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Renowned plastic surgeon Daniel Man, MD, has been chosen as the cover artist for JMCP’s annual issue featuring an artist with a pharmaceutical or medical background. It is not too surprising to hear that a plastic surgeon is also an artist—after all, plastic surgeons “sculpt” many parts of the human body. What is surprising, however, is the remarkable success that Man has achieved in both sculpture and painting in a fairly short time. A practicing artist only since 1995, he has been called a “Renaissance Man” by Plastic Surgery Products magazine.

Man was born in Israel in 1946 and grew up in the city of Kfar Saba in central Israel’s coastal plain. The son of general surgeon Boris Man, he attended the best schools even though the family had little money. “Physicians in Israel at that time were making less than bus drivers,” Man says.

As a child, he learned to appreciate fine art from his mother Lusia, an art aficionado. Man used to look for olive-tree wood scraps to use as raw material for sculptures that he gave as gifts to family and friends. When he was a bit older, he learned about a medical specialty called plastic surgery that would be a good field for someone skilled with his hands. He eventually decided to pursue the specialty.

Man earned his medical degree from Sachler Medical School at Tel Aviv University and became a physician in the Israeli army. Toward the end of his military service, he traveled to New York, and the trip sparked his interest in furthering his medical studies in America. Man did his residencies at hospitals in New York and Delaware from 1974 to 1978. His plastic surgery residency was done afterward at the University of Louisville, Kentucky.

In 1981, Man received his board certification in plastic and reconstructive surgery from the American Board of Plastic Surgery. He has been in private practice in Boca Raton, Florida, ever since. Because Man likes to surround himself with beauty and art, his medical office also serves as an art gallery; it is filled with his paintings and sculptures.

Described as a “doctor with heart,” Man received the Humanitarian of the Year award in April 2001 from the Palm Beach County Division of Victim Services for his pro bono plastic surgery work for victims of domestic abuse. In addition, some of his paintings and lithographs have been sold to raise funds for abused women and children.

During the mid-1990s, it was science that inspired Man to renew his interest in art. “I knew that learning how to draw and paint would improve my plastic surgery skills,” he says. “In 1995, I started from scratch. I looked at art in books and attended art festivals.” He decided to take a few art classes, but things did not go too well at first. “I had been away from painting and sculpting too long and needed help. I went to see an art exhibit and met an artist there—Michel Pellus—who is well known for his realistic style,” Man says. “I told him that I was very impressed with his work and asked him to teach me to paint.” Pellus invited Man to his studio once a week for art lessons. The physician’s painting skills soon improved, and a year later, Pellus said that he had nothing left to teach his devoted student.

Man’s enchanting acrylic painting, Woman in Headdress, appears in his book The New Art of Man: Faces of Plastic Surgery. This portrait of a green-eyed beauty depicts one of Man’s former patients. He painted her with the classic features of a Greek goddess; she looks radiant in her multicolored blouse and matching headdress.

One of Man’s most impressive paintings, The Handshake (1997), was based on a famous photo taken at the signing of the Oslo Accords on September 13, 1993. In the picture, Yitzhak Rabin and Yasser Arafat shake hands as President Bill Clinton looks on. Man wrote a letter to Clinton, offering to donate his painting in honor of the historic effort to achieve peace. The White House accepted his offer, and The Handshake hung on the wall outside the Oval Office for 3 years.

Besides being a noted artist and author, Man is also an educator and inventor. Among his many innovations is the minimally invasive “SpaceLift,” an improved method of facelift surgery. The SpaceLift helps patients achieve a more natural-looking appearance by using fillers to mitigate surgery and shorter incisions that are hidden within the curve of the ear.

To learn more about this fascinating physician/artist, visit his Web sites. Man’s plastic surgery site is www.drman.com and his artistic site is www.theartofman.com. There you will find an online gallery of his art, information about commissions and exhibitions, and much more.

Sheila Macho
Cover Editor

COVER CREDIT

SOURCE
Interview with the artist.
ABSTRACT

BACKGROUND: As new treatment options for chronic hepatitis B virus (HBV) become available, evaluations of cost-effectiveness become important. Entecavir is a deoxyguanosine nucleoside analogue approved by the U.S. Food and Drug Administration in March 2005 for HBV infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (alanine aminotransferase or aspartate aminotransferase) or histologically active disease. Entecavir has demonstrated greater suppression of viral replication compared with lamivudine, but also has a relatively higher drug acquisition cost in the United States.

OBJECTIVE: To estimate the long-term health and economic impact of treating HBV with entecavir versus lamivudine in patients who are positive for hepatitis B e antigen (HBeAg) based on the efficacy and safety results of the Phase 3, double-blind, randomized controlled trial, Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD).

METHODS: A decision tree model was developed to evaluate the cost-effectiveness of entecavir compared with lamivudine in suppressing HBV DNA to an undetectable level. Risks for compensated cirrhosis (CC), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC) were derived from the published Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV, 2006) study, a longitudinal (mean follow-up: 11.4 years) cohort study of community residents who were seropositive for the hepatitis B surface antigen; 85% of REVEAL-HBV participants were HBeAg-negative. To estimate future risks of CC, DC, and HCC, the REVEAL-HBV study’s multivariate-adjusted relative risks of CC, DC, and HCC for 5 HBV DNA (viral load level) categories were applied to posttreatment HBV DNA levels obtained from the BEHoLD trial of 709 HBeAg-positive HBV patients treated with entecavir (n = 354) or lamivudine (n = 355). Entecavir and lamivudine were assigned annual costs of $7,365 and $2,604, respectively, based on the wholesale acquisition cost. Life expectancy for DC and HCC was estimated by the declining exponential approximation of life expectancy method. Other model parameter values, such as utilities and event medical costs, were derived from published sources. The joint uncertainty of projected event time distribution and treatment failure rates beyond the trial period were considered using probabilistic sensitivity analyses (PSA) with 1,000 replicates. The analytic perspective was that of a U.S. third-party payer responsible for all direct healthcare expenditures.

RESULTS: In the BEHoLD clinical trial (AI463022), subjects were predominantly male (75%), Asian (57%), or white (40%) with a mean age of 35 years. Entecavir was superior to lamivudine in the proportion of subjects who achieved undetectable HBV DNA (<300 copies per mL) by polymerase-chain reaction assay at week 48 (69.1% vs. 39.8%, respectively) (P<0.001). In the REVEAL-HBV study after statistical adjustment for age, gender, cigarette smoking, and alcohol consumption, rates of CC, DC, and HCC were associated with higher HBV DNA levels (e.g., compared with the reference category [<300 copies per mL], adjusted hazard ratios for HCC were 1.2, 2.9, 9.5, and 15.2 for serum HBV DNA levels of 300–9,999, 10,000–99,999, 100,000–999,999, and ≥1 million copies per mL, respectively). In the reference case, for a hypothetical cohort of 1,000 HBV patients aged 35 years, 52 weeks of entecavir treatment compared with lamivudine treatment avoided 71 cases of CC, 8 DC cases, and 42 HCC cases within 10 years, resulting in a 0.728 quality-adjusted life-year (QALY) gain at an incremental cost of $2,350, with a 3% annual discount. The incremental cost of using entecavir was $3,230 per QALY gained (95% confidence interval [CI], $2,312–$4,528), with 99.3% of PSA-derived estimates below $5,000 per QALY. Results were robust and most sensitive to efficacy, drug cost, and treatment duration.

CONCLUSIONS: Assuming that (1) the efficacy of entecavir after 1 year is sustainable and (2) liver disease risk levels from the REVEAL-HBV study population (a primarily HBeAg-negative group) adequately represent risk for a treated HBeAg-positive patient group, entecavir given for up to 10 years would be highly cost-effective in HBeAg-positive patients.

What is already known about this subject

• Chronic hepatitis B virus (HBV) infection is a complex disease, with 15%-40% of infected persons progressing to severe liver disease including cirrhosis, liver failure, and liver cancer. Manifestations of HBV usually occur late in life, resulting in substantial life years lost as well as a negative economic impact among individuals during the most productive decades of life. About 1.25 million HBV-infected people live in the United States, and most of the chronically infected persons in the United States are of Asian descent.

• Current analyses of the cost-effectiveness of HBV drugs have been based on a disease progression paradigm focused heavily on the ability to achieve hepatitis B e antigen (HBeAg) seroconversion (to HBeAg-negative status and HBe antibody) following treatment intervention. However, recent evidence suggests that the incidence of liver cirrhosis and hepatocellular carcinoma (HCC), as well as the risk of progression to liver cirrhosis and HCC in HBV patients, are strongly linked to the level of circulating virus independent of HBeAg status. A cost-effectiveness analysis of HBV therapies based on this paradigm of disease progression to cirrhosis and HCC does not exist in the literature.

What this study adds

• This study is the first to evaluate the cost-effectiveness of HBV antiviral therapy based on an ability to suppress viral replication. Our decision tree model indicates that initiating therapy in HBeAg-positive HBV patients with entecavir (both short-term and long-term use) would be very cost-effective at $3,176 per quality-adjusted life-year (QALY) gained (93% CI, $2,202–$4,482), with 99.3% of PSA-derived estimates below $5,000 per QALY.

Note: Two commentaries and an editorial on the subject of this article appear on pages 61-64, 65-69, and 83-85 of this issue.
Chronic hepatitis B (CHB) virus infection is defined by the presence of hepatitis B viral surface antigen (HBsAg) in the blood for >6 months. Besides HBsAg, other antigens are detected in the blood, such as hepatitis B e antigen (HBeAg). However, HBeAg may be absent after several decades of infection as hepatitis B mutants, which do not secrete HBeAg, replace the hepatitis B wild types. HBeAg-negative CHB infection is defined by no detectable HBeAg, but evidence of viral replication as indicated by the presence of deoxyribonucleic acid (HBV DNA) in the blood.

Both HBeAg-positive and HBeAg-negative infection can potentially result in progressive liver disease and affect about 350 million people worldwide, 1.25 million of whom live in the United States. Hepatitis B virus (HBV) patients are at increased risk of developing liver cirrhosis and hepatocellular carcinoma (HCC). Although most patients will not develop hepatic complications from CHB, 15%-40% will eventually develop serious sequelae during their lifetime.

Even in countries such as the United States where the prevalence of HBV is relatively low (<1% of the population), the burden of illness and health care costs associated with the disease are substantial. In the United States, health costs associated with HBV were estimated at $500 million annually (expressed in 1997 U.S. dollars). Other studies have found that the average cost per hospitalization for a HBV patient with cirrhosis is $14,063 and that the cost of a liver transplant is an estimated $89,076 (expressed in 1999 U.S. dollars). In determining the value of new medicines to treat HBV, drug acquisition costs must be balanced against the expected benefits in future morbidity, mortality, and costs avoided from disease progression.

Six drugs are currently approved for treating CHB virus infection in the United States. Interferons, including alfa-2b, recombinant (Intron-A), and peginterferon alfa-2a (Pegasys), are associated with several side effects and cannot be used in patients with decompensated liver disease. Additionally, many patients cannot tolerate the adverse events associated with interferons, resulting in treatment discontinuation. Lamivudine (Epivir) was the first oral antiviral agent approved by the U.S. Food and Drug Administration (FDA) for HBV in November 1995, and provided a well-tolerated, effective option for patients. However, the occurrence of drug-resistant HBV mutants became a major limitation with lamivudine therapy.

Adefovir dipivoxil (Hepsera) was approved by the FDA for HBV in September 2002. Adefovir is generally well tolerated and effective against lamivudine-resistant hepatitis B strains. However, with adefovir therapy, only about 21% of HBeAg-positive patients and 50% of HBeAg-negative patients achieve a viral load <300 copies per mL after 1 year of therapy, making adefovir the nucleoside analogue with the slowest viral kinetics of the approved agents. Additionally, the level of viral response after 1 year of adefovir therapy predicts the risk of future resistance, and the 5-year risk of resistance with adefovir therapy is 29%.

Entecavir (Baraclude), a deoxyguanine nucleoside analogue, is a selective inhibitor of the replication of HBV. Entecavir was approved by the FDA in March 2005 and is currently the most potent antiviral agent for HBV treatment, suppressing viral replication to <300 copies per mL in approximately 87% of treatment-naive patients after 96 weeks of therapy. Throughout 96 weeks, no patient experienced a virologic breakthrough due to entecavir resistance. Telbivudine (Tyzeka) is the most recent antiviral drug for treating HBV, approved by the FDA in October 2006. Based on registrational studies, telbivudine's initial antiviral effect is better than that of lamivudine; however, its utility is limited by viral resistance that continues even through the second year of therapy. No head-to-head clinical trials have investigated the safety and efficacy of telbivudine versus entecavir.

Our study aims to evaluate the cost-effectiveness of entecavir compared with lamivudine in chronic HBeAg-positive infection by using a statistical model that applied (1) community cohort study data on risks of HBV disease sequelae to (2) randomized clinical trial data on outcomes for HBV-treated patients.

Methods

Overview of Modeling Structure
A decision tree model with a fixed 10-year window was developed to evaluate the cost-effectiveness of initiating therapy with entecavir in nucleos(t)ide-naive HBeAg-positive HBV patients compared with a strategy of initiating therapy with lamivudine and adding adefovir to rescue patients once they developed drug resistance. The model was based on the ability of each strategy to achieve HBV DNA suppression to an undetectable level. An illustrative conceptual model framework is shown in Figure 1.

A hypothetical cohort of 1,000 HBV patients received either lamivudine or entecavir at model entry. Because patients might develop viral resistance with continued drug use or experience viral rebound after treatment cessation, their HBV DNA values were updated annually to incorporate first-year trial efficacy results as well as the impacts from subsequent development of viral resistance or viral rebound after treatment cessation. The decision model consisted of 5 disease stages: CHB (HBV without cirrhosis and HCC as entry point), compensated cirrhosis, decompensated cirrhosis, HCC, and death. Based on the pattern and rates of observed liver complications from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study, the majority of patients developing HCC were from the cirrhosis health state, but the decision model was modified to allow some HBV patients to progress to a HCC health state directly without passing through the compensated cirrhosis health state. However, all patients experiencing decompensated cirrhosis had to progress through the compensated cirrhosis health state. The base case model assumed treatment for 1 year, and sensitivity analyses allowed drug treatment for up to 10 years. Any
Evaluation of the Cost-Effectiveness of Entecavir Versus Lamivudine in Hepatitis BeAg-Positive Chronic Hepatitis B Patients

**FIGURE 1** Illustrative Model Diagram of 10-Year Disease Progression

This modified tree model projects disease risks based on current HBV DNA levels.

