medication, can be offset through a decrease in adverse events, such as hospitalizations.”41 In other words, does a health plan sponsor that pays for both medical and pharmacy benefits and incurs higher pharmacy benefit costs because of reducing or waiving copayments for medications to treat high-prevalence chronic conditions (e.g., diabetes, hypertension, dyslipidemia) reap the benefit of healthier enrollees who incur fewer catastrophic medical events (e.g., myocardial infarctions [MIs], strokes) as a result of increased medication use? More importantly, do health plan members—who ultimately pay a portion of the cost of health policy decisions in their share of health plan premiums—experience increased, decreased, or unchanged health benefits when the health plan sponsor implements VBID copayment reduction?

A transparent “plausibility calculator” analysis, designed and reported by Melnick and Motheral in the March 2010 issue of JMCP, suggests that “health plan sponsors are highly unlikely to experience net savings by implementing VBID programs, even under generous assumptions, for 2 reasons.”42 First, price elasticity for medications is generally low in commercially insured groups, meaning that most copayment reductions go to patients who would have been equally compliant without the copayment savings. Second, in a population of commercially insured enrollees “with varying risk levels,” the baseline risk of avoidable expensive medical events (e.g., emergency room [ER] visits and hospitalizations) is low, meaning that it is mathematically nearly impossible for increased medication compliance to prevent a sufficient number of expensive events to offset the costs of copayment reductions.42

Advocates of VBID have argued based on “break-even” economic modeling that VBID “can be effective”43 but acknowledge that “direct medical savings from increased use of services with strong evidence of clinical benefit are unlikely to finance the entire [VBID] investment in the short term.”44 Thus, these VBID proponents support “investments in processes to define low-value care” and a benefit design that “couples cost-sharing reductions for high-value services with cost-sharing increases for services not identified as high value.”44 This suggestion has led to an important emerging issue for employers considering VBID adoption—provider and patient acceptance of higher levels of cost-sharing for services deemed “low-value.”19,41,44

The Payer’s Dilemma: Value to Whom?

Methods for defining a “low-value” service are in their nascent and are far from straightforward. Fendrick et al. (2010) have suggested that services should be defined as “low-value” if they “result in harm—for example, services with D designation that are discouraged by the [U.S.] Preventive Services Task Force” (USPSTF)—or, more broadly, if their cost is “deemed too expensive for the health benefits produced.”44
Health economist James Robinson has argued that “low-value” services should be subsets of “high-cost health services,” such as “biopharmaceuticals, implantable medical devices, advanced imaging modalities, and specialized surgical procedures.”

Various methods would be used to determine which high-cost services would fall into the “low-value” subset, depending on the clinical circumstances. For biopharmaceuticals, for example, Robinson proposes that value might be defined based on the patient’s “clinical indication, disease severity, and comorbidities,” perhaps in conjunction with practice setting characteristics including “physician specialty, the presence of care coordination, and patient education services.” He suggests that U.S. Food and Drug Administration (FDA) approval might also be used as an indication of value (i.e., drugs used off-label would be subject to higher patient cost sharing), perhaps in conjunction with a drug compendium or an “authoritative, evidence-based care pathway.”

For implantable devices (e.g., stents, pacemakers), he proposes that payers “cover the basic-function device, leaving the patient to buy up to a higher-function alternative—unless the higher-function device were known to offer a clinically better outcome to this particular type of patient” as determined by “the health plan’s medical management professionals in consultation with the patient’s physician.” And, for common surgeries, such as knee replacements, “the insurer could specify a contribution that it would make, with the contribution based on the payment rate for the most efficient provider team in the local market. The patient would be assigned responsibility for paying the extra costs incurred if a higher-price provider team is chosen.”

Putting aside the complexity of designing, maintaining, and administering a system like that envisioned by Robinson, 2 important and potentially controversial issues are apparent.

Whose “Evidence-Based Conclusion” Prevails in Determining “Value?” First, key organizations, viewing the same evidence, often reach different conclusions about the value of medical services. For example, the suggestion by Fendrick et al. to assign a “low-value” designation to USPSTF “D” services is reasonable, but the USPSTF currently has a D designation for teaching women to perform monthly breast self-examinations (BSE) and, at this writing, appears poised to give prostate cancer screenings for men in all age groups a D designation in an upcoming meeting. In contrast, screening guidelines promulgated by the American College of Radiology (ACR) goes a step further in describing the value of screening mammography for women aged 40 to 49 years, calling the USPSTF recommendations “ill advised and dangerous” and “unconscionable,” describing annual mammography screening for women aged 40 years or older as “one of the major health care advances of the past 40 years,” and arguing that the USPSTF “selectively reviewed the literature, ignoring hundreds of well-regarded studies on the subject.”

This controversy leaves a payer that is trying to define cost-sharing levels based on “value” with an obvious and seemingly irreconcilable conundrum: which evidence-based conclusion should the payer adopt in determining the value of mammography for women aged 40 to 49 years—that of the USPSTF, the ACS, or the ACR?

Ethical Considerations in Deeming Services “Low-Value” When Evidence is Uncertain. Second and more important, a policy of redirecting scarce resources from one patient group (users of high-cost medical services, often for catastrophic illness) to another patient group (users of chronic medication therapy for high-prevalence conditions, often for primary prevention) has profound ethical implications that require thoughtful consideration of the evidence about the proposed policy change. In other words, consistent with the principles of comparative effectiveness research, appropriate and ethical resource allocation requires reliable and valid evidence about the costs and benefits of available alternatives. Yet, as Choudhry et al. (2010) observed in a recent review, “there is a paucity of data to indicate for which services cost sharing should be increased,” as well as a “lack of evidence” about whether drug copayment reductions “will yield better health outcomes and lead to reductions in other health care costs.”

This lack of evidence makes the resource allocation shifts suggested by VBID proponents ethically questionable at the present time.

These ethical implications become even more cogent when one considers the possibility that reduced brand drug copayments could potentially incentivize patients to use brand medications for therapeutic purposes that could be served with generics, a phenomenon of “unintended incentives.” Such incentives reduce the affordability of the benefit, both overall
and—a point that often goes unnoticed—for the individual patient who pays an unnecessarily high, albeit reduced, copayment for the brand drug.

The clinical implications of potentially encouraging greater first-line brand drug use should also be thoughtfully considered because the risks and benefits of newer medications are sometimes not as fully understood prior to FDA approval as they are in the postmarketing phase. The history of rosiglitazone—a top-selling diabetes drug that was initially approved in 1999 but "significantly" restricted by the FDA in September 2010 because new studies suggested that it elevated cardiovascular event risk—provides a case in point.53,54

Early Responses to Defining “Low-Value” Services. Given these uncertainties, it is perhaps not surprising that early efforts to implement VBID programs encompassing both copayment reductions for “high-value” services and copayment increases for “low-value” services have been met with skepticism and controversy. In March 2010, Kaiser Health News reported that 5 insurers in Oregon had begun offering a benefit design that provided free or low-cost physician visits and prescription drugs for certain chronic conditions (asthma, congestive heart failure, diabetes, depression, heart disease, chronic bronchitis, and emphysema) but required much higher patient cost sharing for “treatments deemed overused.”55 Patients using targeted “overused” treatments—such as knee or hip replacement, coronary artery bypass surgery, stent placement, hysterectomy, certain imaging examinations, and ER visits—would pay double the usual plan deductible, double the office visit copayment, and up to one-half of hospitalization and ER cost, up to an annual out-of-pocket maximum of $1,500 for individuals and $3,000 for families. Only 1 employer, a steel manufacturer, adopted the plan offering, and its head of benefits estimated that only 7% of workers would select it.55

Detractors of this and similar VBIDs argue that the designs fall into a “danger zone of limiting access to medical care” and that they represent “too much of a blunt instrument.”55 For example, not every patient with heart disease can be treated medically instead of surgically, and “while researchers say that, overall, too many hysterectomies are performed, women with uterine cancer have little choice.”55 When the state of Oregon implemented a similar VBID for its public employees in 2010, its planning group “ruled out including cardiac treatments and hysterectomy in the higher-cost category of coverage because they are in the postmarketing phase. The history of rosiglitazone—a top-selling diabetes drug that was initially approved in 1999 but “significantly” restricted by the FDA in September 2010 because new studies suggested that it elevated cardiovascular event risk—provides a case in point.53,54

Unfortunately, much of the literature on cost sharing has tended to overstate or misstate previous research findings, suggesting that cost sharing had a greater influence on medication adherence than was actually documented in the original work. For example, in discussions of cross-sectional analyses comparing higher versus lower cost sharing levels, one sometimes sees references to “price responsiveness” to “[copayment] changes” when no copayment change was measured56 or to “adherence” outcomes from studies that included no measures of adherence;57 and seemingly small but often substantively important discrepancies are common. In a recent example, a 2008 study by Sedjo and Cox58 of changes in statin utilization following simvastatin (Zocor) patent expiration was among the studies cited in the introduction to a research article to support a statement that medication adherence increases by 2%-5% in the first year after VBID implementation.59 Sedjo and Cox did find that following simvastatin patent expiration and the resulting change from a brand to generic copayment (not a VBID program implementation), the medication possession ratio (MPR) for simvastatin users increased by a mean adjusted 0.52%, compared with an MPR decline of 2.02% for users of brand statins other than simvastatin, who experienced no copayment decrease. However, they also found that among patients who experienced the greatest copayment decreases measured in the study, more than $15, price elasticity was −0.02—that is, no meaningful price responsiveness; and, they found that the percentages of patients whose MPR increased from less than 80% before patent expiration to at least 80% after patent expiration were 10.5% in the simvastatin group and 10.0% in the group using other brand statins—that is, no meaningful difference.60

A more serious discrepancy appeared in the introduction to a recently published research article, in which a study by Huskamp et al. (2003) was cited to support the statement that “prescription drug benefits that shift greater costs to consumers or increase barriers to access can result in lower rates of drug treatment, poorer adherence, and increased rates of treatment discontinuation.”61 This description is inconsistent with the actual finding of Huskamp et al. that a change from a single-tier $7 copayment to a 3-tier $8/$15/$30 benefit, but not a change from a 2-tier $6/$12 to a 3-tier $6/$12/$24 benefit, was associated with a reduced probability of using medication in 3 therapy classes (proton pump inhibitors,
angiotensin-converting enzyme [ACE] inhibitors, and statins).61 More importantly, Huskamp et al. found that treatment discontinuation rates were significantly higher for patients who experienced a $23 copayment increase (from $7 to $30) but not for patients who experienced a $12 copayment increase (from $12 to $24). And, perhaps because of type 1 error or an unmeasured confounder, among patients taking ACE inhibitors, treatment discontinuation rates were lower (not higher) for the patients who experienced a copayment increase from $12 to $24 than for patients whose copayments remained unchanged at $12—that is, persistence with ACE inhibitor therapy was better for patients with a higher copayment.61

The Huskamp et al. study has been inaccurately described elsewhere including a 2008 commentary, which indicated that “when an employer increased cost-sharing requirements by about $10 to $20 per prescription … 21% of patients stopped taking their medication for high cholesterol (compared with 11% in a control group);”64 the actual research finding by Huskamp et al. for a group experiencing a copayment increase of approximately $10 was that 3 of 33 (9.1%) statin users whose copayment increased by $12 versus 1 of 25 (4.0%) statin users without a copayment increase discontinued statin use, a non-significant difference (P = 0.45).61

The same commentary, an assessment of policy implications from the Rand Health Insurance Experiment (RHIE) and selected observational studies, indicated that by discouraging use of appropriate health care services, cost sharing “could lead to additional hospitalization, emergency department visits, and even death.”64 The RHIE did find that higher levels of cost sharing led to reduction in use of health care services, including both those deemed essential and nonessential by RHIE investigators; yet, the RHIE found that these service use reductions had no effects on health except for a few minor outcomes (e.g., vision, dental, and increase of an average 3 millimeters mercury [mm Hg] in diastolic blood pressure) that were limited to low-income RHIE enrollees only.65,66 In contrast to the commentary’s portrayal, RHIE authors even argued in 1987 and 1992 that their finding of “enormous potential savings” from cost sharing, with “little apparent health impact on the kind of people who typically are covered under employer health insurance,” may have prompted plan sponsors to increase coinsurance and deductibles in the years immediately following the RHIE’s publication, resulting in large health care cost savings nationwide.65,67

**New Observational Evidence About VBID Copayment Reduction**

Since publication of our earlier observations about deficiencies in research on VBID,8,57 new copayment reduction studies using nonrandomized comparison groups have been published 29,62,63,64-71 and an additional study31 measured the association between medication adherence and all-cause health care costs (Appendix). Although all the VBID studies provided evidence that implementation of VBID might have a small favorable effect on medication adherence, none provided the information that payers need to make an informed decision about VBID because of serious problems in reporting, program design, and effect calculation.

**No Information About Generic Utilization.** None of the new studies of VBID reported its effect on generic utilization,29,63,64-71 an especially important omission for programs in which copayment reductions either included brand drugs69,70 or were limited to brand drugs.69,71 Failure to report the effects of brand drug copayment decreases on generic drug utilization is especially problematic because previous observational investigations have found an association between prescription drug cost-sharing increases and increased use of lower-cost medications (i.e., generic and preferred brand drugs) in the same therapeutic class.58,61

**No Information About Payer Cost.** None of the new VBID studies reported the cost of the intervention to the payer.29,63,64-71 A report by Gibson et al. (2011a) of a program in which coinsurance rates for brand antidiabetic drugs were reduced—from 20% for tier 2 and 35% for tier 3 to the 10% level previously in place only for generic medications—is especially notable because it purported to show a favorable return-on-investment (ROI) attributable to medical cost offsets but actually measured total costs, not payer costs.71 In other words, the calculation ignored the cost to the employer for the copayment waivers (i.e., the cost shift from patient to payer); thus, its results do not represent ROI from the payer perspective. The report also indicated significant effects for VBID only for a subgroup of patients enrolled in a DMP but did not report the cost of the DMP. This omission of DMP costs is especially important because the program was intensive, including nurse telephone outreach, coaching, and monitoring, in addition to numerous written educational components.71 Thus, despite the indication in the article’s title that VBID coupled with a DMP “produced savings,” the study did not address that research question.

In another report by Gibson et al. (2011b) of a copayment reduction intervention for medications to treat diabetes, asthma, and hypertension, the authors “raise the prospect that this program may have saved the company money by reducing other medical costs” because “clinical effects such as changes in glucose levels, blood pressure, and lung functioning might have occurred,” but no assessment of these measures was made, and the report’s quantitative analysis indicated no significant association between VBID and any of 3 measures of spending (pharmaceutical, medical, or total) during the 3-year post-implementation period.70 The study report also transparently disclosed 2 important confounding factors—a DMP was phased in for the VBID employer during the post-implementation period, and the VBID employer was a pharmaceutical manufacturer that provided its brand drugs free of
charge to employees. Unfortunately, the brand drugs were not named and the DMP was not described, making it difficult for decision makers to interpret or use the study results in estimating the costs and benefits of VBID. Finally, as in the other recent report by Gibson et al., the authors indicated that “the program was mostly cost-neutral to the company;” however, the measure of expenditures was “eligible charges,” which was not defined specifically but appears to be a total (rather than a net after copayment) that does not represent the health plan sponsor’s costs.70

Unfortunately, in addition to failing to report the cost of the intervention to the health plan sponsor, none of the new VBID study reports contained even enough quantitative information for readers to calculate the intervention cost. Although most provided some information about mean copayment amounts paid per claim by the intervention and/or comparison groups before and/or after the intervention, only a few provided quantitative information for both time periods and groups, and none provided information about utilization (number of claims), which is essential to translating cost per claim into total cost. Additionally, tier-specific utilization data were not included in any of the new VBID study reports but are necessary to determine whether utilization shifts to drugs in higher or lower tiers affected/payers’ ingredient cost expenditures.

Problems in Study Design and/or Reporting. Several problems in recent VBID research reports, including discrepancies between study methods and either methodological or clinical guidelines, are apparent (Appendix). For example, in an analysis of therapy discontinuation rates for a VBID program for antidiabetic medications, Chang et al. (2010) removed from the denominator patients who made a medication switch from one antidiabetic subclass to another (e.g., from a thiazolidinedione [TZD] to metformin or to a sulfonylurea).29 This decision had the mathematical effect of inflating the discontinuation rate overall, and especially in the presence of even appropriate and desired switches from brand to therapeutically equivalent generic drugs, thereby systematically biasing the analysis to find higher “discontinuation” rates for the comparison group than the VBID group (Table 1). Unfortunately, the report does not contain the patient subgroup counts necessary to calculate unbiased discontinuation rates for the study groups.