The entecavir arm follows the same pathways as the lamivudine arm.

CHB = chronic hepatitis B; CC = compensated cirrhosis; DC = decompensated cirrhosis; HBV = hepatitis B virus; HCC = hepatocellular carcinoma.
patient developing resistance was rescued by a strategy of adding adefovir to the current drug therapy. Data on treatment efficacy were obtained from a randomized, controlled, double-blind, Phase 3 registrational trial (Benefits of Entecavir for Hepatitis B Liver Disease [BEHoLD]). Using the week-48 HBV DNA data from this trial, future disease progression was projected based on observed rates from the aforementioned REVEAL-HBV study. Progressions to compensated cirrhosis (DC) and hepatocellular carcinoma (HCC) were evaluated. Cox proportional hazards models were used with adjustment for gender, age, and habits of cigarette smoking and alcohol drinking.

### TABLE 1 Reference Case Model Parameters, Inputs, Data Sources, and Methodology

<table>
<thead>
<tr>
<th>Estimated relative risk by serum HBV DNA levels (copies/mL)</th>
<th>Entecavir 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>Source</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 300 (undetectable)</td>
<td>1.0 for cirrhosis, DC, and HCC</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,28,29&lt;/sup&gt;</td>
<td>Cox proportional hazards models were used with adjustment for gender, age, and habits of cigarette smoking and alcohol drinking.</td>
</tr>
<tr>
<td>300-9,999</td>
<td>1.4 for cirrhosis (2.7 for DC), 1.2 for HCC</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,28,29&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>2.5 for cirrhosis (2.7 for DC), 2.9 for HCC</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,28,29&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>100,000-999,999</td>
<td>5.9 for cirrhosis (5.9 for DC), 9.5 for HCC</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,28,29&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>≥1 million</td>
<td>9.8 for cirrhosis (19.3 for DC), 15.2 for HCC</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,28,29&lt;/sup&gt;</td>
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</tbody>
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<thead>
<tr>
<th>Proportion of patients with HBV DNA levels (copies/mL)</th>
<th>Entecavir 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>Source</th>
<th>Methodology</th>
</tr>
</thead>
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<tr>
<td>&lt; 300 (undetectable)</td>
<td>69.1%</td>
<td>39.8%</td>
<td>BEHoLD&lt;sup&gt;27&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>300-9,999</td>
<td>24.7%</td>
<td>18.2%</td>
<td>BEHoLD&lt;sup&gt;27&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>10,000-99,999</td>
<td>4.4%</td>
<td>11.7%</td>
<td>BEHoLD&lt;sup&gt;27&lt;/sup&gt;</td>
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<tr>
<td>100,000-999,999</td>
<td>0.6%</td>
<td>9.3%</td>
<td>BEHoLD&lt;sup&gt;27&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>≥1 million</td>
<td>1.2%</td>
<td>21.0%</td>
<td>BEHoLD&lt;sup&gt;27&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annual incidence rates with undetectable HBV DNA</th>
<th>Entecavir 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>Source</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>0.34%</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,26&lt;/sup&gt;</td>
<td>Estimated based on 873 patients with undetectable HBV DNA at study entry.</td>
</tr>
<tr>
<td>DC</td>
<td>0.02%</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,26&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>0.11%</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,26&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annual mortality rate</th>
<th>Entecavir 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>Source</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC</td>
<td>14.4%</td>
<td></td>
<td>Reference 33</td>
<td>Life expectancy estimated based on the DEALE method.</td>
</tr>
<tr>
<td>HCC</td>
<td>23.3%</td>
<td></td>
<td>Reference 32</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average time to event from study entry (years)</th>
<th>Entecavir 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>Source</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>8</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,26&lt;/sup&gt;</td>
<td>Estimated based on actual patient-level data.</td>
</tr>
<tr>
<td>DC</td>
<td>9</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,26&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>7</td>
<td></td>
<td>REVEAL-HBV&lt;sup&gt;25,26&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annual medical costs</th>
<th>Entecavir 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>Source</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>$1,130</td>
<td></td>
<td>Reference 36</td>
<td>Reimbursed cost (not provider-submitted charges) from U.S. third-party payers.</td>
</tr>
<tr>
<td>DC</td>
<td>$15,095</td>
<td></td>
<td>Reference 37</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>$9,923</td>
<td></td>
<td>Reference 37</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Utilities</th>
<th>Entecavir 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>Source</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHB</td>
<td>0.81</td>
<td></td>
<td>Reference 34</td>
<td>Survey of a U.S. sample of 100 uninfected individuals using standard gamble method.</td>
</tr>
<tr>
<td>CC</td>
<td>0.82</td>
<td></td>
<td>Reference 34</td>
<td></td>
</tr>
<tr>
<td>DC</td>
<td>0.36</td>
<td></td>
<td>Reference 34</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>0.41</td>
<td></td>
<td>Reference 34</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study drugs</th>
<th>Entecavir 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>Source</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily cost/patient</td>
<td>$20.52</td>
<td>$7.61</td>
<td>Reference 35</td>
<td>Officially published figures.</td>
</tr>
<tr>
<td>Actual days of use/patient/year</td>
<td>359</td>
<td>342</td>
<td>BEHoLD&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Estimated based on number of days of drug use recorded in the trial.</td>
</tr>
</tbody>
</table>

All costs are expressed in 2006 U.S. dollars.

BEHoLD = Benefits of Entecavir for Hepatitis B Liver Disease; CHB = chronic hepatitis B; CC = compensated cirrhosis; DEALE = declining exponential approximation of life expectancy; DC = decompensated cirrhosis; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; REVEAL-HBV = Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus.
cirrhosis, decompensated cirrhosis, and HCC were modeled separately, and we subsequently estimated the cost consequences and life year impacts from the modeled progression. All model assumptions and data inputs used in the reference case analysis are presented in Table 1.

This decision tree model structure was chosen instead of a state transition or patient-level simulation model to capture chronic disease progression because of lack of data access and reliable details for estimating the disease state transition rates for HBV DNA levels over time. The decision tree model with a fixed-time window made our model as simple as possible while still retaining sufficient structure to specify the assumed relationship between inputs and outcomes.

The study perspective was that of a U.S. third-party payer responsible for all direct health care expenditures. The cost-effectiveness of entecavir compared with lamivudine was expressed as the incremental cost per life-year gained or quality-adjusted life-years (QALYs) gained. Indirect medical costs and lost productivity were not included in the analyses. A 3% discount rate was applied to both costs and life-year projections beyond the model base year.

Statistical software (SAS, SAS Institute, Cary, NC) was used for patient-level data analyses, and an Excel spreadsheet-based model using Visual Basic for Applications (Microsoft Corporation, Redmond, WA) was created for all modeling and simulation executions.

**Efficacy and Safety Data From the BEHoLD Phase 3 Clinical Trial**

We obtained efficacy and safety data from a randomized Phase 3 trial of HBeAg-positive subjects (BEHoLD-A1463022 trial). 27 Briefly, this was a randomized, double-blind, double-dummy study of entecavir 0.5 mg given once daily for 52 weeks compared with lamivudine 100 mg once daily. A total of 709 eligible subjects were randomized (1:1) to receive either entecavir (n=354) or lamivudine (n=355). Subjects who had previously received a nucleoside analogue active against hepatitis B, interferon alfa, or thymosin alfa within 24 weeks prior to randomization were excluded. Any subject with a prior exposure to lamivudine lasting >12 weeks was also excluded. Response to treatment was assessed based on a primary endpoint of histologic improvement and other secondary efficacy endpoints, including our primary study endpoint of interest—serum HBV DNA by polymerase-chain reaction (PCR) assay at the week-48 visit.

Entecavir was well tolerated, with a safety profile comparable with that of lamivudine 100 mg. The most frequent adverse events in the entecavir group were headache, upper respiratory tract infection, nasopharyngitis, upper abdominal pain, fatigue, and pyrexia, all of which occurred with comparable frequency in the lamivudine group. As a result, the risk and costs of drug-related adverse events were not included in the analysis.

All intent-to-treat patients were considered in this analysis. All patients with missing HBV DNA data at either baseline or week 48 (n=45) were treated as missing and excluded in the primary analyses. An alternative imputation method, using Last Observation Carried Forward or treating noncompleters as failures, was also implemented, but it had minimal impact on our modeling results. The study period ranged from a patient’s randomization to the end of blinded treatment or week 48, whichever came first.

**Data on Disease Progression Risk**

Data on risk of disease progression based on the level of viral load was derived from the REVEAL-HBV study. 25,26 This prospective cohort study was conducted as part of a community-based cancer screening program in Taiwan and designed to evaluate the relationship between baseline (cohort entry) risk factors and progression to cirrhosis and HCC.

In brief, of 4,115 REVEAL-HBV participants who were HBsAg-seropositive, free of HCC at cohort entry, and followed until June 30, 2004, 3,653 participants (88.8%) were determined to be seronegative for anti-hepatitis C virus (HCV) antibody and were thus included in the analyses of cirrhosis and HCC risk in HBV patients. During a mean follow-up time of 11.4 years and 41,779 person-years, 365 subjects (10.0%) were newly diagnosed with cirrhosis, 31 of whom (0.8%) were determined to have decompensated cirrhosis events; there were 164 incident cases of HCC (4.5%). Adjusted relative risks for liver cirrhosis and HCC for each of 5 defined serum HBV DNA levels were estimated using Cox proportional hazards models, with adjustment for gender, age, and habits of cigarette smoking and alcohol drinking. 25,28

Two steps were followed to apply the REVEAL-HBV results to the 709 subjects from the BEHoLD randomized clinical trial to project future events over a 10-year period. First, everyone with a week-48 posttreatment HBV DNA level <300 copies per mL was assigned the baseline event rate for participants with undetectable viral loads observed from the REVEAL-HBV cohort study. The risks of liver events for subjects with HBV DNA in the higher categories were then estimated based on the adjusted hazard ratio associated with that viral load category in the REVEAL-HBV study cohort. To stratify all cirrhosis events into compensated and decompensated cirrhosis so as to assign respective medical costs and QALYs, we further developed a submodel for predicting decompensated cirrhosis, and then subtracted this predicted number from the total cirrhosis estimate to derive the number of compensated cirrhosis events. 29

**Life Year Gain and Utility Estimates**

Age- and gender-specific life expectancy estimates for HBV and compensated cirrhosis were based on data from National Vital Statistics Reports. 30 Life expectancy for decompensated cirrhosis or HCC was estimated based on the declining exponential
approximation of life method: inverse of annual event mortality.\textsuperscript{31} Annual mortality was set at 23.3\% for HCC\textsuperscript{32} and 14.4\% for decompensated cirrhosis.\textsuperscript{33} To avoid double-counting life years lost for those patients with multiple events, we assumed that (1) all patients with decompensated cirrhosis had a prior compensated cirrhosis, and 72\% of patients with HCC had a prior compensated cirrhosis, and (2) if patients had both HCC and compensated cirrhosis or both decompensated cirrhosis and compensated cirrhosis, only life expectancy for HCC or decompensated cirrhosis was assigned. These assumptions were based on the final REVEAL-HBV study sample, in which all patients with decompensated cirrhosis had prior compensated cirrhosis, and 72\% of patients with HCC had prior compensated cirrhosis, but no one was observed to experience both decompensated cirrhosis and HCC.

All trial patients were assigned a baseline utility of 0.81 at entry, meaning that 1 year of life in a person with HBV would be equivalent to 0.81 years of healthy life, and faced a sudden decline in the utility value—in other words, a tariff—as they developed liver complications.\textsuperscript{34} To adjust for the health-related quality of life associated with different health states, the relative value, or utility, of each health state was rated compared with a year in perfect health. We used the ratings of HBV-associated health states elicited from a representative sample of 100 uninfected individuals in the United States using a visual analogue scale and weighted using the standard gamble method.\textsuperscript{34} In this study, probability wheels with 2-color pie charts for the relative probabilities of perfect health and death were used as props for the standard gamble, and a feeling thermometer was used for the visual analogue scale. As a result, we assigned an estimated utility weight of 0.82 for compensated cirrhosis, 0.36 for decompensated cirrhosis, and 0.41 for HCC (Table 1).

Cost Estimates
Two cost components were considered in the analyses: study drug costs and medical costs of HBV-related complications. The medical component of the Consumer Price Index (2006 Bureau of Labor Statistics data) was used to adjust all costs to 2006 values.

In the base case analysis, it was assumed that the duration of drug treatment was 1 year; we also considered longer-term drug treatment in the sensitivity analyses. Drug compliance was estimated based on the actual usage of study drugs recorded on the clinical trial Case Report Forms. Total costs of study drugs were estimated by the wholesale acquisition cost (WAC) per day multiplied by the mean number of days of drug use (359 for entecavir, 342 for lamivudine) observed in the trial.\textsuperscript{35} Annual drug costs were $7,365 for entecavir 0.5 mg and $2,604 for lamivudine 100 mg.

Annual medical costs updated to 2006 U.S. dollars were $1,130 for compensated cirrhosis,\textsuperscript{36} $15,095 for decompensated cirrhosis, and $9,923 for HCC.\textsuperscript{37} The annual medical cost was applied to a patient from the time an event occurred until that patient died. Costs of clinical trial outpatient physician visits and laboratory tests were excluded from cost estimates because we assumed that they would be equivalent in both groups.

Modeling Assumptions
In the REVEAL-HBV cohort, the average times to event from study entry were 8 years for compensated cirrhosis, 9 years for decompensated cirrhosis, and 7 years for HCC, with times ranging from 1 to 14 years. To appropriately discount the subsequent medical costs and life years lost after all of these events had occurred, in the reference case analysis we deterministically assigned these averages (at 8, 9, and 10 years) to the trial patients who later developed a compensated cirrhosis, decompensated cirrhosis or HCC event during the follow-up period, while we also modeled time to event probabilistically later in the sensitivity analyses.