Less serious but still important is a problem with attributed causal linkage that appears in a transparent and clearly reported analysis by Roebuck et al. (2011) of the association between medication adherence and all-cause health care costs.31 In that analysis, the authors made no assessment of whether the observed all-cause utilization could reasonably be clinically attributed to medication nonadherence (e.g., cardiovascular events vs. automobile accidents); the authors chose instead to rely solely on fixed-effects statistical modeling techniques to establish causal linkage, a suboptimal method for observational analysis.72 Additionally, the authors assumed that a patient with a chronic disease diagnosis (heart failure, diabetes, hypertension, or dyslipidemia) but without pharmacy claims had medication adherence of zero, regardless of whether any medication was prescribed. This decision excludes the possibility of nonpharmacologic interventions based on lifestyle modification and is, although appropriate for heart failure, inconsistent or only partly consistent with treatment guidelines for the other 3 disease states.73-75

Another problem common to varying degrees in the new VBID studies is lack of specificity in the descriptions of sample construction. For example, only 1 included a sample selection flowchart to enable the reader to determine the effect of each sample inclusion and exclusion criterion,69 although this information is considered a standard for research reporting.72 Moreover, it was difficult to determine key details, such as the specific criteria used to define a “user” of a particular drug class or to qualify for DMP entry, in many reports. Similarly, in many VBID reports it was difficult or impossible to identify the pre-intervention values and/or the absolute change amounts for the outcome measures.

Still No Randomized Trials. As Roebuck et al. candidly acknowledge, even a well-done multivariate statistical analysis controlling for fixed effects (e.g., as a proxy for “healthy adherer” effects) is “not as good as a randomized controlled trial in establishing causality.”71 The report by Gibson et al. of the brand antidiabetic drug copayment reduction program is

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### Table 1

<table>
<thead>
<tr>
<th>Hypothetical Plan</th>
<th>Number of Users</th>
<th>Number Switching to Generic Medication</th>
<th>Number Discontinuing Therapy</th>
<th>Actual Discontinuation Rate</th>
<th>Discontinuation Rate After Removing Switching Patients from Denominator</th>
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<td>10</td>
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<td>10.0%</td>
</tr>
<tr>
<td>Plan B—tiered benefit</td>
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<td>20</td>
<td>10</td>
<td>10.0%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

aThis example assumes, for purposes of illustrating the mathematical effect, that patients in the VBID had no incentive to switch from brand to generic medication, in contrast to patients in the traditional tiered benefit plan.

VBID = value-based insurance design.

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What Do We Really Know About VBID?
Quality of the Evidence and Ethical Considerations for Health Plan Sponsors
especially notable in this regard because its findings strongly suggest that the “effects” of the program were actually due to confounding. Specifically, the study found that among DMP participants, compliance with recommended screening and monitoring (i.e., primary care provider visits, hemoglobin A1c tests, lipid tests, and urinalysis) was higher for VBID enrollees than for comparison group patients.71 However, the study report indicated that the VBID program changed pharmacy copayments only. There is no logically apparent causal linkage between pharmacy copayments and receipt of guideline-based medical care, and the study authors offered none in the report. Like the finding of Dormuth et al. (2009) that patients compliant with statin therapy were less likely than noncompliant patients to have automobile and workplace accidents,70 the findings of Gibson et al. sound a cautionary note for those who attempt to equate association with causation; the resulting conclusions may be biologically or logically implausible.

In contrast, an observational analysis by Maciejewski et al. (2010) is commendable for its inclusion of a comparison group of patients treated with therapy classes in which copayments were reduced in both the VBID intervention and comparison groups. The authors made the reasonable case that the lack of VBID “effect” in these classes, coupled with the positive association of VBID with adherence in the other study drug classes, strengthened the internal validity of their findings.63 A study by Choudhry et al. of copayment elimination for statins and copayment reduction for clopidogrel, effective January 1, 2007, appears to have good internal validity;68 however, the intervention was conducted among enrollees whose employer coupled widely publicized copayment reductions with intensive educational interventions in 2002,77 making the context and external validity of the 2007 intervention unclear.

Costs and Benefits of VBID Interventions

The 2 new VBID studies with the strongest internal validity, one by Choudhry et al. and the other by Maciejewski et al., suggest a VBID effect size of approximately 1.5 to 4 percentage points in adherence measured by MPR or proportion of days covered (PDC).63,68 Effect sizes of about 2.6 to 4.0 percentage points annually were reported previously by Chrenew et al. (2008) for copayment reductions (for tier 1/tier 2/tier 3) from $5/$25/$45 to $0/$12.50/$22.50 for diabetes drugs, statins, and antihypertensive drugs (ACE inhibitors and angiotensin II receptor blockers [ARBs]).79 Despite the statistical significance of MPR or PDC changes of 2 to 4 percentage points measured using large samples, these changes represent only 7 to 15 added days of therapy per year on average (e.g., 0.02 X 365 = 7.3 days).

The costs and benefits of these small adherence improvements have not yet been reported. In a previous editorial on the study by Chrenew et al., we used national data to compensate for missing information in the study report and estimated that the approximate payer cost per member per year (PMPY) for that VBID program after full phase-in was $18.60 ($1.86 million per year in a drug plan with 100,000 members) for statins to achieve a 3.4 percentage point increase in MPR, or about 12 added days of therapy each year on average.57 Although the VBID for statin drugs reported recently by Choudhry et al.68 was limited to patients using prescription medications for diabetes or cardiovascular disease, one could reasonably assess the cost of providing free statins to all statin users in a health plan by using the mean pre-intervention statin copayment of $24 per claim reported by Choudhry et al., coupled with the use prevalence rate of 12.1% and 10.0 claims per user per year reported by a PBM for 200976 to calculate an estimated VBID cost of approximately $29 PMPY (12.1% X 10.0 X $24). For the VBID group in the study by Maciejewski et al., the cost would be lower because the intervention consisted of a generic copayment waiver; however, the estimate of VBID cost would be somewhat misleading because in both the VBID and comparison groups, all tier 3 brand drugs in the study drug classes were set to a tier 2 copayment. Putting aside that limitation, and assuming that the pre-intervention generic dispensing ratio for statins (38%) was unchanged in the post-intervention period, the cost of waiving the approximately $11 generic copayment in the study by Maciejewski et al. would be $5.06 PMPY (38% X 12.1% X 10.0 X $1).

Three key points about these calculations are noteworthy for payers. First, these figures illustrate the conclusion reached by Melnick and Motheral based on their VBID plausibility calculator that mathematically, it is nearly impossible for a health plan sponsor to achieve cost neutrality in VBID programs using medical cost offsets, with the possible exception of programs applied only to generic medications.52 Assuming that a private payer incurs a cost of approximately $60,000 per patient for a major cardiovascular event (in 2006, costs per hospital stay billed to private insurance were $44,733 for coronary artery disease, $54,697 for MI, and $44,239 for stroke),79 achieving cost neutrality for a VBID program that costs $29 PMPY in a plan with 100,000 members would require prevention of an additional 48 cardiovascular events per year ($2.9 million divided by $60,000). Thus, using clinical trial data as indicators of the baseline effectiveness of statins in preventing major cardiovascular events (Table 2)50-52 for the health plan’s assumed 12,100 statin users (use prevalence of 12.1% X 100,000) and assuming a baseline MPR of 50%-80%, a VBID copayment reduction program that costs $29 PMPY would have to increase the effectiveness of statin treatment by approximately 41%-49% in secondary prevention (e.g., an increase of 48 over a baseline of 97 to 118 patients in whom events are prevented annually) and 68%-79% in primary prevention—despite increasing medication adherence by only about 4%-6% (3 percentage points improvement over a baseline MPR of 50%-80%) to break even. As VBID proponents have observed, additional cost offsets
from improved worker productivity (e.g., reduced absenteeism and disability days), although not easily measured, are possible for active employee groups; however, it is difficult to imagine that these effects would be substantial given the small size of the medication adherence effects.

Second, the results of the Maciejewski et al. analysis suggest, consistent with PBM observations, that the adherence effects of dispensing medication in 90-day supplies may overwhelm those of VBID. In the Maciejewski et al. analysis, enrollees with at least 1 pharmacy claim for a 90-day supply had adherence rates 17 to 22 percentage points higher than those of patients without any 90-day supplies. Notably and unfortunately, none of the other new VBID studies reported utilization rates of 90-day supplies or mail order pharmacy or analyzed the effect of 90-day supplies on medication adherence.

Third, the need to calculate these “back-of-the-envelope” estimates from published research articles highlights deficiencies in the base of evidence about copayment reduction programs, especially for payers that need actionable, quantitative estimates of the impact of adherence promotion strategies on economic and clinical outcomes.

What to Expect When You’re Expecting Information About VBID

In their 2008 report of the association of VBID with MPR changes of 2.6 to 4.0 percentage points, Chernew et al. predicted that “because clinical evidence supports adherence to these medications, we expect health improvements, although we do not quantify them in this study.” In an accompanying press release from the sponsoring institution, the study’s lead author speculated that “while future studies need to be done to actually quantify this specifically, there is considerable evidence that use of the classes of medication in this study will reduce the frequency of adverse clinical events and associated hospitalizations or ER visits—consequences of the “adverse clinical events” that the investigators had suggested would be prevented by the VBID—were reported.