Distributions of subjects to different HBV DNA levels beyond the first year after entecavir or lamivudine treatment cessation were assumed based on HBV DNA data observed at week-24 postdosing in those BEHoLD patients with a protocol-defined “response” (defined as HBV DNA <0.7 MEq per mL and loss of HBeAg at week 48). This was the only and best data source available to allow us to estimate viral rebound rates for both entecavir and lamivudine. This assumption is essential because viral rebound is an important phenomenon accompanying cessation of therapy, and rebound will occur in a significant proportion of patients. For entecavir, 37\% had <300 copies per mL, 40\% had between 300 and 10^4 copies per mL, 11\% had between 10^4 and 10^5 copies per mL, 1\% had between 10^5 and 10^6 copies per mL, and 11\% had >10^6 copies per mL. For lamivudine, these percentages were 34\%, 26\%, 12\%, 5\%, and 23\%, respectively. The number of events was first projected based on the observed first-year HBV DNA data and then repeated for each year based on rebound-adjusted viral data from years 2-10. An average of these projections was used for our final estimate of the number of liver cirrhosis or HCC events.

Sensitivity Analyses
To investigate the robustness of the model findings, we ran univariate sensitivity analyses (with a change of ±10\% for continuous variables and use of the closest alternative category for categorical variables) on the following variables: age, gender, discount rate, efficacy, drug price, and event medical costs. We also ran sensitivity analyses on the 4 input parameters based on their available alternative values: utility, hepatic flares (defined as an elevation in serum alanine aminotransferase [ALT] to a level >2 times the patient’s stable baseline and >10 times the upper limit of normal), length of treatment, and lamivudine resistance.

Because utility scores have rarely been measured for HBV patients, utilities for liver complications used in our study relied on a single but large sample survey of HBV patients. To test the
Results

Patient characteristics were balanced between the 2 treatment groups in the BEHoLD AH63022 study (Table 2). The majority of treated subjects were predominantly male (75%) and either Asian (57%) or white (40%), with a mean age of 35 years. Distribution of baseline histology scores was balanced between groups. Mean baseline Knodell necroinflammatory scores were balanced between the 2 groups (entecavir 7.8, lamivudine 7.7). Mean baseline fibrosis scores using the Ishak scoring system suggested mild to moderate fibrosis for both groups (2.3, both groups). No evidence of decompensated HBV disease was apparent in these subjects based on baseline laboratory tests related to HBV disease.

Mean baseline serum HBV DNA by PCR assay was 9.62 log_{10} copies per mL for entecavir and 9.69 log_{10} copies per mL for lamivudine. All BEHoLD subjects had detectable serum HBsAg, and all subjects were HBeAg-positive. Baseline laboratory tests related to HBV disease characteristics (albumin, total bilirubin, prothrombin time, and international normalized ratio) were

---

**TABLE 2** Baseline Demographics and HBV Characteristics (BMS-AH63022)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ETV 0.5 mg (N = 354)</th>
<th>LVD 100 mg (N = 355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>274 (77)</td>
<td>261 (74)</td>
</tr>
<tr>
<td>Female</td>
<td>80 (23)</td>
<td>94 (26)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>204 (58)</td>
<td>202 (57)</td>
</tr>
<tr>
<td>White</td>
<td>140 (40)</td>
<td>141 (40)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (3)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>HBV DNA by PCR, log_{10} copies per mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV surface antigen, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>354 (100)</td>
<td>355 (100)</td>
</tr>
<tr>
<td>HBV e antigen, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>348 (98)</td>
<td>351 (99)</td>
</tr>
<tr>
<td>ALT, U per L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [SD]</td>
<td>140.5 [114.33]</td>
<td>146.3 [132.27]</td>
</tr>
<tr>
<td>Knodell necroinflammatory score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [SD]</td>
<td>7.8 [2.98]</td>
<td>7.7 [2.99]</td>
</tr>
<tr>
<td>Ishak fibrosis score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [SD]</td>
<td>2.3 [1.27]</td>
<td>2.3 [1.29]</td>
</tr>
</tbody>
</table>

*Chang TT et al. for the BEHoLD AH6522 Study Group (2006).*

**JMCP** Journal of Managed Care Pharmacy    27
TABLE 3  Cost-Effectiveness Results for Entecavir Versus Lamivudine

<table>
<thead>
<tr>
<th></th>
<th>Entecavir 0.5 mg</th>
<th>Lamivudine 100 mg</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CHB patients at entry</td>
<td>1,000</td>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment (year)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total discounted drug costs</td>
<td>$7,364,799</td>
<td>$2,603,508</td>
<td>$4,761,291</td>
</tr>
<tr>
<td>Projected liver complication in 10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>78</td>
<td>149</td>
<td>71</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>8</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>34</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td>Total discounted medical costs</td>
<td>$2,252,523</td>
<td>$4,663,540</td>
<td>-$2,411,017</td>
</tr>
<tr>
<td>Discounted life-year lost</td>
<td>682</td>
<td>1,499</td>
<td>817</td>
</tr>
<tr>
<td>Discounted QALY lost</td>
<td>608</td>
<td>1,336</td>
<td>728</td>
</tr>
<tr>
<td>Cost per life-year saved</td>
<td>$2,877</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per QALY saved</td>
<td>$3,230</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHB = chronic hepatitis B; QALY = quality-adjusted life-years.

discord comparable between groups. Mean (standard deviation) baseline ALT was 140.5 (114.33) U per L and 146.3 (132.27) U per L for entecavir and lamivudine, respectively.

Entecavir was superior to lamivudine for the portion of subjects who achieved undetectable HBV DNA (<300 copies per mL) by PCR assay at week 48. At the end of the 48-week trial period, 69.1% of patients in the entecavir arm and 39.8% of patients in the lamivudine arm reached the defined undetectable HBV DNA level (Table 1).

Of the 3,653 participants in the REVEAL-HBV cohort study, 565 (15.5%) were HBeAg-positive. Of the HBeAg-positive patients, 92.6% had HBV DNA levels >100,000 copies per mL, and 1.4% had HBV DNA levels <300 copies per mL. Annual incidence rates of compensated cirrhosis, decompensated cirrhosis, and HCC for subjects with undetectable (<300 copies per mL) hepatitis B viral load were 0.34%, 0.02%, and 0.11%, respectively (Table 1). In the Cox proportional hazards models adjusting for sex, age, cigarette smoking, and alcohol consumption, hepatitis B viral load was a strong independent predictor of liver cirrhosis and HCC events. Incidence of cirrhosis and HCC events increased with the serum HBV DNA level at study entry in a dose-response relationship.

Estimated clinical and economic outcomes are reported in Table 3. Among a hypothetical cohort of 1,000 patients, we projected 71 fewer cases of compensated cirrhosis, 8 fewer cases of decompensated cirrhosis, and 42 fewer HCC events in the entecavir arm compared with the lamivudine arm. These avoided events would translate into medical cost offsets of approximately $2.4 million and a gain of 817 life years over a period of 10 years.

On a per-person basis, 1 year of entecavir therapy gained 0.728 QALYs at an incremental cost of $2,350, with a 3% annual discount. Compared with lamivudine, entecavir cost an incremental $3,230 per QALY gained (95% confidence interval [CI], $2,312-$4,528).

Univariate sensitivity analyses demonstrated that our findings are robust to individual variables and are most sensitive to efficacy, drug costs, and treatment duration. Assuming alternative utility scores derived from a hepatitis C patient survey study of 0.99 for HBV, 0.80 for compensated cirrhosis, 0.60 for decompensated cirrhosis, and 0.73 for HCC, the incremental cost per QALY gained was $2,752, a more favorable result. A sensitivity analysis showed that inclusion of severe hepatic flares in our modeling assumption had very little impact on our economic results due to a very low event rate observed in the trial, even though this is a costly and clinically important event.

Cost-effectiveness acceptability curves are shown in Figure 2. The cost-effectiveness results are robust, with 98.4% of simulation-derived incremental cost-effectiveness ratio (ICER) estimates below $5,000/QALY. Longer-term modeling, assuming that the treatment-resistant patients would use add-on adefovir, showed that 3, 5, or 10 years of entecavir would still be cost-effective, yielding incremental costs per QALY of $9,966, $11,685, and $12,233, respectively, with 100% of PSA-derived ICER estimates below $50,000/QALY. Alternatively, in a separate sensitivity analysis assuming that lamivudine-resistant patients would switch to adefovir monotherapy, ICERs were higher, ranging from $11,582 (3 years) to $20,662 (10 years), primarily due to the relatively lower cost of adefovir monotherapy.

**Discussion**

Despite the development of safe and effective HBV vaccines that have been available since 1982, HBV infection remains a global problem. In the United States, HBV infection remains more prevalent in certain groups such as immigrants from endemic areas, men who have sex with men, injecting drug users, and persons with multiple sex partners. As long as these underlying sources of HBV remain, these subgroups would maintain a reservoir of this infectious virus. Patients with HBV should be actively counseled regarding lifestyle modifications and prevention of transmission. These steps are important because HBV can be transmitted by percutaneous and sexual exposure as well as by close person-to-person contact, presumably through open cuts and sores. It should be noted that carriers with high HBV DNA levels are more likely to be infectious.

Major health risks and economic impacts associated with HBV infection seem to be driven primarily by the development of HCC and complications of decompensated cirrhosis. HBV infection is a complex disease that can manifest in a variety of ways. The heterogeneous nature of the disease with its slow and variable progression to distinct endpoints of liver failure, cirrhosis, HCC, and death means that it is often diagnosed late in life. Current management options for liver complications remain limited partly because of a paucity of sensitive methods for early
diagnosis, resulting in the diagnosis of HBV for most patients late in the disease course. Liver transplantation remains the only effective therapy for late complications like decompensated cirrhosis and HCC.

Therefore, the benefits of early treatment for HBV in suppressing viral load and reducing consequent risk of cirrhosis and HCC can be substantial. A consensus seems to have been reached that antiviral therapy, especially if started early, can delay the progression and reduce the severity of liver disease due to HBV. An evaluation of the cost-effectiveness of such treatments would be quite informative to decision makers.

A number of factors can increase the rate of liver disease progression in patients infected with hepatitis B, including coinfection with HCV. We limited our analysis to patients without HCV coinfection to better delineate the natural history of hepatitis B alone, thus making our results generalizable only to monoinfected patients. Coinfection with human immunodeficiency virus (HIV) is also an important variable in HBV treatment, but for a reason unrelated to liver disease progression. The Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents (October 2006) were modified in April 2007, to clarify that entecavir should not be used for the treatment of HBV infection without concomitant treatment for HIV in patients coinfected with HBV and HIV.

In the present analysis extrapolated from observed HBV DNA efficacy results, we estimated that in patients initiating lamivudine therapy, 15% would progress to compensated cirrhosis within 10 years, 1.6% to decompensated cirrhosis, and 7.6% to HCC. For patients initiating entecavir therapy, 7.8% would progress to compensated cirrhosis within 10 years, 0.8% to decompensated cirrhosis, and 3.4% to HCC. These estimates are well within the range of published figures.

Compared with lamivudine, the incremental cost per QALY gain ranges from $3,230 for 1 year of entecavir treatment to $12,233 for 10 years of entecavir treatment. These estimated cost-effectiveness ratios fall well within the range that is traditionally considered acceptable in cost-effectiveness analyses of new health technologies.

Although the clinical benefits of reducing viral load have been demonstrated in recent literature, to the best of our knowledge, very few economic analyses have been conducted based on the endpoint of antiviral therapy-induced suppression of viral replication. HBsAg seroconversion (loss of HBsAg and presence of anti-HBsAg antibody) was uniformly thought to be a good outcome for patients, but recent data have shown that many patients who have undergone HBsAg seroconversion continue to develop severe complications (including HCC). HBsAg loss and seroconversion are important clinical endpoints, but the risk of disease progression even when these endpoints are met still depends on the degree of ongoing viral replication in the host. Besides the REVEAL-HBV study, several studies have demonstrated a dose relationship between hepatitis B viral load and hepatic complications, with higher hepatitis B viral load associated with progressive liver disease, including the development of cirrhosis and HCC.

A key question arises when interpreting our findings: Is it appropriate to assume that patients treated down to an undetectable viral load (BEHoLD patients with HBV DNA <300 copies per mL at study endpoint) have risks of disease progression and hepatic complications that approximate the risks for community residents with an undetectable viral load (REVEAL-HBV)? This hypothesis is supported by evidence from a large meta-analysis of 26 prospective studies totaling 3,428 study subjects (2,524 HBsAg-positive at baseline) in whom the level of viral replication and the change in viral replication were significantly correlated with several outcomes including histological grading, and change in histological grading, serological and biochemical response. An Italian study published in 2004 showed that in 656 HBeAg-negative CHB subjects treated with lamivudine, patients who developed resistance as determined by viral breakthrough and rebound had a worse outcome in all parameters, including mortality, when compared with those whose viral load was effectively suppressed by lamivudine. This study was conducted in patients with e antigen-negative disease in which immune-induced HBeAg seroconversion is not an option; therefore, the benefit of therapy is from the direct antiviral effect of the drug. Indeed, a decrease in viral load through antiviral therapy has been associated with histologic improvement, increased survival of patients with decompensated liver disease from...
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hepatitis B, and improved clinical outcome in patients with HBV reactivation following chemotherapy.

Our analyses are conservative in the following aspects. First, longer-term clinical trial data consistently showed substantially better suppression of viral DNA levels with entecavir at week 96 for HBeAg-positive treatment-naive subjects undergoing 2 years of entecavir treatment. These results were recently published in a peer-reviewed journal and therefore were not included in our current analysis. Second, we modeled HBV DNA reduction efficacy only at the end of follow-up, even though viral load reduction can be observed as soon as the first 6 months after randomization; this process may have underestimated the benefits of entecavir therapy that suppresses viral load to a very low level in a relatively short time period. Third, due to the limitation of the observation period in the REVEAL-HBV study, we were able to project events only up to 10 years; however, because the average age of trial patients was only 35 years, we could expect more events to be observed beyond 10 years. Fourth, we did not include indirect medical costs, caregiver support cost, and lost productivity in our study; however, we believe that these indirect disease burdens could be very significant and costly to U.S. society and individual patients.

Limitations

First and foremost among study limitations was the application of data on hepatic outcomes from a prospective cohort study (REVEAL-HBV) of community residents, all of whom were seropositive for HBsAg but only 15% of whom were seropositive for HBeAg, to clinical trial (BEHoLD) data for 715 patients with HBeAg-positive CHB. Of the 873 REVEAL-HBV participants with undetectable viral load at study entry whose outcomes were used in our model to indicate baseline risks of cirrhosis and HCC, only 0.9% (n=8) were HBeAg-positive. Additionally, only 4% (n=24) of the REVEAL-HBV study’s 565 HBeAg-positive participants had HBV DNA <10,000 copies per mL. Thus, the present pharmacoeconomic model’s assumed dose-response relationship between HBV disease sequelae and viral load for HBeAg-positive patients was based almost entirely on community residents who were HBeAg-negative.

Second, reliable long-term treatment rebound rates after treatment discontinuation are not yet available for either entecavir or lamivudine. In the BEHoLD results, 6 patients (2%) in the entecavir group and 63 patients (18%) in the lamivudine group experienced virologic rebound during the first year of drug administration. Among patients with a protocol-defined response, only 37% in the entecavir group and 34% in the lamivudine group had a sustained response 6 months after discontinuation of treatment. The optimal duration of entecavir or lamivudine administration in HBV patients requires further study.

Third, the appropriateness of extrapolation of the BEHoLD clinical trial results and REVEAL-HBV data to non-Asian populations is unknown. The REVEAL-HBV epidemiologic data that provided the disease progression rates were derived from a Chinese patient population. Inherent environmental and genetic factors in the cohort may not be seen in other populations. However, REVEAL-HBV is the largest study of HBV-infected persons to examine detailed information on viral factors. Its results have been replicated in a second study that was also conducted in Chinese patients. The relationship between viral load and liver disease outcome has been found in other studies around the world including West Africa, China, and Japan, but primarily in Asians.

Fourth, potential cost-effectiveness for entecavir compared with other drugs, such as adefovir or interferon, was not evaluated due to lack of head-to-head randomized trial data at the time of this study. Future studies should explore the cost-effectiveness of other treatment strategies.

Fifth, although we accounted for the actual compliance rate in the BEHoLD clinical trial, we would expect the compliance rate in real-world practice to be much lower. However, there is no reason to believe that compliance rates between entecavir and lamivudine will differ based on their dosages (oral), frequency of administration (once daily), and side effect profiles.

Sixth, we did not consider those patients with lamivudine-resistant virus who require larger doses of entecavir. Finally, we did not evaluate the cost-effectiveness of entecavir in patients coinfected with HBV and HIV. Patients in our analysis were assumed to be naïve to antiretroviral treatment and not to be coinfected with HIV, even though ≤10% of all HIV-infected persons are coinfected with HBV. As we have noted, the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents no longer recommends entecavir in patients coinfected with HBV and HIV who are not receiving simultaneous HIV drug treatment; entecavir’s package labeling has been changed accordingly.

Conclusion

Based on published data for a Chinese population outside the United States, our modeling consistently demonstrated that a strategy of initiating therapy with entecavir in HBeAg-positive HBV patients (both short-term and long-term use up to 10 years) will be cost-effective and therefore economically attractive to U.S. health care payers assuming that (1) the efficacy of entecavir after 1 year is sustainable and (2) liver disease risk levels from the REVEAL-HBV study population (a primarily HBeAg-negative group) adequately represent risk for a treated HBeAg-positive patient group. While eradication of hepatitis B is rarely achieved using current treatment options, the availability of entecavir as part of an early treatment strategy is economically attractive for current HBV patients without coinfection with either HCV or HIV.
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Authors

YONG YUAN, PhD, is director, Global Epidemiology and Outcomes Research, Pharmaceutical Research Institute, Bristol-Myers Squibb Co., Plainsboro, New Jersey; UCHENNA H. ILOEJE, MD, MPH, is group professor, Departments of Medicine and Surgery, David Geffen School of Medicine at UCLA, University of California at Los Angeles.

AUTHOR CORRESPONDENCE: Yong Yuan, PhD, Bristol-Myers Squibb Company, P.O. Box 4500, Princeton, NJ 08543-4000. Tel.: 609.897.2688; Fax: 609.897.6319; E-mail: yong.yuan@bms.com

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Evaluation of the Cost-Effectiveness of Entecavir Versus Lamivudine in Hepatitis BeAg-Positive Chronic Hepatitis B Patients


Evaluation of Clostridium difficile-Associated Diarrhea With a Drug Formulary Change in Preferred Fluoroquinolones

Molly A. Walbrown, PharmD, CACP, CDE; Sherrie L. Aspinall, PharmD, MSc; Nichole K. Bayliss, BA; Roslyn A. Stone, PhD; Francesca Cunningham, PharmD; Cheryl L. Squier, RN, BSN; and Chester B. Good, MD, MPH

ABSTRACT

BACKGROUND: Recent publications report that gatifloxacin might be associated with a greater incidence of Clostridium difficile-associated diarrhea (C. difficile, CDAD) than are other fluoroquinolones. We performed a drug use evaluation to examine this issue after adding gatifloxacin to the formulary and changing from levofloxacin to gatifloxacin as the preferred oral fluoroquinolone in 10 Department of Veterans Affairs (VA) medical centers in the northeastern United States.

OBJECTIVES: To estimate (1) the overall incidence of CDAD before and after the change from levofloxacin to gatifloxacin as the preferred oral fluoroquinolone and (2) the incidence rates for ciprofloxacin, levofloxacin, and gatifloxacin separately.

METHODS: Using the VA's Pharmacy Benefits Management database, the total number of days of antibiotic therapy was determined for all inpatients and outpatients of the 10 medical centers who filled at least 1 antibiotic prescription between July 1, 2003, and June 30, 2004. This time frame was chosen because it included 6 months before and 6 months after the change in the preferred oral fluoroquinolone from levofloxacin to gatifloxacin for the VA health system on January 1, 2004. For the same study period and medical centers, the electronic medical records of all inpatients and outpatients with an entry for a positive C. difficile toxin were reviewed.

Positive toxins that occurred within 6 weeks of a previous positive result in the same patient were excluded. Exact Poisson tests were used to compare the incidence rates of CDAD (number of CDAD cases per 1,000 days of antibiotic treatment) for antibiotics overall, the fluoroquinolones as a group, non-fluoroquinolone antibiotics, and the individual fluoroquinolones, comparing the 6-month time periods before (pre-change) versus after (post-change) the addition of gatifloxacin as the preferred oral fluoroquinolone.

RESULTS: Of 505 cases of CDAD in the 12-month study period, 413 (81.7%) were associated with antibiotic use in the previous 6 weeks. Among antibiotic users, incidence rates of CDAD were 166 per 72,114 days of antibiotic therapy in the pre-change period (2.3 cases per 1,000 days of antibiotics) versus 247 per 72,354 days in the post-change period (3.4 cases per 1,000 days of antibiotics, $P<0.001$). Fluoroquinolones accounted for 54.8% of the CDAD cases in the pre-change period and 67.2% in the post-change period, representing a 22.6% relative increase in the percentage of CDAD cases that were associated with fluoroquinolone use. The CDAD incidence rates per 1,000 days of fluoroquinolone therapy were 3.7 in the pre-change period versus 7.0 in the post-change period ($P<0.001$). Among fluoroquinolone users, gatifloxacin accounted for none of the cases of CDAD in the pre-change period when it was nonformulary and 65.1% of the cases in the post-change period, for an incidence rate of 7.6 (108 per 14,239 days). The CDAD incidence rates per 1,000 antibiotic days for patients treated with ciprofloxacin were 4.6 (24 per 5,260 days) in the pre-change period and 7.4 (40 per 5,429 days) in the post-change period, a nonsignificant trend ($P=0.079$). The incidence rate of CDAD for levofloxacin increased significantly from 3.9 (75 per 19,417 days) in the pre-change period to 10.7 (44 per 4,108 days) in the post-change period ($P=0.001$). The incidence rates of CDAD in the post-change period did not differ significantly for ciprofloxacin, levofloxacin, and gatifloxacin ($P=0.119$).

CONCLUSIONS: There was an increase in the incidence of CDAD among all antibiotic users and fluoroquinolone users, but not among users of non-fluoroquinolone antibiotics, in the period following the formulary change from levofloxacin to gatifloxacin as the preferred fluoroquinolone. However, rates of CDAD among the 3 fluoroquinolone antibiotics in the post-change period were not significantly different, and levofloxacin was the only fluoroquinolone that was associated with a significant increase in the rate of CDAD between the pre-change and post-change periods. These findings suggest that the increase in the CDAD incidence rate was probably not attributable to the addition of gatifloxacin to the formulary.

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What is already known about the subject

• In studies of outbreaks of Clostridium difficile-associated diarrhea (CDAD) with increasing virulence, fluoroquinolones have been identified as a risk factor for the development of the infection. Because of its extended antimicrobial spectrum, which includes enhanced anaerobic coverage, there are concerns that gatifloxacin, in particular, may be associated with an increased incidence of CDAD.

What this study adds

• Although we found an increase in the incidence of CDAD after changing to gatifloxacin as the preferred oral formulary fluoroquinolone, the CDAD incidence rates for gatifloxacin, ciprofloxacin, and levofloxacin were not significantly different. This finding suggests that the increase was probably not attributable to the formulary change.

• Because simple pre- versus post-drug use evaluations may produce confusing results, more detailed patient-level analyses are necessary to assess the impact of formulary changes.

Clostridium difficile-associated diarrhea (CDAD) is recognized as the leading cause of health care-associated diarrhea. The annual incidence of CDAD in the United States is more than 250,000 cases, according to the Centers for Disease Control and Prevention,1 with a mortality rate of 1% to 2.5% and an estimated cost of $1.1 billion.2,3 The incidence and severity
of CDAD have increased over the past 2 decades, resulting in extended hospitalizations, increased health care costs, and poor outcomes. The major risk factor for developing CDAD continues to be the recent use of antibiotics. Earlier reports of CDAD implicated clindamycin, ceftazidime, and ampicillin. However, since the fluoroquinolone antibiotics have become widely prescribed, there have been case reports and observational studies linking them with CDAD. In addition, several studies specifically found an association between prior levofloxacin and gatifloxacin use and an increased incidence of CDAD. In a case-control study conducted by Gaynes et al. in a long-term care facility, the attack rate for CDAD was 17% when levofloxacin was on the formulary versus 30% after the change to gatifloxacin (P < 0.02). The rate declined when the preferred fluoroquinolone was changed back to levofloxacin. In their multivariable analysis, the number of days of gatifloxacin therapy was independently associated with CDAD (P < 0.0001). However, a correspondence by Mohr emphasizes that the authors did not account for infection control measures that were instituted just prior to changing back to levofloxacin.

In contrast with the study by Gaynes et al., an analysis by Muto et al. found an association between the use of levofloxacin and CDAD at a community-based hospital. Similarly, Changela et al. found that prior use of levofloxacin was a risk factor for the development of CDAD among hospitalized veterans. Finally, recent reports have documented widespread outbreaks of CDAD with increased virulence, leading to a higher proportion of colectomies and deaths. Prior exposure to a fluoroquinolone was a significant risk factor for acquisition of the infection, with an odds ratio (OR) of 3.9 (95% confidence interval [CI], 2.3-6.6) in one of the studies.

Prior to January 2004, the only fluoroquinolones available in the Department of Veterans Affairs (VA) formulary were ciprofloxacin and levofloxacin. On January 1, 2004, gatifloxacin was added to the formulary and replaced levofloxacin as the preferred oral fluoroquinolone. In response to internal concerns that gatifloxacin might be associated with a greater incidence of CDAD than other fluoroquinolones because of its broader spectrum of activity that includes enhanced anaerobic coverage, we performed a drug use evaluation (DUE) to estimate the incidence of CDAD before and after the change to gatifloxacin as the preferred oral fluoroquinolone within a group of VA medical centers in the northeastern United States. On February 15, 2006, the U.S. Food and Drug Administration issued a warning regarding severe hypoglycemia and hyperglycemia associated with gatifloxacin and its contraindication in patients with diabetes. In response to this warning, Bristol-Myers Squibb, the manufacturer of gatifloxacin, voluntarily withdrew the antibiotic from the market effective June 2, 2006. Although gatifloxacin is no longer available, concerns remain that fluoroquinolones may play a major role in the development of CDAD and that specific fluoroquinolones may be associated with a greater risk of CDAD.

### Methods
The study consisted of (1) an assessment of the incidence rates of CDAD per 1,000 days of antibiotic therapy and (2) a retrospective electronic medical record review of patients with a positive C. difficile toxin. The Drug Use Evaluation Subcommittee of the Pharmacy and Therapeutics (P&T) Committee at the VA Pittsburgh Healthcare System (VAPHS) developed the assessment protocol in cooperation with the regional VA P&T committee. Exempt status was granted by the VAPHS Institutional Review Board because this was a quality assurance project for the VA Center for Medication Safety.

### Patient Eligibility
Study subjects were patients of 10 VAPHS medical centers in Pennsylvania, Delaware, and northern West Virginia. To provide a denominator for the assessment of incidence rates, the total number of days of antibiotic therapy for all inpatients and outpatients who filled at least 1 antibiotic prescription between July 1, 2003, and June 30, 2004, were identified using the VA's Pharmacy Benefits Management database. This time frame was chosen because it included 6 months before and 6 months after the switch from levofloxacin to gatifloxacin as the preferred oral fluoroquinolone for the VA health system on January 1, 2004.