Similarly, an analysis plan for a study of the MHealthy initiative, a VBID program that was implemented for University of Michigan employees and their dependents with diabetes on July 1, 2006, was published in April 2009. The analysis plan indicated that study follow-up would end 30 months

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**TABLE 2** Effectiveness of Statin Treatment in Preventing Major Cardiovascular Events in a Hypothetical 100,000-Member Health Plan

<table>
<thead>
<tr>
<th>Study</th>
<th>Description of Events Avoided by Statin Treatment</th>
<th>Per-Patient Probability of Having at Least 1 Avoided Event During Follow-Up Period (Years)</th>
<th>Length of Follow-Up Period (Years)</th>
<th>Annual Probability of Event Avoidance</th>
<th>Number of Treated Patients</th>
<th>Annual Number of Patients with at Least 1 Avoided Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIPID Secondary Prevention Trial</td>
<td>Events (30 deaths, 28 nonfatal MIs, and 9 nonfatal strokes) were avoided in an unduplicated 48 patients for every 1,000 treated.</td>
<td>0.048</td>
<td>6.1</td>
<td>0.008</td>
<td>12,100</td>
<td>97</td>
</tr>
<tr>
<td>Meta-analysis of all statin users, secondary prevention</td>
<td>Events were avoided in 48 patients per 1,000 treated.</td>
<td>0.048</td>
<td>5</td>
<td>0.0098</td>
<td>12,100</td>
<td>118</td>
</tr>
<tr>
<td>Meta-analysis of all statin users, primary prevention</td>
<td>Events were avoided in 25 patients per 1,000 treated.</td>
<td>0.025</td>
<td>5</td>
<td>0.0051</td>
<td>12,100</td>
<td>61</td>
</tr>
<tr>
<td>JUPITER, primary prevention</td>
<td>0.59 composite endpoint events per 100 person-years of follow-up.</td>
<td>NA</td>
<td>NA</td>
<td>0.0059</td>
<td>12,100</td>
<td>71d</td>
</tr>
</tbody>
</table>

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* * *
after implementation, or approximately January 2009, and
that the analysis would assess the primary outcomes of
medication utilization and adherence, as well as secondary
outcomes including health care costs and utilization rates for
outpatient visits, ER visits, and hospitalizations.83 Although
the MHealthy study follow-up was scheduled to end more
than 2 years ago at this writing, to date the only reported
findings of which we are aware include a brief mention,
reported in a 2010 review article, of “preliminary results"
indicating that the MHealthy intervention was associated
with “a 7 percent increase in adherence to blood pressure-
lowering medication and a nonsignificant 4 percent increase
in adherence to statins.”11
Against this shortfall of evidence promised but not yet
reported, several reasons for a “caveat emptor” approach to
VBID research are apparent, including the following key
points.
Isolated Significant Findings. Because of cumulative type 1
(false positive) error, it is mathematically expected that at least
1 finding in a series of numerous statistical tests will be statisti-
cally significant solely because of chance. For example, in 20
statistical tests at an alpha of 0.05, the probability of at least 1
false positive finding is 64%.84 In the presence of publication
bias, these multiple tests are not necessarily apparent to readers
of a single research article. We encourage health plan sponsors
to be mindful of the history of VBID research reporting (or
nonreporting) in considering the results reported in any single
publication, especially for hospitalizations and ER visits.
Causal Linkages. In viewing published results of observational
studies of VBID programs, payers should consider whether the
findings are plausible. For example, one would not expect large
medical cost offsets from tiny medication adherence gains, large
adherence gains from small cost-sharing changes, or changes
in a measure of quality of care that is not affected by pharmacy
copayments (e.g., receipt of guideline-based medical care, such
as examinations and laboratory tests). Although understanding
complex nuances of methodological and statistical techniques
may be difficult for managed care decision makers who lack
research training, consideration of basic clinical and practical
causal logic is not difficult and will go a long way toward
assessing the validity of VBID studies.
Total Cost Versus Health Plan Sponsor Cost: A Major
Difference for Payers. To date, 3 assessments of costs associ-
ated with VBID have either measured70,71 or estimated45 change
in total cost, including both the payer cost and the patient
cost share. Although this method is not inherently erroneous
because it is common for health policy research to examine
cost outcomes from a societal perspective, it produces a result
that is uninformative for health plan sponsors making a
decision about VBID. The financial effects of VBID on plan
sponsors are the sum of (a) increased medication adherence
(an effect that is captured in the total cost measure), and (b)
the reduction in copayment (an effect that is not captured in
the total cost measure). Because of the inelasticity (lack of price
responsiveness) in drug purchasing behavior in commercially
insured groups, a calculation of total cost change in a VBID
program will produce a small estimated effect that understates
the actual cost of VBID to the payer. Yet, only 1 of the 3 reports,
the economic “break-even” analysis by Chernew et al.,43 trans-
parently disclosed in the study report the implications of the
analytic perspective for plan sponsors. Thus, when provided
with information about VBID costs and benefits, health plan
sponsors should check carefully to determine if payer costs
were measured.
Overextension. Completion of the first randomized trial
of a copayment reduction intervention is expected in early
2011.11 That study, the Post-MI FREEE (Free Rx and Economic
Evaluation), is a test of eliminating copayments for secondary
prevention medications (statins, beta-blockers, ACE inhibitors,
and ARBs) for patients aged 64 years or younger following
hospitalization for MI.85 Because the baseline probability of
adverse cardiovascular events is higher in a patient population
with a previous MI than in the population of cardiovascular
medication users as a whole, the likelihood of finding clinical
benefits is higher in this patient sample than in a typical
patient population in which medications are used both for
primary and secondary prevention. Yet, an unfortunately com-
mon occurrence in health policy research is the overextension
of findings from a study sample manifesting one set of charac-
teristics to a larger population with completely different clinical
or demographic characteristics. We have previously pointed
out the frequent inappropriate extensions of a study conducted
in a small group of low-income elderly with numerous chronic
illnesses to healthier patient populations and to different out-
comes—even to outcomes that were not studied in the original
research.86 In assessing the information presented in popular
press accounts and literature reviews, payers should compare
the assertions made about the Post-MI FREEE findings with
the study report—or the study abstract for decision makers
who lack the time to read the entire report—to determine if
findings are represented accurately or misstated.
VBID: What Should Health Plan Sponsors Do Now?
We predicted in 2008 that managed care was approaching
a crossroads at which policymakers would have to decide
whether to reject cost-sharing policies based on high-quality
evidence in favor of weaker, but more vigorously promoted,
evidence.86 That issue has become more acute and ethi-
cally important with the recent suggestions that the costs of
drug copayment reductions—often for primary prevention
using brand medications in therapeutic classes with generic
alternatives—should be offset by increasing cost-sharing
requirements for patients using expensive treatments for serious or catastrophic illness. Assessment both of the evidence and, more importantly, the limitations of the evidence regarding VBID suggests 4 important steps going forward.

First, as Choudhry et al. observed in their recent review, important questions about the effects of drug copayment reductions on clinical and economic outcomes “should be answered before [VBID] is used more widely.” Because VBID has been associated with only minimal medication adherence increases documented only in observational research, and because no health or medical utilization outcomes (e.g., ER or hospital use) have yet been reported for VBID programs, the evidence is insufficient to support expanding its use at the present time.

Second, managed care decision makers should refuse to accept studies that lack transparent reporting necessary to make even basic estimates of the costs and benefits of VBID. Nontransparent study reports do not provide useful information and should not be used for policymaking. For promulgators of research information, the logical corollary is that continuing to publish suboptimal work will eventually cause decision makers to be indifferent to study findings—exactly the opposite of the goal that the AHRQ has set for evidence-based decision making in health care policy.

Third and related, although it would seem that health care decision makers should not have to be responsible for critical appraisal of the information provided in peer-reviewed articles, it appears that such critique is unfortunately necessary in cost-sharing research because of a pattern of inaccurate statements about research findings. In reading literature reports about VBID, health care decision makers will find it helpful to read the source materials—at least the study abstract and the results tables if time is short—instead of relying solely on secondary descriptions of what previous research has shown. Summary study tables including critical appraisal of the evidence, such as those that we have reported here and in previous JMCP issues, as well as that reported by Motheral in the current issue, are also helpful, and we encourage other health policy researchers to provide summaries of this type for health care decision makers.