For the same study period and medical centers, all inpatients and outpatients with a positive C. difficile toxin between July 1, 2003, and June 30, 2004, were identified using the VAPHS electronic medical record. Patients could be included more than once during the study period; however, repeat positive toxins that occurred within 6 weeks of a previous event in the same patient were excluded to eliminate any confusion regarding classification (recurrence vs. reinfection). Patients were also excluded if their electronic medical records could not be accessed through the VAPHS.

### Data Collection
For the incidence rate analysis, data collection included the total numbers of days of antibiotic therapy, overall and by antibiotic agent, for all patients receiving antibiotics during the review period. For the review of CDAD cases, data collection included demographics, signs and symptoms of infection with C. difficile, treatments, outcomes (i.e., infection resolved, surgical intervention required, or death), inpatient and outpatient antibiotic use within 6 weeks prior to the date of the positive toxin, and the setting in which the infection developed (i.e., outpatient vs. inpatient).

### Analysis
Exact Poisson tests were used to assess changes in the CDAD infection rates before and after the change to gatifloxacin as the preferred oral fluoroquinolone. Analyses were done separately for all antibiotics, the fluoroquinolones as a group, nonfluoroquinolone antibiotics, and the individual fluoroquinolones.
Exact Poisson tests and 95% CIs were used because some numerators were small. To describe the change in incidence rates over time, we calculated exact Poisson tests and CIs for the rate ratios using exact Poisson regression in LogXact version 8. We estimated the rate ratios by fitting models of the form log(rate) = B0 + B1*X, where X = 1 for the post-period and 0 for the pre-period. The estimated rate ratio comparing the CDAD rate for a particular antibiotic in the post-change period versus the pre-change period is exp(B1).

Throughout the 10 facilities evaluated, 559 cases of CDAD were identified between July 1, 2003, and June 30, 2004. Of the identified cases, 42 were excluded because the positive toxin occurred within 6 weeks of a previous event. Finally, 12 cases were excluded because the medical records were not accessible, leaving 505 cases of CDAD during the study period. These cases occurred in 460 unique patients.

Among these patients with CDAD, 444 (96.5%) were male and the mean age was 69.2 years (SD 12.9). Most of the 460 patients accounted for a single case of CDAD during the study period (n = 420). However, 35 patients had 2 episodes of CDAD >6 weeks apart, and 5 patients had 3 episodes of CDAD >6 weeks apart. Table 1 describes the characteristics of the cases of CDAD before and after the formulary change to gatifloxacin. Among those episodes involving antibiotics, the average number of previous and/or concurrent antibiotics per episode within 6 weeks prior to the positive toxin was 2.9 (SD 1.7) in both time frames. There were 40 cases of CDAD (19.4%) that involved no documented receipt of prior antibiotics in the pre-change period compared with 52 cases (17.4%) in the post-change period.

Among the 413 episodes involving antibiotics (in 374 patients), the overall CDAD incidence rate increased significantly after the formulary change, from 166 per 72,114 days in the pre-change period (a rate of 2.3 cases per 1,000 days of antibiotics) to 247 per 72,354 days in the post-change period (a rate of 3.4 cases per 1,000 days of antibiotics), P < 0.001 (Table 2). The incidence rate associated with the fluoroquinolones (i.e., ciprofloxacin, levofloxacin, and gatifloxacin) also increased significantly (P < 0.001). Among fluoroquinolone users, rates of CDAD per 1,000 days of antibiotic treatment were 3.7 in the pre-change period (91 per 24,708 days) and 7.0 in the post-change period (166 per 23,776 days). Fluoroquinolones accounted for 54.8% of the CDAD cases in the pre-change period and 67.2% in the post-change period, a change that represents a 22.6% relative increase in the percentage of CDAD cases that were associated with fluoroquinolone use. No significant change over time was seen in the incidence rates associated with non-fluoroquinolone antibiotics (1.6 vs. 1.7 per 1,000 days; P = 0.805).

The increased incidence of CDAD in the time period after the formulary switch to gatifloxacin was significant for levofloxacin (P < 0.001) but not for ciprofloxacin (P = 0.079). The CDAD incidence rate for patients treated with ciprofloxacin increased from 4.6 (24 per 5,260 days) in the pre-change period to 7.4 (40 per 5,429 days) in the post-change period, but the incidence of CDAD for levofloxacin increased from 3.9 (75 per 19,417 days) in the pre-change period to 10.7 (44 per 4,108 days) in the post-change period. There were no cases of CDAD among patients who received gatifloxacin when it was nonformulary, although
there was some limited use of the antibiotic. After gatifloxacin was added to the formulary, there were 108 cases, for an incidence rate of 7.6 cases per 1,000 days of antibiotics. The change in incidence between the 2 time periods was not statistically significant (P = 0.628); however, this comparison is limited by the vast uncertainty in the pre-change rate for gatifloxacin. The CDAD incidence rates did not differ significantly among patients who received ciprofloxacin, levofloxacin, or gatifloxacin in the post-change period (P=0.119, data not shown in table).

The rate ratios, describing the change in incidence rates over time, were statistically significant for patients receiving any antibiotic (1.5; 95% CI, 1.2-1.8), the fluoroquinolones as a group (1.9; 95% CI, 1.5-2.5), and levofloxacin (2.7; 95% CI, 1.9-4.1).

### Discussion

The increased use of fluoroquinolones has been a concern because it promotes the emergence and spread of fluoroquinolone-resistant bacteria, including *Streptococcus pneumoniae*, *Enterobacteriaceae*, and *Pseudomonas aeruginosa*.\(^{20-24}\) Now, outbreaks of CDAD caused by a strain associated with high morbidity, mortality, and fluoroquinolone resistance\(^ {11,14,15}\) have led to additional focus on appropriate antibiotic use and efforts to improve infection prevention measures.

Clindamycin, ampicillin, and cephalosporins are frequently associated with CDAD, but essentially all antibiotics have been reported to cause the infection.\(^ {3,6}\) Although the fluoroquinolones have been considered relatively low risk for causing CDAD,
it is difficult to ascertain a difference in the incidence rate of CDAD among antibiotics because, to our knowledge, no large prospective studies have been conducted. \cite{3,4} Even if their relative risk is comparatively low, the overall incidence will increase as fluoroquinolone-prescribing increases. A number of recent retrospective case-control and cohort studies have reported an independent association between prior fluoroquinolone use—specifically, ciprofloxacin, levofloxacin, and gatifloxacin—and the development of CDAD. \cite{8,12} In some of these studies, increased fluoroquinolone use was reported. \cite{9,11}

In our evaluation, the overall incidence of CDAD increased after the change to gatifloxacin as the preferred oral fluoroquinolone among patients receiving antibiotics. In addition, the incidence rate increased among patients receiving any of the fluoroquinolones. However, in the post-change period, the incidence rates for gatifloxacin, ciprofloxacin, and levofloxacin were not significantly different. These findings suggest that the increased incidence of CDAD was unrelated to the gatifloxacin formulary change. This pattern could imply an infection prevention issue, other unmeasured confounding variables, or a seasonal variation. Our results demonstrate that limiting DUE analyses to simple pre-versus post-measures potentially produces confusing information, suggesting the need for more detailed patient-level analyses of the impact of formulary changes.

Some studies have reported an increase in the number of CDAD cases when the formulary fluoroquinolone was changed from ciprofloxacin to levofloxacin \cite{10,13} or from levofloxacin to gatifloxacin. \cite{8} In Gaynes et al.’s study of long-term care facility patients, exposure to clindamycin (\( P=0.005 \)) and duration of gatifloxacin use (\( P<0.001 \)) were independently associated with CDAD. The facility’s CDAD rate decreased after levofloxacin replaced gatifloxacin on the formulary, and the authors posited that gatifloxacin is more prone to causing CDAD because it possesses anaerobic coverage that levofloxacin lacks. \cite{8} However, Gaynes et al. did not account for infection control practices that were implemented just prior to switching back to levofloxacin. In addition, the rate of CDAD may have already been increasing prior to the initial formulary change to gatifloxacin. \cite{15}

In an analysis of \textit{Clostridium difficile} infections at a tertiary care teaching hospital, Muto et al. found that the increased incidence of CDAD was associated with the use of levofloxacin, but not with other fluoroquinolones. In addition, the number of cases declined when gatifloxacin and ciprofloxacin replaced levofloxacin on the formulary. \cite{10} Clindamycin (OR 4.8; 95% CI, 1.9-12.0), ceftriaxone (OR 5.4; 95% CI, 1.8-15.8), and levofloxacin (OR 2.0; 95% CI, 1.2-3.3) were independent risk factors for CDAD. Finally, a retrospective case-control study examined whether an increase in the incidence of CDAD among inpatients and outpatients within the VA health care system in Seattle in 2004 was associated with a formulary change from levofloxacin to gatifloxacin. \cite{25} By analyzing seasonal trends in CDAD rates from 1998 to 2005, the authors concluded that the higher incidence rate following the formulary change was attributable to seasonal variation (higher CDAD rates in the fall and spring each year) and not to increased gatifloxacin use.

Most of our cases of CDAD occurred among inpatients, 65.0% in the pre-change period and 70.2% in the post-change period. This finding is consistent with the literature and not surprising because the primary reservoirs of \textit{C. difficile} are colonized or infected patients and contaminated environments and objects in the hospital or nursing home. \cite{9} In response to the increase, several of the medical centers implemented additional infection prevention measures to try to decrease the incidence of CDAD. These prevention measures included the following: cleaning the rooms of patients who had CDAD with a 1:10 bleach solution upon their discharge from the room, adding a statement to the Contact Precautions signs to wash hands for 15 seconds before exiting the room, educating staff on proper hand hygiene and contact precautions, and monitoring adherence to these practices.

Although episodes of CDAD without prior antibiotic use were not the focus of our evaluation, it is interesting that, in almost one fifth of the episodes of CDAD, there was no record of the patients receiving an antibiotic within the 6 weeks prior to the positive toxin (19.4% in the pre-change period vs. 17.4% in the post-change period). It is possible that these patients received an antibiotic prescription from a non-VA physician, although we did search the medical record for documentation of this information. Perhaps more important, these patients could have acquired CDAD from person-to-person transmission or the environment, or they had other risk factors for CDAD. \textit{C. difficile} spores remain viable in the environment for years, and contamination can be a problem in hospitals and long-term care facilities. \cite{5} Other risk factors for CDAD can include receipt of chemotherapy, exposure to gastric acid suppressants, advanced age, admission to an intensive care unit, length of hospital stay, and severity of underlying disease. \cite{2,5,26-28}

Of note, gatifloxacin remained the preferred oral fluoroquinolone in the 10 medical centers until March 2006, when it was replaced by moxifloxacin because of warnings regarding hypoglycemia and hyperglycemia with gatifloxacin. We have not reevaluated our CDAD incidence rate since the change from gatifloxacin to moxifloxacin. There are few published reports of CDAD associated with moxifloxacin, but it has not been prescribed as frequently as levofloxacin or ciprofloxacin. \cite{16,29} However, as the use of moxifloxacin expands within the VA health care system, there is an opportunity to evaluate the incidence of CDAD in a large patient population.

**Limitations**

Our results should be interpreted with several limitations in mind. First, because this project was conducted as a DUE, we did not collect data on other risk factors for \textit{C. difficile} colonization, and, therefore, we could not control for the presence of any confounding variables in our analyses, including concomitant...
antibiotics. Second, we also do not know which strains of C. difficile circulated in the hospitals at that time, or particularly whether there was a new epidemic strain. Third, because we do not know the indication for antibiotics, it is possible that there were differences among the patients that accounted for the selection of a particular fluoroquinolone—namely, patients who received levofloxacin after the change to gatifloxacin as the preferred fluoroquinolone. We did not collect person-level information about either the characteristics or counts of patients receiving antibiotics during our study period. Fourth, relatively small denominators limited the power in our analyses of ciprofloxacin (both time periods) and gatifloxacin (pre-change period). Fifth, given the pre-post design, we might have been observing an ongoing trend in the rate of CDAD (e.g., seasonal variation).30

Conclusion

After a formulary change from levofloxacin to gatifloxacin as the preferred fluoroquinolone, there was a significant increase in the incidence of CDAD among all antibiotic users and all fluoroquinolone users, but not among users of non-fluoroquinolone antibiotics. However, the CDAD incidence rate for levofloxacin increased significantly from the pre-change period to the post-change period. In the post-change period, the incidence rates for gatifloxacin, ciprofloxacin, and levofloxacin were not significantly different. The increase in CDAD incidence could not be attributed to the addition of gatifloxacin to the formulary, suggesting the influence of other risk factors, infection prevention issues, or a seasonal variation. Limiting DUE analyses to simple pre- versus post-measures may produce misleading information and underscores the need for more detailed assessments, ideally a prospective analysis. Given the concern regarding recent outbreaks of CDAD and the possible association between CDAD and fluoroquinolone use, attention should continue to focus on appropriate antibiotic use and infection prevention measures.

Authors

MOLLY A. WALBROWN, PharmD, CACP, CDE, is a clinical pharmacist, York Hospital, York, Pennsylvania (at the time of the project, she was a pharmacy practice resident at the VA Pittsburgh Healthcare System [VAPHS]); SHERRIE L. ASPINALL, PharmD, MSc, is a clinical pharmacist, VA Center for Medication Safety; a faculty member, Center for Health Equity Research and Promotion, Pittsburgh; and an assistant professor, School of Pharmacy, University of Pittsburgh (at the time of the project, she was a VA Health Sciences Research and Development Research Career Development awardee); she served as the faculty advisor and project mentor for Walbrown; NICHOLE K. BAYLISS, BA, is a research assistant, Center for Health Equity Research and Promotion; ROSLYN A. STONE, PhD, is the cochief, Biostatistics and Informatics Core, Center for Health Equity Research and Promotion, and an associate professor, Graduate School of Public Health, University of Pittsburgh; FRANCESCA CUNNINGHAM, PharmD, is the director, VA Center for Medication Safety; CHERYL L. SQUIER, RN, BSN, is an infection control nurse, VAPHIS; and CHESTER B. GOOD, MD, MPH, is a staff physician, VAPHIS; a faculty member with the Center for Health Equity Research and Promotion; codirector, VA Center for Medication Safety; and an associate professor, School of Medicine and School of Pharmacy, University of Pittsburgh.

AUTHOR CORRESPONDENCE: Molly A. Walbrown, PharmD, CACP, CDE, York Hospital Pharmacy Services, 1001 South George St., P.O. Box 15198, York, PA 17405-7198. Tel.: 717.851.2832; Fax: 717-851-2089; E-mail: mwalbrown2@wellspan.org

DISCLOSURES

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Author Chester Good was primarily responsible for the study concept and design, with input from Molly Walbrown, Sherrie Aspinall, and Francesca Cunningham; data collection was the work of Walbrown, Nichole Bayliss, and Cheryl Squier; data interpretation was performed by Walbrown, Aspinall, Good, Bayliss, and Roslyn Stone. Walbrown was primarily responsible for writing the manuscript, with input from Aspinall and Good; and Walbrown, Aspinall, Good, Squier, and Stone revised the manuscript.

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Evaluation of Clostridium difficile-Associated Diarrhea With a Drug Formulary Change in Preferred Fluoroquinolones

ABSTRACT

BACKGROUND: In 1989, the National Asthma Education and Prevention Program (NAEPP) convened an expert panel to develop a report that would provide a general approach to the treatment of asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3) was published in 1991 and was subsequently updated with 2 other reports, EPR-2 in 1997 and the EPR update in 2002. Advances in science and a greater understanding of the pathophysiology of asthma prompted the NAEPP to convene a 3rd expert panel in 2004. After nearly 3 years of work, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Full Report 2007, or EPR-3, was released on August 29, 2007.

EPR-3 update from the NAEPP provides health care professionals with new information to improve the care of patients with asthma, including (1) more comprehensive discussion of asthma severity with expanded descriptions of impairment and risk, (2) increased focus on asthma control as a goal of therapy, and (3) expanded discussion of pharmacologic therapy for asthma with updated treatment algorithms.

OBJECTIVES: To (1) extract key educational messages from the EPR-3 update that effectively summarize the appropriate management of the patient with asthma and (2) provide supporting literature to substantiate the development of these educational messages.

METHODS: A consensus meeting of 9 asthma experts (4 pharmacists and 5 physicians) was held to discuss the EPR-3 update and condense its content into a usable format for the health care professional. Experts were selected on the basis of several criteria, including (1) affiliation with the NAEPP, (2) expertise in asthma management, and (3) familiarity with managed care processes. The author served as the 10th member and moderator of the meeting.

RESULTS: Thorough review of the EPR-3 update resulted in the development of 7 key educational messages that can assist the health care professional in improving the management of the patient with asthma. Each educational message is presented with supporting literature to substantiate its distinction as a key point to be referenced when developing protocols for asthma management within managed care organizations.

CONCLUSION: The complexity of asthma and its treatment has necessitated the development of several guidelines from the NAEPP, with the most recent EPR-3 update being released in late August 2007. One expert consensus has distilled the EPR-3 document into 7 key educational messages that can assist the health care professional in improving the care of the patient with asthma.

What is already known about this subject

- The NAEPP has produced 2 prior expert reports and 1 update report that have addressed the diagnosis and management of patients with asthma.
- Greater knowledge of the pathophysiology of asthma has necessitated the development of another guideline update, EPR-3.

What this study adds

- EPR-3 differs from the previous asthma diagnosis and management guidelines in:
  - providing an expanded discussion on the use of spirometry and the concept of airflow reversibility;
  - placing a stronger emphasis on the use of the written asthma action plan;
  - adding immunomodulatory therapy (i.e., omalizumab) as an option for certain patients with allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose inhaled corticosteroids (ICSs) and long-acting beta-2 agonists (LABAs);
  - providing equal weight to increasing the dose of an ICS or adding a LABA in patients with moderate persistent asthma that is not controlled on a low-dose ICS;
  - expanding the discussion of asthma severity to include the domains of current impairment and future risk;
  - greatly expanding the discussion of asthma control as a target of asthma therapy; and
  - making several changes to the stepwise approach to managing asthma and to managing asthma exacerbations.

Asthma is a chronic inflammatory disease of the airways that causes a high burden on the global health care system.
In the United States alone, approximately 15.7 million adults and 6.7 million children have asthma, and in 2004, approximately 3,780 patients died from asthma and its complications.
Direct costs of asthma were estimated to be $11.5 billion in 2004, with the largest components of cost being prescription drugs and hospital care.

Despite advances in therapy, asthma remains a disease that, in many patients, is not optimally controlled. Patient surveys show that approximately 60% of people with moderate persistent...
While reviewing the entire document is certainly possible and is obviously desirable, it is probably impractical for the average health care professional. The imposing size of the EPR-3 document precipitated the convening of a meeting of 9 asthma experts (including 1 member of the NAEPP Coordinating Committee, 1 member of the Third Expert Panel, and 1 consultant reviewer for EPR-3) on June 7-8, 2007, to discuss the forthcoming guidelines and to extract from them the key points judged to be the most important and clinically relevant. The major differences between EPR-3 and the previous versions of the asthma guidelines were discussed. The result of that discussion in this group of 9 asthma disease experts was the creation of 7 key points that summarize the content of the guidelines (Table). These 7 key points and their associated scientific rationale are discussed below.

### 1. Establishing an Accurate Diagnosis Is Essential

Clinicians should consider the diagnosis of asthma when patients present with episodic symptoms of airflow obstruction that is at least partially reversible, and when alternative diagnoses have been excluded. Indicators for a diagnosis of asthma include wheezing, cough, chest tightness, dyspnea, worsening of symptoms in the presence of environmental stimuli, and worsening of symptoms at night. Diagnosis of asthma is established through the use of medical history, physical examination, and spirometry.

All versions of the asthma guidelines have used the aforementioned approach in the diagnosis of asthma. EPR-3 places a strong focus on the use of spirometry, which is recommended both before and after the inhalation of a short-acting bronchodilator in all patients suspected of having asthma. Studies have shown that while history and physical examination can provide clues to the diagnosis of asthma, objective measures of lung function, such as spirometry, are necessary for the accurate diagnosis of asthma. EPR-3 also discusses the concept of reversibility in further detail, indicating that some patients who have signs and symptoms of asthma may not initially demonstrate reversibility on spirometry. In these patients a short course of oral corticosteroid therapy may be required to improve their asthma control in order to demonstrate reversibility.

Many other clinical disorders may mimic asthma, and therefore other diagnostic possibilities should be considered in the patient presenting with signs and symptoms suggestive of asthma. Conditions to be considered include allergic rhinitis and sinusitis; congestive heart failure; pulmonary embolism; chronic obstructive pulmonary disease; drug-related cough; and other pulmonary conditions. EPR-3 specifically adds a discussion on cough-variant asthma and vocal cord dysfunction as potential disorders that may present similarly to classical asthma. A careful diagnostic workup for asthma should always include consideration of the diagnostic entities mentioned above.
2. Successful Management Depends on a Comprehensive Approach

Management of the patient with asthma requires an approach that considers many factors. In previous versions of the guidelines, as well as in EPR-3, a comprehensive approach has been stressed, including education, control of environmental factors, and use of appropriate pharmacologic therapies. Education should begin early and involve all members of the health care team delivering the same key message to the patient. Patients should be taught what asthma is and what defines well-controlled asthma; the roles of the different medications used to treat asthma; the proper use of an inhaler; how to recognize worsening asthma; when and where to seek additional care when necessary; and methods to control environmental exposures and triggers. EPR-3 places a stronger emphasis on the written asthma action plan, which should include providing instructions for daily management and recognizing and handling worsening asthma, including adjusting the dose of medications. The evidence supporting the use of such written plans is inconclusive, but they are generally believed to be beneficial in preventing or managing asthma exacerbations. Education of providers who treat patients with asthma is also stressed, although studies are once again inconclusive. In general, EPR-3 recommends that provider education be multifaceted and involve interactive learning strategies, on the basis of studies that show significant long-term benefits of such education on the quality of asthma care.

Controlling environmental factors improves long-term management of asthma. Methods that can be used to achieve control of environmental factors include reducing or eliminating exposure to allergens (e.g., animal dander, cockroaches) and indoor/outdoor pollutants (e.g., perfumes, volatile organic compounds), as well as stopping smoking, including by others who live in the home. As with education, this should involve a multifaceted approach, since programs that focus on educating patients and providing tools for reducing environmental exposures have demonstrated success in reducing asthma morbidity. Appropriate pharmacologic therapy for asthma is the cornerstone of its management. All versions of the guidelines have acknowledged the key distinction between long-term controller medications and short-term quick-relief medications. Inhaled corticosteroids (ICSs) are still considered the most potent and consistently effective long-term control medications for asthma. They are more effective than any other class of controller medications, and they are safe and well tolerated. Cromolyn sodium, nedocromil, inhaled long-acting beta-2 agonists (LABAs), leukotriene modifiers, theophylline, and omalizumab are all considered possible adjunctive therapies to ICS therapy. The 2 major changes in EPR-3 with regard to pharmacologic therapy include (1) the addition of immunomodulators, specifically anti-IgE (omalizumab) therapy, for patients with severe persistent asthma and allergies, and (2) equal weight given to increase the ICS dose or the option of adding a LABA in patients with moderate persistent asthma or asthma inadequately controlled on a low-dose ICS.

The immunomodulatory agent omalizumab is a humanized monoclonal antibody to the Fc portion of the IgE antibody, which prevents IgE from binding to its receptor on mast cells and basophils and consequently inhibits the release of allergic mediators. Since asthma and atopy have been linked, an agent such as omalizumab would be expected to have a beneficial effect on asthma control. Studies have shown that use of omalizumab is associated with reductions in asthma exacerbations, reductions in the dose of ICS needed for control of symptoms, and improvements in quality of life. EPR-3 recommends that its use be limited to those patients with allergies and severe persistent asthma that are inadequately controlled with the combination of high-dose ICS and LABA, since omalizumab has not yet been compared with other adjunctive therapies in moderate asthma. Anaphylactic reactions have been reported with omalizumab, and “clinicians who administer omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.” LABAs, including salmeterol and formoterol, are effective because of their ability to cause bronchodilation up to 12 hours after administration. EPR-3 recommends that LABAs be used as an adjunct to ICS therapy for providing long-term control of symptoms, and that they are the preferred adjunctive therapy to combine with ICSs in youths ≥12 years of age and adults. The major change in EPR-3 is that in patients who have asthma not sufficiently controlled with ICS alone, acceptable therapeutic options of equal weight include either (1) increasing the dose of the ICS, or (2) adding a LABA to the ICS. This recommendation is based on a thorough review of the evidence comparing LABA add-on therapy with increasing ICS dose. EPR-3 also recommends that for patients who have more severe persistent asthma, the combination of LABAs and ICSs should be used as the most effective therapy. Finally, EPR-3 also notes that daily use of LABAs should generally not exceed 100 mcg of salmeterol or 24 mcg of formoterol.

The safety of LABAs was also considered by EPR-3 due to initial postmarketing surveillance that suggested an increase in asthma deaths in patients treated with LABAs. Subsequent studies provided conflicting results, but a large placebo-controlled postmarketing trial of salmeterol added to usual therapy in 2006 found an increased risk of asthma-related deaths and combined asthma-related death or life-threatening experiences in the population treated with LABAs. For this reason, the U.S. Food and Drug Administration issued a public health advisory regarding the potential risk associated with LABAs in 2006, and all products containing a LABA now have a black box warning.

3. Assessment of Severity Determines Initial Therapy

Once a diagnosis of asthma has been established, it is important to characterize the severity of the patient’s asthma in order to guide the initial therapeutic choice. Severity is defined by EPR-3 as...
the intrinsic intensity of the disease process, as measured by the degree of current impairment and the assessment of future risk or by defining the least amount of medication needed to achieve control of symptoms.8 While the concept of asthma severity is not a new one and was present in earlier versions of the asthma guideline, it has been refined and expanded in EPR-3 to include the additional concepts of current impairment and future risk.

The term “impairment” refers to the degree to which asthma interferes with the normal functioning of the patient. Domains included in impairment are nighttime awakenings; need for quick-relief medications; work or school days missed; ability to engage in normal activities; quality of life; and lung function as measured by spirometry. Studies have confirmed that these domains are important predictors of general health status, symptoms, limitations in normal daily activities, resource utilization (such as emergency department [ED] visits and hospitalizations), and costs.24-25 The term “future risk” refers to the individual risk of asthma exacerbations and death, adverse effects from medications, and progressive loss of lung function (Figure 1). An increased risk for exacerbations or death may be predicted by several factors, including more severe airflow obstruction,26 more frequent ED visits or need for intensive care unit care,27 depression,28 and poorer attitudes about use of asthma medications.29

EPR-3 contains 3 tables that can be used to assess asthma severity in children aged 0-4 years, 5-11 years, and ≥12 years.8 In this version of the guidelines, the term “mild intermittent” is replaced with the term “intermittent” to emphasize that patients who have intermittent asthma may also have severe exacerbations.8 The 3 severity tables in EPR-3 contain the domains of impairment and risk identified previously. On the topic of asthma severity, an important emphasis in EPR-3 is the fact that FEV1/FVC may be a more sensitive indicator of asthma severity than the other components of the impairment domain in children.30 Conversely, FEV1 is suggested as a useful measure of the risk of exacerbations in this age group.31

4. Monitoring Control Determines Ongoing Therapy

After therapy for asthma has been initiated, it is important to periodically assess and monitor the individual patient’s progress to ascertain whether the therapy is effective and the goals of therapy are being met. In previous versions of the guidelines, asthma severity was emphasized more than ongoing monitoring and assessment of asthma control. EPR-3 greatly expands the concept of asthma control as a measure used to determine the effectiveness of asthma therapy. According to EPR-3, asthma control is achieved by considering the same domains that one considers when classifying severity of impairment and risk. Reducing impairment includes preventing chronic and troublesome symptoms, reducing the need for short-acting bronchodilators, maintaining normal or near-normal lung function, maintaining normal or near-normal activity levels, and meeting patient and family expectations of therapy.8

Asthma control has been added as a target of guideline-based management of asthma because of observations regarding the effects of asthma control on clinical and other parameters. Studies have shown that patients with well-controlled asthma can have improved quality of life32 and decreased health care resource utilization.33 The Gaining Optimal Asthma Control (GOAL) study was a randomized, double-blind study of 3,421 patients with uncontrolled asthma. It compared fluticasone propionate and salmeterol/fluticasone in achieving 2 rigorous, composite, guideline-based measures of control: totally and well-controlled asthma.34 In the GOAL study, well-controlled asthma was achieved in 33% to 71% of patients, while totally controlled asthma was achieved in 8% to 42% of patients. Those patients who achieved either well-controlled or totally controlled asthma had a significantly lower rate of exacerbations and significantly higher quality of life scores. These data served to reinforce the importance of achieving asthma control, and EPR-3 refers to the results of this trial when discussing its expanded focus on asthma control.