Fourth, and most important from a policy perspective, deliberations about whether to fund drug copayment reductions, especially for primary prevention, by directing scarce resources away from a subset of prescribed medical and pharmaceutical treatments should demand high-quality evidence. Yet at this writing, nearly a decade after pharmacy benefit copayment reduction was initially proposed as a means to improve the outcomes of patients with chronic health conditions, health plan sponsors have little of the information that they need to assess the costs and benefits of VBID. Available evidence is of suboptimal quality, much of it so opaque that it is uninterpretable; outcomes critically important to enrollees and health plan sponsors, such as cost to the payer and effects on generic drug utilization and patient health, remain either unexamined or unreported; and the only randomized trial of VBID of which we are aware, the Post-MI FREEE, is laudable for its design and transparency but limited to secondary prevention. An evidence base that falls so far short of the AHRQ’s ideal for health care policy research—timely, clear, transparent, solid, and actionable—should be viewed as an example of how not to inform health care system change.

DISCLOSURES

The authors report no financial conflicts of interest related to the subjects or products discussed in this article. Fairman reports that she works and volunteers a few hours each month in nursing homes, primarily with bedbound patients who have catastrophic illnesses.

REFERENCES


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### APPENDIX

#### Summary of Recent Observational Studies of Copayment Reductions and Medication Adherence

<table>
<thead>
<tr>
<th>Study</th>
<th>Overview</th>
<th>Sample</th>
<th>Groups</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang (2010)&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Study of copayment reductions for antidiabetic medications—free generics and insulin, reductions in copayments for tier 2 brand drugs, no change for tier 3, effective January 1, 2007; study period was January 1, 2006, through December 31, 2007.</td>
<td>Enrollees with at least 1 claim for an antidiabetic medication during the study period, classified as initiators (no claims in 2006) and continuers/discontinuers (use in 2006 including final 45 days of the year); all were continuously enrolled throughout the study period.</td>
<td>Intervention: 3 PBM clients without concurrent educational or DSM programs; n = 20,173 (however, outcomes were reported for only 2,538 patients). Copayments changed from $15 to $0 for generic, $30 to a range of $10-$15 for tier 2, a range of $30-$35 for tier 3 in both periods; mean copayments changed from $28 to $0 for insulin and from $21 to $10 for OADs.</td>
<td>Comparisons of MPR, treatment initiation and DC rates pre-intervention vs. post-intervention for intervention and comparison groups; DC rate calculations excluded patients switching to a different therapeutic antidiabetic subclass. Logistic regression models of discontinuation and linear regression models of MPR adjusted for age, sex, and mail order use.</td>
</tr>
<tr>
<td>Choudhry (2010)&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Study of elimination of all statin copayments for patients with vascular disease or diabetes and reduction of copayments for clopidogrel, effective January 1, 2007.</td>
<td>Employees and dependents of Pitney Bowes; n = 2,051 statins and 779 clopidogrel; mean copayments changed from $24.18 to $0.60 for statins and from $17.22 to $8.86 for clopidogrel.</td>
<td></td>
<td>Comparisons of daily drug use per prescriber for the 12 months following implementation and adjusted for covariates including age, sex, baseline usage, zip code, and sponsor.</td>
</tr>
</tbody>
</table>

#### Results
- Treatment initiation rates were 2.3% intervention vs. 1.6% comparison group.
- Among initiators, DC rates were 16.0% intervention vs. 24.3% comparison; MPR was 0.857 intervention vs. 0.858 comparison.
- Among continuers, DC rates were 26.0% intervention vs. 29.8% comparison; MPR change was +0.049 intervention vs. −0.023 comparison.

#### Comments
- Calculations difficult to interpret because of missing information in study data tables, especially presentation of data for only a small fraction of study cases.
- Pre-intervention values of most outcome variables not reported, making it difficult to interpret the practical/clinical significance of study results.
- Prior to the intervention, use prevalence rates were about 1-2 percentage points higher, and the percentage with MPR more than 80% was much lower, in the VBID group than the comparison group; MPR change results could represent RTM, but pre-intervention MPRs were not documented, making RTM effects difficult to ascertain.
- The effect of $4 generic programs among large community pharmacies is unknown; it is possible that higher treatment “initiation” rates reflect switch from $4 generics (not in database and paid by patient) to $0 generics (in database and paid by health plan sponsor).
- The decision to exclude from the DC calculation patients who made a subclass switch (a) masked the potentially positive result of switching to lower cost medication and (b) artificially inflated DC rates in presence of elevated switch rates (Table 1), thereby biasing the analysis to find higher DC rates in the comparison group.
- Insulin copayments increased by 22% in the comparison group from pre- to post-intervention.

#### Choudhry (2010)<sup>68</sup>

<table>
<thead>
<tr>
<th>Overview</th>
<th>Sample</th>
<th>Groups</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview: Study of elimination of all statin copayments for patients with vascular disease or diabetes and reduction of copayments for clopidogrel, effective January 1, 2007.</td>
<td>Patients who from January 2006 through December 2007 either (a) had at least 1 statin claim and proxy measure for diabetes and vascular disease (at least 1 claim for diabetes medication or supply, beta blocker, or platelet inhibitor) or (b) had at least 1 claim for clopidogrel; there was no continuous enrollment requirement for sample inclusion.</td>
<td>Intervention: Employees and dependents of Pitney Bowes; n = 2,051 statins and 779 clopidogrel; mean copayments changed from $24.18 to $0.60 for statins and from $17.22 to $8.86 for clopidogrel.</td>
<td>Comparisons of MPR, treatment initiation and DC rates pre-intervention vs. post-intervention for intervention and comparison groups; DC rate calculations excluded patients switching to a different therapeutic antidiabetic subclass. Logistic regression models of discontinuation and linear regression models of MPR adjusted for age, sex, and mail order use.</td>
</tr>
</tbody>
</table>

#### Analysis
- Unadjusted: Statin PDC 2.8 percentage points higher for VBID than comparison immediately after implementation; clopidogrel PDC 4.0 percentage points higher for VBID than comparison 12 months post-implementation.
- Adjusted: 3.1 percentage point “immediate” increase in PDC level for statins; 4.2 percentage point “immediate” increase in PDC level for clopidogrel; no significant changes in slope in either group.

#### Comments
- Pitney Bowes implemented widely publicized copayment reductions and education beginning in 2002, 5 years prior to this copayment reduction: context of present study not clear. Analysis “unable to account” for the extent of participation in DMPs that were available to both study groups.
- Mean copayment in comparison group was essentially unchanged for statins in pre- and post-intervention periods but increased by 35% (from $10.65 to $14.43) for clopidogrel.
- Generic simvastatin became available in June 2006, midway through the pre-intervention period; it is not clear whether plans encouraged switches to generic simvastatin during post-implementation period.
- Positive methodological decisions included the following: (a) days spent in a hospital or nursing home were subtracted from the denominator; (b) statin PDC accounted for all drugs (i.e., switching did not count against PDC); and (c) numerous sensitivity analyses were performed (producing similar findings).
What Do We Really Know About VBID?  
Quality of the Evidence and Ethical Considerations for Health Plan Sponsors

### APPENDIX

#### Summary of Recent Observational Studies of Copayment Reductions and Medication Adherence (continued)

<table>
<thead>
<tr>
<th>Gibson (2011a)71</th>
<th>Overview: Study of reduction in copayment to 10% for all diabetes medications, including both generic and brand, effective January 1, 2006; a DMP also became available to both intervention and comparison group employees on January 1, 2006.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample</strong></td>
<td>Enrollees aged 64 years or younger who either participated in DMP or opted out of DMP and were continuously enrolled in at least 4 consecutive quarters from 2005 through 2008; use of antidiabetic medication was not required for sample inclusion, and the authors note that “our enrollee pool may have included patients who were using diet and exercise to manage their condition.”</td>
</tr>
</tbody>
</table>
| **Groups** | Intervention: Employees and dependents of 2 units of a large multi-industry firm (n = 33,160); n = 3828 who opted out of DMP. Copayments for diabetes medications changed from 10% generic, 20% tier 2, and 35% for tier 3 to 10% for all diabetes medications (generic and brand).  
Comparison: Employees and dependents in the rest of the firm’s units (n = 59,038), enrollees were propensity matched for probability of being in the intervention group based on demographic characteristics, health status (CCI and psychiatric diagnosis groups), employment characteristics (e.g., salary vs. hourly, active vs. retiree), relationship to employee, and ZIP-level income and education, n = 1,876 in DMP and n = 3,282 who opted out of DMP. Copayments remained constant at 10% generic, 20% tier 2, and 35% tier 3. |
| **Analysis** | Time-series panel data analysis of 1 baseline year (2005) and 3 post-implementation years (2006 through 2008), with calendar quarter as unit of time; analyses were stratified by participation in DMP. Costs and utilization were analyzed using GEE, and costs were measured as total payments (not payer costs). |
| **Results** |  
- Among DMP participants, MPR for VBID (copayment reduction) group compared with non-VBID group was 3.7 percentage points higher in 2006; 5.1 percentage points higher in 2007, 6.5 percentage points higher in 2008; similar trends were observed for percentage of patients with MPR at least 80%.  
- Among DMP participants, percentages complying with recommended tests and services were higher in VBID group than in non-VBID group (e.g., percentage point differences in 2008: 4.5 for HbA1c tests, 5.0 for lipid tests, 7.7 for PCP visits, 4.0 for urinalysis).  
- In non-DMP group, few significant differences between VBID and non-VBID groups, but (a) OAD MPR was 3.8-4.7 percentage points higher with VBID in 2006 and 2007 (but not 2008) and (b) compliance in the first year was significantly lower with VBID for HbA1c (5.2 percentage points) and urinalysis (3.1 percentage points).  
- In DMP group, diabetes-related medical costs were lower and medication costs higher in all 3 years for VBID than non-VBID group, authors estimated an ROI of 1.33.  
- No consistent cost pattern for VBID vs. no VBID in non-DMP group. |
| **Comments** |  
- Enhanced compliance with screening/monitoring tests and medical examinations was described as an “effect” of VBID although the VBID intervention changed drug copayments only.  
- Report measured “ROI” on total costs paid by all sources (including the patient cost share) instead of payer costs. Thus, cost to payer was not reported; results do not represent the ROI that should be expected by the payer; and description of VBID program as “cost-neutral” does not accurately describe the payers’ cost outlays.  
- Cost of DMP was not reported although the DMP was extensive and the positive results for VBID were limited to DMP participants. Study report acknowledged that “to obtain a full cost estimate, some form of assignment into disease management, to measure [DMP] effects and costs, would be necessary.”  
- Criteria for invitation into the DMP were not specified, making the clinical characteristics of the sample unclear (e.g., any diabetes diagnosis, use of particular services, such as hospitalizations, for diabetes, or what, specifically?); proportion of patients who opted-out not reported for the comparison group.  
- The authors apparently measured MPR as zero (0) for patients using diet and exercise alone, regardless of whether any medication was prescribed—for example, pre-intervention insulin MPR was reported as 10% or less for all 4 groups. |

| Gibson (2011b)70 | Overview: Study of a “large, global pharmaceutical firm” that implemented a VBID (copayment reduction) on January 1, 2005, for drugs to treat asthma (SABAs, LABAs, leukotriene modifiers, inhaled corticosteroids, methylxanthines, mast cell stabilizers, and combinations); HTN (ACE inhibitors, ARBs, diuretics, alpha-2 agonists, aldosterone receptor blockers); and diabetes (insulin and OADs). In addition to the VBID, DMPs for “asthma, cardiac conditions, and diabetes were also implemented for enrollees in the company’s indemnity and point-of-service plans in 2005 and ... across all of the company’s self-insured plans in 2007,” with educational materials about the programs “communicated to all employees... starting in the fourth quarter of 2004.” |
Summary of Recent Observational Studies of Copayment Reductions and Medication Adherence (continued)

Analysis
Pre-post design with matched comparison group for 2004 (year prior to implementation) and each of 3 subsequent years—2005 through 2007, data file contained 1 observation per enrollee per calendar quarter, analyzed using GEEs with VBID treated as a time-varying effect (trend) set to zero in Q1 2005 and 11 in Q4 2007. Outcomes were (a) use rate (percentage with at least 1 claim in therapeutic class), (b) adherence based on PDC (at least 50% for asthma, at least 80% for HTN and diabetes), (c) number of 30-day equivalent fills both overall and for VBID classes; and (d) total “eligible charges” for drugs and medical services.

Results
• Average drug spending on VBID medications in Q4 2007 was $68 for VBID group and $51 for comparison group.
• For diabetes drugs, use rates and number of fills did not significantly differ in any year; adherence was lower for the VBID group in the first 2 post-implementation years and not significantly different in the third year.
• For asthma drugs, no significant differences on most measures in most years; only exception was that adherence to asthma medications (but not use rates or number of fills) was significantly higher in the third year only.
• For HTN drugs, adherence, user percentage, and number of fills were significantly higher in the VBID group in all years.
• GEEs showed no significant differences on any measure of total charges (prescription drug, medical, or total) in any of the 3 years.

Comments
• Results are impossible to interpret because of the absence of specific cost-sharing information and because of 2 unusual confounding factors—provision of coincident DMP and of unnamed brand drugs free-of-charge in the intervention group.
• Abstract implies that adherence was higher with VBID in all classes, but data tables indicate that adherence and medication use increased only for HTN medications.
• Authors “raise the prospect that this program may have saved the company money by reducing other medical costs” because “clinical effects such as changes in glucose levels, blood pressure, and lung functioning might have occurred,” but these effects were not measured.
• Cost-sharing change for the VBID program appears to be small (only a 7.2% decrease), making it likely that results for the intervention group are at least partly attributable to the DMP or to another confounding factor.
• “Eligible charges” were not specifically defined (perhaps total provider-billed charges) but do not appear to represent the payer’s outlays; thus, the authors’ description of the intervention as “mostly cost-neutral to the company” appears to be incorrect.
• Discussion describes nonsignificant cost differences as if they were significant.
• Authors indicate that results were similar in a subset of enrollees with pre-intervention drug use; however, description of results in text does not match exhibit table, and the table names what appears to be the wrong pharmaceutical company (employer). Thus, these results cannot be interpreted.

Maciejewski (2010)\textsuperscript{63}

Overview: Study of a VBID (copayment reduction) in which (a) for both the intervention and comparison groups, all tier 3 brands were made tier 2 in 8 classes, including 2 without generic drugs (ARBs and cholesterol absorption inhibitors) and (b) for the intervention group, generic copayments were waived in 6 classes, effective January 1, 2008.

Sample
Enrollees of BCBS-NC who were continuously enrolled from January 2007 through December 2008, and who “were taking a medication” from at least 1 of the study classes (time period for criterion not clear).

Groups

Intervention: Enrollees whose employers opted into the VBID (n = 638,796), n = 5,077 metformin, 15,605 diuretics, 14,250 ACE inhibitors, 11,137 beta-blockers, 18,346 statins, 7,191 CCBs, 7,445 ARBs, 4,019 cholesterol absorption inhibitors. Pre-intervention copayments (reported as means per claim) were $10.74-$11.38 generic, $33.79-$34.39 brand, and overall $13-$17 for ACE inhibitors, beta-blockers, diuretics, and metformin; $22-$25 for statins and CCBs; $36-$37 for ARBs and cholesterol absorption inhibitors.\textsuperscript{4} Post-intervention copayments were 50% generic, $30.50-$30.75 brand, and overall not reported.

Comparison: Enrollees of BCBS-NC whose employers did not opt in (n = 638,091), n = 2,826 metformin, 9,137 diuretics, 7,668 ACE inhibitors, 6,343 beta-blockers, 10,162 statins, 4,099 CCBs, 4,514 ARBs, 2,291 cholesterol absorption inhibitors. Pre-intervention copayments were not reported for generics, were same as intervention group for brands, and overall: $14-$18 for ACE inhibitors, beta-blockers, diuretics, and metformin; $24-$27 for statins and CCBs; $39-$40 for ARBs and cholesterol absorption inhibitors.\textsuperscript{4} Post-intervention copayments were not reported except that brand copayments were the same as in the intervention group.

Analysis

DID (GLM) model of MPR with person-year as unit of analysis, controlling for age, sex, ERG comorbidity burden measure, and pre-intervention medication burden (count of medications, mean copayments, at least 1 90-day supply, GDR).\textsuperscript{e}

Results
• Pre-to-post changes in MPR (percentage points) were slightly higher for intervention than comparison group in classes with generic copay waiver: metformin 3.8, diuretics 3.3, ACE inhibitors 2.9, beta-blockers 2.5, statins 1.8, CCBs 1.5.
• In 2 classes consisting entirely of brand drugs (i.e., copayment reductions in both groups), groups did not significantly differ.
• Filling at least 1 prescription with a 90-day supply was associated with MPR increases of 17 to 22 percentage points.
• Authors stated that “significantly higher medication costs given the number of people participating in the program” posed a potential threat to “the long-term viability of this innovative policy change.”