EPR-3 contains 3 tables that can be used to monitor asthma control in children aged 0-4 years, 5-11 years, and ≥12 years.8 These tables contain the previously mentioned domains of asthma control, impairment, and risk, and classify asthma control into 3 categories—well controlled, not well controlled, and very poorly controlled. Individual components that should be considered when classifying the level of asthma control are indicated in Figure 2. When using these tables, clinicians should base the level of control on the most severe impairment or risk category. Ultimately, the level of asthma control should be used to determine if changes to therapy are necessary to improve the patient’s control.

5. A Stepwise Approach Should Be Used for Initial and Ongoing Therapy

In previous and current versions of the guidelines, a stepwise approach to therapy has been recommended. Using such a
scheme, therapy is initiated after initial severity is determined. Those patients classified with intermittent asthma should be treated with short-acting bronchodilators on an as-needed basis, while those classified with persistent asthma should be treated by initiating the lowest step therapy that will control their symptoms. EPR-3 states that the goal of asthma therapy should be to maintain long-term control of asthma with the least amount of medication, thereby exposing the patient to the least risk for adverse effects from pharmacologic therapy. Accordingly, once therapy is initiated and the level of asthma control is assessed, changes can be made to therapy according to this stepwise approach. This includes step-down therapy as well.8

EPR-3 contains 3 tables that may be used to guide the stepwise approach to managing asthma. Unlike previous versions, children have now been divided into 2 age groups, 0-4 years and 5-11 years, while youths and adults ≥12 years remain a separate group.8 In addition, EPR-3 now recognizes 6 steps in the stepwise approach rather than 4 in order to simplify the actions in each step.

According to EPR-3, there have been several notable changes to the stepwise approach in comparison with previous guidelines. In the 0-4-year age group, for patients not well controlled on low-dose ICS, increasing the dose of ICS to medium dose is recommended before adding adjunctive therapy. This recommendation is based on a study that showed that increasing the dose of ICS in this age group results in an improvement in asthmatic symptoms in 1- to 3-year-olds35 and a lack of data to support the use of adjunctive therapies in this age group. For other age groups, increasing the dose of ICS to medium dose or adding adjunctive therapy to a low dose of ICS is considered an equal option8 (Figure 3). Because of a lack of comparative data, several adjunctive therapies may be considered as add-on therapy for the patient uncontrolled on low-dose ICSs, including LABAs, leukotriene receptor antagonists (LTRAs) (such as montelukast), and theophylline. While the data are not strong, of these choices, LABAs are preferred by EPR-3 on the basis of studies that show that addition of a LABA to an ICS improve lung function and symptom control.36-37

An additional change to the stepwise approach in youths and adults ≥12 years is the addition of omalizumab as an option for therapy in patients who are uncontrolled on a high-dose ICS and LABA and have a demonstrated sensitivity to perennial allergens (Figure 3). Since such therapy is placed at steps 5 and 6 of the algorithm and because of the risk associated with the use of omalizumab, consultation with an asthma specialist is recommended for patients who require this step of therapy.8

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**FIGURE 2** Components of Asthma Control

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| Impairment            | • Nighttime awakenings  
                       | • Interference with normal activity  
                       | • Short-acting beta-2 agonist use for symptom control  
                       | • Lung function\(^a\)  
                       | • Validated questionnaires\(^b\)  
| Risk                  | • Exacerbations requiring oral systemic corticosteroids  
                       | • Progressive loss of lung function\(^c\)  
                       | • Treatment-related adverse effects  

\(^a\) Not a component of control in children aged 0-4 years.  
\(^b\) Only in patients 12 years old.  
\(^c\) Referred to as “reduction in lung growth” in children aged 5-11 years.  
Derived from Figures 3-5a, 3-5b, 3-5c, Expert Panel Report 3, 75-77.8

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**FIGURE 3** Stepwise Approach of Managing Asthma in Youths ≥12 Years of Age and Adults

| Step 1 | Preferred: Low-dose ICS, LABA, or Mometasone Furoate  
         | Alternative: Short-acting bronchodilators  
         | SABA (Betaxolol)  
         | PRN (Propranolol)  
| Step 2 | Preferred: Low-dose ICS + LABA, or Mometasone Furoate  
         | Alternative: Long-acting beta-2 agonist, or Leukotriene Receptor Antagonists (LTRAs)  
         | Step 3 | Preferred: Medium-dose ICS + LABA  
         | Alternative: Medium-dose ICS + LTRAs  
         | Step 4 | Preferred: High-dose ICS + LABA  
         | Alternative: High-dose ICS + LTRAs  
         | Step 5 | Consider omalizumab for patients who have allergies  
         | Step 6 | High-dose ICS + LABA  
         | Consider omalizumab for patients who have allergies  

Quick-Relief Medication for All Patients

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA > 2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Abstracted from Figure 4-5, Expert Panel Report 3, 343.8

EIB = exercise-induced bronchospasm; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; LTRA = leukotriene receptor antagonist; PRN = as needed; SABA = short-acting beta-2 agonist.
6. Effective Control Includes Managing Special Situations

In addition to inherent variability in the course of asthma, adjustments to therapy may be required based on additional factors, including special situations. EPR-3, as well as other versions of the guidelines, discusses exercise-induced bronchospasm (EIB), surgery and asthma, pregnancy, and racial and ethnic disparities in asthma as 4 special situations that must be considered in the comprehensive management of the patient with asthma.

EIB is characterized by cough, dyspnea, chest pain or tightness, wheezing, or endurance problems during exercise and in some patients may be the only manifestation of asthma. All patients with asthma should be queried to determine if they experience EIB, since EIB may represent inadequately controlled asthma. Comprehensive management of EIB includes use of long-term controller therapy (if appropriate) and pretreatment before exercise with any of a number of asthma therapies, including short-acting beta-2 agonists (SABAs), LABAs, or LTRAs.

Patients with asthma who undergo surgery may be at increased risk for respiratory complications. Accordingly, EPR-3 recommends that patients with asthma have a preoperative evaluation that includes review of symptoms, present medication use, and objective measurement of lung function. Attempts should be made to improve the lung function before surgery, if possible. Finally, stress-dose corticosteroids may be considered for patients who have received oral systemic corticosteroids during the past 6 months and for selected patients on a long-term high dose of an ICS. Studies have shown that if a patient's asthma is well controlled, the risk of perioperative complications is low.

Maintenance of adequate asthma control in pregnant patients is well known to be important for both the health of the mother and the child. To achieve this control, EPR-3 recommends that several actions be carried out, including routine monitoring of asthma status during all prenatal visits; use of albuterol as the preferred SABA when required; use of ICS, and specifically budesonide, as the preferred long-term controller medication when one is required; and use of intranasal corticosteroids to treat concomitant allergic rhinitis, if present. Data suggest that the outcome of most mothers with asthma and their newborn infants is usually favorable, particularly if the women's asthma is well controlled during pregnancy.

As with many other conditions, racial and ethnic disparities may influence asthma management. Studies have shown that minorities are less likely to use anti-inflammatory and preventive medications for asthma and are also less likely to pursue adequate follow-up care for asthma. This is likely due, in part, to socioeconomic barriers. Additionally, minorities are more likely to live in urban areas where a high exposure to indoor allergens (such as cockroaches) is present. Efforts to eliminate racial disparities in asthma care are underway.

7. Managing Exacerbations Is an Important Part of Asthma Care

Asthma exacerbations are defined as episodes of progressively worsening dyspnea, cough, wheezing, and chest tightness (or any combination thereof) and are characterized by decreases in expiratory airflow that can be documented and quantified by spirometry. The burden of such exacerbations is substantial, with approximately 1.5 million ED visits for asthma in 1995, of which 20%-30% required hospital admission. Accordingly, prevention of asthma exacerbations is very important, and this topic has been addressed in previous versions of the asthma guideline and again in EPR-3.

Early treatment of asthma exacerbations is the most effective approach to management. Early treatment includes patient education, recognition of early signs and symptoms of an exacerbation, appropriate intensification of therapy, removal or withdrawal of any offending environmental substance, and ongoing communication between patient and clinician. EPR-3 updates the existing asthma guideline by simplifying the classification of asthma exacerbation into mild, moderate, severe, and life-threatening and by applying peak flow cutoff points for each of the classifications.

Management of asthma exacerbations includes therapies that can be delivered in the home and those used in urgent or emergency care. Home management includes increasing inhaled SABA use and, in some cases, adding a short course of oral systemic corticosteroids. EPR-3 removes the recommendation that suggests that an appropriate therapeutic option for home management of an asthma exacerbation is doubling the dose of ICS, on the basis of data that show this practice is ineffective.

Urgent or emergent management of an asthma exacerbation includes use of oxygen, SABAs, systemic corticosteroids, and consideration of adjunctive treatments in certain clinical circumstances. During this time, ongoing monitoring is vital, and once the patient is discharged, adequate follow-up is important. Studies have shown inconsistent results on the effectiveness of facilitated follow-up from the ED on asthma outcomes, but interventions such as appointment assistance have been shown to significantly increase the likelihood that discharged asthma patients will obtain primary care follow-up.

EPR-3 makes several recommended changes to the existing asthma guideline regarding management of asthma exacerbations. First, levalbuterol is added as a potential treatment for asthma exacerbations. Second, for prehospital management (i.e., in the ambulance), standing orders for SABAs and protocols are suggested to improve airflow before the patient reaches the ED. Such protocols have been shown to be safe and effective. Third, magnesium sulfate and heliox are added as potential adjunctive therapy for asthma exacerbations for patients in the ED unresponsive to initial therapy.
Conclusion

The recent release of the EPR-3 update from the NAEPP has provided managed health care professionals with new information to improve the care of patients with asthma. More comprehensive definitions of severity, including the domains of current impairment and future risk, as well as an increased focus on achieving asthma control will result in better asthma management protocols within managed care organizations (MCOs) by allowing for more precise asthma classification in accordance with improved knowledge of asthma pathophysiology and assessment. EPR-3 provides a wealth of scientific literature to refer to when constructing MCO algorithms and guidelines for asthma management. EPR-3 is lengthy, and further revision to NAEPP guidelines for asthma diagnosis and management will be necessary as knowledge about this disease increases and more pharmacologic therapies become available. Until the next update, EPR-3 represents the best of what is available to improve the care of patients with asthma.

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Members of the discussion panel of asthma experts convened on June 7-8, 2007, in Hallandale, Florida.

Michael Baxley, MD, MS, MPH
Chief Medical Officer
Senior Marketing Medical Executive
Cigna South Florida
Sunrise, Florida

Kathryn Blake, PharmD
Clinical Research Scientist
Center for Clinical Pediatric Pharmacology
Nemours Children’s Clinic
Jacksonville, Florida

Craig A. Jones, MD
Director of Vermont Blueprint for Health
Montpelier, Vermont

H. William Kelly, PharmD, BCPS, FCCP
Professor Emeritus of Pediatrics and Pharmacy
University of New Mexico Health Sciences Center
Albuquerque, New Mexico

Daren Knoell, PharmD, FCCP
Associate Professor of Pharmacy, Medicine and Medical Pharmacology
Ohio State University
David Heart and Lung Research Institute
Columbus, Ohio

Todd A. Lee, PharmD, PhD
Senior Investigator
Midwest Center for Health Services and Policy Research
Hines Veterans Affairs Medical Center
Hines, Illinois
Research Assistant Professor
Institute of Healthcare Studies and Division of General Internal Medicine
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Bruce Sherman, MD
Board-Certified Pulmonologist
Medical Director, Global Services
The Goodyear Tire and Rubber Company
Director, Health and Productivity Initiatives
Employers Health Coalition of Ohio
Shaker Heights, Ohio

E. Rand Sutherland, MD, MPH
Associate Professor of Medicine
Director, Carl and Hazel Felt Laboratory for Adult Asthma Research
Medical Director, Pulmonary Physiology Services
National Jewish Medical & Research Center
University of Colorado at Denver Health Sciences Center
Denver, Colorado

Michael Wechsler, MD
Associate Director
Brigham and Women’s Asthma Research Center
Assistant Professor
Harvard Medical School
Boston, Massachusetts
REFERENCES


BACKGROUND: The Medicare Drug Benefit (Part D) was implemented on January 1, 2006. The principal emphasis in the first year was education of beneficiaries as part of the effort by health plans and prescription drug providers to enroll beneficiaries. There was continued emphasis on enrollment in the second year in 2007, with some refinement of the benefit such as removal of coverage for erectile dysfunction drugs.

OBJECTIVE: To (1) review policy statements released by the Centers for Medicare & Medicaid Services in 2007 for the Medicare drug benefit, (2) compile an abridged version of the highlights from the policy statements, and (3) describe implications that affect Part D plan sponsors, pharmacists, and beneficiaries in 2008.

METHODS: We reviewed more than 200 policy statements, including guidance, memos, announcements, and other communications that were released between January 1, 2007, and September 30, 2007. We selected those policy statements that described substantive changes in the Medicare drug benefit and summarized those that were determined to be most relevant to plan sponsors, pharmacists, and beneficiaries for 2008.