Comments
• Methodologically strengthened by comparison of 6 VBID (generic drug copayment waiver) classes with 2 drug classes (ARBs and cholesterol absorption inhibitors) consisting entirely of brand drugs (copayments reduced in both groups).
• Title includes the term “targeted patients;” but no patients were excluded from copayment reduction in the 6 drug classes studied (i.e., there was no targeting for secondary prevention or specific risk factors).
• Abstract and discussion erroneously indicate that the study VBID included both generic and brand copayment reductions; actually, brand copayments were reduced in both the intervention and comparison groups.
• GDR was reported pre-intervention but not post-intervention.
## APPENDIX: Summary of Recent Observational Studies of Copayment Reductions and Medication Adherence

### Sedjo (2008)\(^62\)

Naturalistic study of patent expiration for simvastatin effective June 23, 2006, there was no intervention—enrollees who used brand simvastatin prior to expiration were compared with those who used other brand statin drugs (no copayment decrease). Study patients were aged 18 years or older and continuously enrolled from June 2005 through May 2007.

#### Groups
- **Copayment reduction group**: Commercially insured health plan enrollees with at least 1 claim for brand simvastatin from June through August 2005 and at least 1 generic simvastatin claim from June through August 2006 (n = 13,319). Pre-expiration copayment was a mean $14.60, post-expiration copayments not reported but patients were subgrouped by amount of reduction (subgroup counts not specified).
- **Comparison group**: Commercially insured health plan enrollees with at least 1 claim for a brand statin (not simvastatin) from June through August 2005 and at least 1 claim for any statin (not simvastatin) from June through August 2006 (n = 26,569); matched to intervention group patients on incident use (binary indicator) and pre-expiration copayment ± $2. Pre-expiration copayment was a mean $14.57, post-expiration copayments not reported.

#### Analysis
- Bivariate and multivariate (linear regression modeling) by-group comparisons of change in MPR from pre-expiration to post-expiration periods; MPR represented any statin drug “to allow for switching within the statin class” and was measured in each period from the first fill date through the subsequent 270 days. Secondary outcomes included percentage adherent (MPR at least 80%) and elasticity (percentage change in MPR divided by percentage change in copayment). Multivariate analyses controlled for age, sex, incident statin use, chronic disease score, and pre-expiration MPR and copayments.

#### Results
- **MPR declined in both groups**: −0.17% in copayment reduction group and −1.67% in comparison group; multivariate analyses suggested 0.52% adjusted mean MPR increase in copayment reduction group and 2.02% adjusted mean MPR decrease in comparison group.
- **Increase in MPR to at least 80% occurred in 10.5% of reduction and 10.0% of comparison patients.**
- **Decrease in MPR to below 80% occurred in 12.1% of reduction and 11.3% of comparison patients.**
- **Elasticity 0.02 for reductions of $0 to $5 and −0.02 for reductions of more than $15 (i.e., a 10% decrease in copayment was associated with a 0.2 percentage point increase in MPR).**

#### Comments
- **Discontinuation rates not reported; results reflect only patients with statin use in both periods.**
- Neither post-change copayments nor counts for copayment change groups were reported, making it difficult to assess the overall magnitude of the cost-sharing change.
- **Mean pre-expiration MPRs were high (85%-89%) in both groups; results may not generalize to less adherent patient populations.**

### Zeng (2010)\(^69\)

Study of the movement of “a comprehensive list of diabetes medications” into tier 1 effective January 1, 2007; tier 1 drugs included SSB (e.g., pioglitazone, rosiglitazone/metformin, exenatide) and MSB (e.g., Amaryl as well as glimepiride). Most diabetes medications and supplies in tier 2 and “few in tier 3” were “moved … into [VBID].”

#### Sample

#### Groups
- **Intervention**: Employees and dependents of the clinic that owned the HMO (n = 71); pre-intervention copayments were $10 for generic, 30% for tier 2, and 50% for tier 3, for an overall mean of $18.80 per 30-day claim. Post-intervention copayments were $10 for tier 1 and not reported for tier 2 and tier 3, for a mean of $10.40 per 30-day claim.
- **Comparison**: Enrollees of the same HMO who were not VBID enrolled (n = 5,037, of whom 639 were selected at random for analysis); pre-intervention copayments were not entirely clear but appear to be the same structure as the intervention group’s, with a mean of $14.30 per 30-day claim. Post-intervention copayments were “unchanged” and a mean of $18.80 per 30-day claim.

#### Analysis
- Propensity-score weighted DID analysis in which each enrollee had 2 observations, one for 2006 and the other for 2007; outcomes were PDC and percentage adherent, defined as PDC of at least 80%. Propensity score was based on age, sex, mean diabetes medication copayment, insulin use, and comorbidities in 2005 measured using RxRisk categories.

#### Results
- **PDC (after propensity-score weighting) 0.88 pre-intervention in both groups; changed to 0.90 in intervention group and unchanged in comparison group, nonsignificant in multivariate analysis.**
- **Percent adherent (after propensity-score weighting) changed from 75.3% to 82.5% in intervention and from 79.1% to 78.5% in comparison group; OR of adhererence in logistic regression controlling for demographics, insulin use, and RxRisk score = 1.56, 95% confidence interval = 1.04-2.34.**
- **Percentage point change in use of TZDs + 1.3 in intervention, −0.6 in comparison group; authors noted “moderate” shift toward increased use of brand drugs in VBID group.**

#### Comments
- **Difficult to interpret without more specific information about the cost-sharing amounts and tier assignments.**
- **RxRisk category assignment used in comorbidity measurement and logistic regression may contain errors; study report indicates that 10% of study sample (mean age approximately 58 years) had cystic fibrosis.**
- **Study abstract does not mention the finding that the by-group differences in PDC change were not significant.**
- Although comparison group copayments were described as “unchanged,” they increased from pre- to post-intervention by 31%; however, the increase was less in the propensity-weighted analysis.
- N of cases in intervention group was small, and the external validity is unclear.
- **Mean pre-intervention PDCs were high (86%-88%) in both groups; results may not generalize to less adherent patient populations.**
- **Transparent reporting of pre- and post-intervention values for outcome measures.**
### Summary of Recent Observational Studies of Copayment Reductions and Medication Adherence (continued)

| Roebuck (2011) outcome | Study measured association between MPR and all-cause health care expense, not a study of copayment reduction, and there was no intervention. |

#### Sample
- Commercially insured members of 9 health plans with primary, secondary, or tertiary diagnoses on at least 2 outpatient visit claims or 1 inpatient stay or ER visit claim for any of 4 chronic conditions: CHF (n = 16,353), HTN (n = 112,757), diabetes (type 1 or type 2, n = 42,080), and dyslipidemia (n = 53,041); all were enrolled continuously from January 1, 2005, through June 30, 2008.

#### Analysis
- Linear fixed-effects modeling of panel data in which each patient contributed 3 (yearly, July through June) observations—2005/2006 through 2007/2008; results represent marginal effects. Models controlled for demographics, CCI, and time trends. MPR for each condition represented “the average of the [MPRs] for all therapeutic classes for each chronic disease, weighted by the days’ supply in each therapeutic class,” with zero (0) adherence assumed for patients with a diagnosis but no drug treatment. Adherence was defined as MPR of at least 80%, and there was no assessment of continuous MPR. Outcomes were 3 measures of annual all-cause service use: inpatient days, ER visits, outpatient physician visits; and 3 measures of all-cause cost: pharmacy, medical, and total.

#### Results
- Adherence was associated with fewer all-cause inpatient days annually (1.18 for patients with dyslipidemia, approximately 2 for patients with HTN or diabetes, 5.72 for patients with CHF).
- Marginal effect for inpatient days was greater for those aged 65 years or older (1.88 dyslipidemia, 3.41 diabetes, 3.14 HTN, 5.87 CHF).
- Associations of adherence with all-cause ER visit use (reduction of 0.01-0.04 visits annually) and outpatient physician visits (increase of about 1 visit annually for patients with CHF and less than 0.5 visits for the remaining patients) were small.
- All-cause medical services costs were lower and pharmacy costs higher for adherent patients, net annual savings estimated at $1,258 dyslipidemia, $3,576 diabetes, $3,908 HTN, $7,823 CHF.

#### Comments
- Transparent and clear report of study methods and limitations.
- Decision to assume zero adherence for patients not treated with medication is inconsistent with treatment guidelines for HTN and dyslipidemia and partially inconsistent with guidelines for type 2 diabetes.
- Results represent all-cause (not disease-specific) utilization, and there was no assessment of whether health care utilization could reasonably be clinically attributable to medication adherence or nonadherence; sole reliance on fixed-effects modeling to establish causality.
- As the authors acknowledge, fixed-effects modeling does not adjust for confounders that change during the study period, such as a patient’s decision to improve both medication adherence and other health-related behaviors simultaneously (i.e. new “healthy adherence” behaviors).
- MPR denominator was apparently not adjusted for inpatient days when patients would be receiving drugs from the hospital or nursing home (not measured with pharmacy claims).
- Analyses and interpretation did not account for possibility that medications could have been obtained through community pharmacy generic drug discount programs during the study period (July 2005 through June 2008).
- Although authors suggest that findings have potential implications for VBID, association of copayment with adherence or utilization was not assessed.

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*All information reported in this table reflects both the study reports and any online appendices, which can be accessed using hyperlinks in the study reports. No study of VBID assessed changes in GDR, generic drug utilization FMPM, or payers’ costs.

*This assessment may be an error because it sounds implausible; however, text indicates: “Users of tier 1 and tier 2 medications in the control group . . . had no changes in their copayment of $10 during the study period.”

*See Mahoney (2005). 77

*For ARBs and cholesterol absorption inhibitors (i.e., containing ezetimibe), which were 100% brand, the average pre-intervention copayment reported in the methodological appendix exceeds the top of the pre-intervention brand copayment range reported in the text for reasons that are not clear from the study report.

*The time period for measurement of the GDR covariate was not clear in the study report. The description appears in the methodological appendix in a section describing “pre-period medication burden;” however, the description of the variable states that the authors “controlled for the [GDR] . . . for the immediate financial benefit of the [VBID] program by switching from brand to generic medications.”

*List of drugs for Zeng et al. VBID program is in a study appendix at http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i6_Zeng.asp. Our assessment that all drugs in the study appendix were tier 1 may be inaccurate, but the text refers to them as tier 1 medications and the study appendix does not specify tier status. Mean copayments shown in this Appendix are per 30-day supply before propensity score weighting. Propensity-score weighted copayments for the intervention and comparison groups were, respectively, $15.30 and $14.60 pre-intervention and $10.10 and $15.10 post-intervention.

*ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BCBS-NC = Blue Cross Blue Shield of North Carolina; CCB = calcium channel blocker; CCI = Charlson Comorbidity Index; CHF = congestive heart failure; DC = discontinuation; DID = difference-in-difference; DMP = disease management program; ER = emergency room; EPG = Episode Risk Groups classification model; GDR = generic dispensing ratio; GEE = generalized estimating equation; GLM = generalized linear model; Hb = hemoglobin; HMO = health maintenance organization; HTN = hypertension; LABA = long-acting inhaled beta agonist; MPR = medication possession ratio; NA = not applicable; OAD = oral antidiabetic drug; OR = odds ratio; PDC = proportion (or percentage) of days covered; PBM = pharmacy benefits management company; PMPM = per member per month; Q = quarter; ROI = return on investment; RTM = regression to the mean; SABA = short-acting beta agonist; SSB = single-source brand; TZD = thiazolidinedione; VBID = value-based insurance design (implemented as drug copayment reduction in these studies); vs = versus.
Case Report of Specialty Pharmacy
Management of Hemophilia

Today it is generally understood that a disproportionately high share of medical claims are attributable to a small minority of patients with rare chronic disease states. Hemophilia is considered to be one of the most expensive chronic conditions currently being treated by any health care system. Antihemophilic medications have been estimated to account for greater than 90% of the total costs of hemophilia care. The annual cost of medications to treat a patient with severe hemophilia may exceed $300,000 per year.

Adherence to antihemophilic medications has been defined as infusing 75%-80% of prescribed doses. Noncompliance with these medications can contribute not only to poor outcomes, but also to significant costs associated with excess inventory. An average adult with severe hemophilia that is infusing 3,000 units 3 times per week as prophylaxis can accumulate 72,000 units of unused factor over the course of 1 year by missing 2 doses per month, or possible waste valued at $96,480 in antihemophilia drug cost (priced at 80% of average wholesale price [AWP]) in January 2011.

Our specialty pharmacy developed a disease management program for hemophilia modeled after the results from the Haemophilia Utilization Group Study (HUGS). The program is designed to provide intensive patient management to improve clinical outcomes and to lower hemophilia-related health care costs. Our program was adopted by a 1.4-million member West Coast health plan in October of 2009 to serve its hemophilia population. At the initiation of this outcomes program, 54 unique patients were identified as potential candidates for the program. Each patient case was carefully evaluated to ensure appropriate utilization of health care resources and to achieve maximum benefits for the health plan. All patients with severe disease were selected as candidates. Other variables included: number of bleeds per year, age, comorbid conditions, annual factor consumption, and number of target joints. At the end of this screening period, 37 of the 54 patients were identified as candidates based on disease severity. Patient participation was optional, and 24 of the 37 patients (65%) elected to participate in our disease management program.

One of the 24 enrolled patients was a 21-year-old male with severe hemophilia A. His disease was complicated, with multiple target joints, obesity, noncompliance, and a general lack of knowledge regarding his disease and treatment. He had a treatment regimen consisting of clotting factor Kogenate FS as primary prophylaxis and as needed for bleeding episodes. His social situation was problematic including a dual residence, unemployment, and a sedentary lifestyle. He did not use alcohol or illicit drugs. On admission to the program, the patient completed a detailed telephonic assessment by a hemophilia specialist and hemophilia self management questionnaire. We then began the disease benchmarking period where it became apparent that his disease severity, bleeding history and utilization were not congruent. This patient averaged 1.75 bleeds per month into his target joints which included both knees and elbows. A home visit by a hemophilia nurse specialist was scheduled to assess the patient.

On the day of the home visit, the patient presented with a notably swollen and painful right knee, bruised and swollen knuckles on both hands, and a recovering bleed in his left forearm. He also presented with limited range of motion in his right knee and left elbow. The patient admitted to discontinuing his primary prophylaxis and treating only the most severe bleeds; he believed that he could over time desensitize his body to the exogenously administered clotting factor, reducing his requirements and possibly the number of bleeds. Additionally, the patient treated his severe bleeds with a single dose of double the prescribed units. He assumed this would stop the bleed quickly and prevent its reoccurrence. This patient interview solidified our initial assessment of a lack of disease knowledge and noncompliance. The patient had an on-hand inventory of over 45,000 units and another 30,000 units at his alternate residence; this was nearly a 2-month supply of clotting factor at an estimated drug cost of $100,500 (priced at 80% of AWP).

The patient was receptive to the hemophilia nurse specialist and was eager to ask questions about his condition. He received education focusing on his disease severity, the mechanisms of joint destruction from bleeds, and the consequences of treatment delays and noncompliance to his prophylaxis regimen. Visual aids were used throughout this process. A treatment plan was developed and discussed with the patient, and he agreed to resume his prophylaxis treatment. He verbalized satisfaction with the therapy management program and agreed to continue enrollment. As part of the disease management program, the patient receives monthly telephonic assessment calls to capture self-reported bleeding episodes and other lifestyle indicators. Three months after the nurse visit, the patient demonstrated compliance with his treatment plan. The patient's telephonic self-assessments indicated an increased level of compliance with his prophylaxis that is also confirmed by his factor utilization history. Bleeding into his target joints was reduced to 1 episode in the 3-month post intervention period. The patient also reported wearing his medical alert identifier. In addition to improved care management, the intervention with the nurse visit reduced the average monthly hemophilia drug cost by $6,490, from $225,832 in the 5 months before the intervention to $193,382 in the 5 months after the intervention.

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References

Online Drug Pricing Tools Deserve More Attention
We read with great interest the article “Evaluation of health plan member use of an online prescription drug price comparison tool” by Carroll and colleagues.1 The research shows how drug information tools are being used by consumers. We (DestinationRx) have been creating innovative drug and plan comparison tools for more than a decade. In the spirit of disclosure, DestinationRx’s Drug Compare and its predecessor Rxaminer are tools that compete with RxEOB, the online tool that was the subject of the study by Carroll and colleagues. We make available drug pricing tools to more than 100 million Americans, and as such we have comments on 3 points that your readers may find helpful.

First, while we do have a consumer version of Drug Compare that shows drug costs based on estimated community pharmacy prices, the vast majority of our users are accessing plan- and/or PBM-sponsored sites. These sites come loaded with member-specific benefit information including formulary, utilization management restrictions, drug tiers, member copay and pharmacy-specific price comparisons. Second, Carroll and colleagues found that approximately 5.2% of families in a large integrated health plan who used the pharmacy benefit throughout the year used the MyPharmacyTools (RxEOB) online pricing tool in a 12-month period from July 2007 through June 2008. We found that 5.8% (n = 4,087) of approximately 71,000 employees enrolled in health savings accounts used our Drug Compare online tool in a 9-month study period through October 2010.2

Third, we agree that drug pricing is of paramount concern to end-users. We believe that filtering the alternatives displayed based on comparative efficacy leads to even greater adoption and behavior change. It is for this reason that we always emphasize that beyond pricing it is imperative to display therapeutic alternatives of similar efficacy.

Our experience shows that drug costs are still one of the most controllable of all health care expenditures, and we are glad to see drug information tools getting the visibility they deserve for allowing members to better manage their health care and drug spend.

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Disclosures
Grunewald is employed by DestinationRx.

References