RESULTS: Policy statements summarized in this article fall into 12 categories that have the greatest relevance to plan sponsors, pharmacists, and beneficiaries in 2008: (1) the standard drug benefit, (2) redetermination of low-income subsidy (LIS) status, (3) reassignment of some LIS beneficiaries whose plan premium exceeds the 2008 benchmark by more than $1, (4) allowable marketing activities for pharmacists, (5) Medicare Advantage special enrollment period, (6) member transition process, (7) “best available evidence” for determination of LIS, (8) formulary review process, (9) redefinition of specialty-tier medication from a cost threshold of $500 in 2007 to $600 in 2008, (10) drugs that have a limited distribution network (i.e., “specialty” pharmacy drugs), (11) formulary reference file, and (12) transfer of reimbursement of the administration fee for Part D vaccines from Medicare Part B to Part D.

CONCLUSION: The Medicare drug program continues to be refined in 2008, including coverage of the cost of Part D vaccines and their administration fee entirely within Part D. Pharmacists will continue to be an integral part of the success of Medicare Part D in 2008 by being informed of the many changes to the benefit and adapting to these policies and regulations in a way that allows beneficiaries maximum access to the improved features and necessary medications.

What this study adds

• The standard benefit design coverage phase thresholds have changed for 2008: (1) the annual deductible increased 3.8% to $275 from $265; (2) the initial coverage limit is $2,510, up 4.6% from $2,400; and (3) beneficiaries must incur $4,050 in true out-of-pocket (TrOOP) costs before entering the catastrophic coverage phase, which is up 5.2% from $3,850 in 2007. After beneficiaries have incurred $4,050 in TrOOP in 2008, the cost-share is the greater of $2.25 for generics and $5.60 for brands or 5% of drug cost.

• Cost-sharing for dual-eligible increased by 5% for generic drugs in 2008 from $1.00/$3.10 (generic/brand) to $1.05/$3.10. Cost-sharing for other low-income subsidy (LIS) beneficiaries increased by 4.7% from $2.15/$5.35 (generic/brand) to $2.25/$5.60.

• The qualifying criterion for specialty-tier prescriptions increased by 20% from $500 per month in 2007 to $600 per month in 2008.

• Beginning in 2008, drugs restricted to a limited distribution network, known as specialty pharmacy medications, must be identified on Part D sponsors’ formulary submissions.

• Coverage of Medicare Part D vaccine administration fees moved from the Part B benefit to the Part D benefit in 2008. This is an important opportunity for pharmacists to administer Part D vaccines and bill Part D plans directly for the vaccine and administration.

What is already known about this subject

• The Medicare Prescription Drug Improvement and Modernization Act of 2003 provided the framework for the Medicare Part D program. Anyone who is eligible for Medicare may elect to participate in this federally funded program.
The Medicare prescription drug benefit was implemented on January 1, 2006. The first year of the benefit was marked by beneficiary education and enrollment. The Centers for Medicare & Medicaid Services (CMS), Part D sponsors, pharmacists, and beneficiaries all worked toward understanding the benefit, ensuring optimum enrollment, and facilitating implementation and coverage of necessary medications. The year was not without challenges, but by the end of 2006, 22.5 million beneficiaries were enrolled in a Medicare Part D plan. Approximately 75% of beneficiaries stated that they were satisfied or very satisfied with their Part D plans. After almost 1 year of experience with Medicare Part D, beneficiaries were given the opportunity to review their coverage and switch Part D plans during the open enrollment period from November 15 through December 31, 2006. Only 6% of beneficiaries reported switching plans during the open enrollment period.

The second year of Medicare Part D implementation in 2007 included changes to the standard prescription drug benefit, extension of the open enrollment period for Medicare Advantage-only plans, coverage exclusion for erectile dysfunction drugs, clarification of payment for Part D vaccines and their administration, and implementation of the national provider identifier for pharmacists and other providers. There was a continued emphasis in 2007 on enrollment, particularly among beneficiaries who were eligible for the low-income subsidy (LIS), also known as Extra Help; enrollment in Medicare Part D plans increased by 7.6% to 24.2 million beneficiaries. A special enrollment period was granted to those who qualified for LIS in 2007, and any late enrollment penalties were waived. Four million Medicare beneficiaries, 11% of all beneficiaries, lacked prescription drug coverage in 2006 and 2007. CMS faces a continuing challenge to reach out to unenrolled individuals so that everyone eligible for Part D is covered.

The third year of the program in 2008 involves continued refinement of Medicare Part D with an emphasis on offering improved choices to beneficiaries, such as a “free first fill” program and “limited gap coverage” in the “donut hole” as part of changes in the standard benefit. Developments of note in 2008 for the standard benefit and 11 other categories are described below.

1. How Did the Standard Benefit Change in 2008?

There was again a change in the standard prescription drug benefit (defined by CMS as the minimum required plan design) and LIS patient cost-sharing amounts in 2008. Each plan sponsor must offer one standard benefit design, or one that is actuarially equivalent. Annual updates to the standard benefit design are statutory requirements of the Social Security Act and will continue throughout the life of the program. These changes are tied to 2 statutorily defined indexes—the annual percentage increase in average expenditures for Part D drugs per eligible beneficiary (annual percentage increase) and the Consumer Price Index (CPI).

The first indexing method, the annual percentage increase, is used to update the following cost-share requirements of the Part D benefit (see table and footnotes):

1. The deductible, initial coverage limit, and out-of-pocket threshold for the defined standard benefit
2. Minimum copayments for costs above the annual out-of-pocket threshold
3. Maximum copayments below the out-of-pocket threshold for full LIS-eligible enrollees (≤ 100% federal poverty level [FPL])
4. The deductible for partial LIS-eligible enrollees (100% to 150% of the FPL)
5. Maximum copayments above the out-of-pocket threshold for partial LIS-eligible enrollees

The second indexing method, the CPI, is used to determine the maximum cost-share amount for dual-eligible beneficiaries (eligible for both Medicare and Medicaid) that fall at or below 100% of the FPL. These changes for the upcoming year are outlined in the Table.

Base Beneficiary Premium

The base beneficiary premium is calculated by CMS each year and is used in determining the late enrollment penalty. In 2008, the base beneficiary premium increased 2.1% from $27.35 to $27.93. The actual Part D premiums paid by beneficiaries equal the base beneficiary premium adjusted by a number of factors, such as application of the low-income premium subsidy (dual-eligibles receive full-premium subsidy). In practice, actual premiums paid by beneficiaries vary widely among Part D plans, but the average monthly premium is $25 in 2008, up 13.6% from $22 in 2007. The base beneficiary premium is used to calculate the late enrollment penalty, if incurred by a beneficiary. For example, if a beneficiary missed the original May 15, 2006, deadline to sign up for Part D and did not sign up until December 15, 2006, he or she incurred a 1% penalty for each month not joined; that is, for 7 months (June-December 2006). The penalty is permanent and is recalculated each year as the base beneficiary premium changes. In 2008, the penalty will be 7% of $27.93, or $1.96 in addition to the normal monthly premium. Late enrollment penalties are waived for beneficiaries who are eligible for LIS (see below).

Low-income Subsidy

The amount of LIS or “extra help” a beneficiary receives is based on his or her income and resources. In 2007, a beneficiary with an annual income below $15,315 ($20,535 for a married couple living together) and resources of less than $11,710 ($23,400 for a married couple living together) qualified for extra help. These income and resource ceilings are based on the FPL and will be updated in early 2008 when the FPL is updated. CMS extended the special enrollment period in which the late enrollment penalty is waived for LIS-eligible beneficiaries who enroll in a Part D plan through the end of 2008. LIS status means that beneficiaries...
The generic copayment tier were covered in the donut hole for a

Previously, plans notified their members if all medications in

materials.

to submit a separate formulary file that will be reviewed by CMS
to display this list on their Web sites and in other marketing

can also offer free first fills for certain medications such as generic
drugs in the donut hole. For example, plans may identify a

specific list comprising a small or large number of brand medi-
cations that are covered in the donut hole. This variation allows

plans to offer some brand name medication in the donut hole while

limiting their financial risk. For plans that choose this

option, a separate formulary file is submitted and reviewed by

CMS to ensure that statutory discrimination provisions are not

violated. Another form of limited gap coverage allowed by CMS

in 2008 is a maximum dollar amount of coverage (e.g., $500) in

the donut hole, thereby limiting the plan’s financial risk.

In 2008, plans are encouraged by CMS to offer drug benefit

offerings that include brand name drug coverage in the donut

hole. Plan sponsors are allowed to offer only 2 drug benefit

offerings per region, unless 1 of the plan offerings provides

coverage in the donut hole. If a plan submits bids, including a

benefit that offers coverage of all generics and brands in the donut

hole, up to 4 different offerings per region will be considered by

CMS as long as they have meaningful variations. Among the

17 national plans available in 2008, 12 offer coverage of generics

in the donut hole.10 None of the national plans offer coverage of

brand drugs in the donut hole in 2008.

**Implications**

The Medicare Part D standard benefit serves as a reference point

for benefit design. In 2007, 14% of Part D beneficiaries were in

plans with the standard benefit and another 51% were in

plans that were actuarially equivalent to the standard benefit.
The remaining 35% of beneficiaries selected a plan that offered

an enhanced benefit.1 Each year plan sponsors must explain to

beneficiaries the changes in the standard benefit design and LIS

copayments. These annual changes are mandated by the Social

Security Act and updated by CMS accordingly each benefit

year. Plan sponsors provide this information to beneficiaries in

print and through their Web sites. However, the task of explain-
ing the changes in LIS copays and out-of-pocket thresholds will

most likely end up with the pharmacist when the patient receives

an unexpected copay or is in the coverage gap longer than the

patient expected. In addition, new plan variations allowed by

CMS such as free first fills and limited gap coverage will most

likely not gain wide acceptance by plan sponsors in 2008.

Although the options sound good in concept, there are opera-
tional and patient education considerations. Significant systems
coding and testing are required to ensure the benefit processes
perform as intended. For free first fills, plans need to anticipate
and manage issues, such as what constitutes a first fill and how is
this communicated to beneficiaries, including the ones who are
already taking medications included on the free first fill list. For
limited gap coverage such as certain brand medications, signifi-
cant beneficiary education is necessary to manage expectations

pay minimal copayments (see Table) and are not subject to the coverage gap (donut hole).

**Free First Fill**

The Final 2008 Call Letter, a CMS document outlining the
agency’s guidance on the Part D programs, describes other
benefit variations that plans may use in 2008.9 One of these
variations is a free first fill program. As the name implies, plans
may offer free first fills on certain medications such as generic
drugs as part of a generic use incentive program to increase
generic utilization rates. Plans that offer free first fills are required to
submit a separate formulary file that will be reviewed by CMS and
to display this list on their Web sites and in other marketing
materials.

**Coverage in the Donut Hole—Limited Gap Coverage**

It has been common for plans to offer an enhanced benefit with
coverage of generic drugs through the coverage gap (donut hole). Previously, plans notified their members if all medications in
the generic copayment tier were covered in the donut hole for a

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**TABLE 2008 Changes to the Medicare Part D Standard Benefit**

<table>
<thead>
<tr>
<th>Benefit Parameters</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual deductible</td>
<td>$265</td>
<td>$275</td>
</tr>
<tr>
<td>Initial coverage limit</td>
<td>$2,400</td>
<td>$2,510</td>
</tr>
<tr>
<td>TrOOP costs</td>
<td>$3,850</td>
<td>$4,050</td>
</tr>
<tr>
<td>Catastrophic threshold</td>
<td>$5,451</td>
<td>$5,726</td>
</tr>
<tr>
<td>LIS copayments</td>
<td>generic/brand</td>
<td>generic/brand</td>
</tr>
<tr>
<td>Institutionalized beneficaries</td>
<td>$0/50</td>
<td>$0/50</td>
</tr>
<tr>
<td>Up to or at 100% FPL</td>
<td>$1.00/$3.10</td>
<td>$1.05/$3.10</td>
</tr>
<tr>
<td>Other LIS</td>
<td>$2.15/$5.35</td>
<td>$2.25/$5.60</td>
</tr>
</tbody>
</table>

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Footnote: The standard benefit design includes the annual deductible, which is the amount of money a beneficiary must spend on medications before the plan starts to pick up any portion of medication expenses. Once the member has satisfied the annual deductible, the member enters the initial coverage phase. As part of the standard benefit design, the plan pays 75% of prescription costs, and the member pays 25% during the initial coverage phase up to the initial coverage limit, above which there is a gap in coverage referred to as the “donut hole” in which the beneficiary pays 100% of medication costs until the TrOOP costs push the beneficiary into the catastrophic phase. For costs above the catastrophic threshold, the beneficiary is responsible for only a small portion of cost-sharing for the remainder of the benefit year. Plan sponsors can offer the standard benefit design or may vary their design as long as it is actuarially equivalent to the basic coverage. Sponsors may offer a wide variation of coverage plans, which could waive the deductible, charge copayments rather than coinsurance, or offer a combination of both. In 2007, many plan sponsors offered “enhanced” benefits, including generic drug coverage in the coverage gap (“donut hole”) as well as inclusion of certain Part D excluded drugs such as benzodiazepines or over-the-counter drugs.

FPL = federal poverty level, defined as an annual income in 2007 below $10,210 or $13,600 for a couple.

LIS = low-income subsidy, available to beneficiaries with annual income below 150% of the FPL and resources below $11,710 for an individual or $14,860 for a couple.

TrOOP = true out-of-pocket.
of coverage in the donut hole. Most plans will likely take a wait-and-see approach as they gather data to determine the marketing and operational costs of offering enhancements and variations to the Medicare Part D standard benefit.

2. Do Beneficiaries Who Qualified for the LIS in 2007 Automatically Qualify in 2008?

CMS performs an annual redetermination of LIS deemed status, known as “re-deeming.” The re-deeming process determines who continues to be deemed LIS for 2008 and whether the individual’s copayment level changes or remains the same. Individuals reported as dual-eligible beneficiaries in July 2007 have had their LIS-deemed status extended to December 31, 2008. The copayment level for 2008 is based on LIS status as of July 2007. Individuals who were previously deemed eligible for LIS but who did not appear eligible in July 2007 are not deemed for 2008. Their deemed status expired on December 31, 2007. CMS mailed notices in September 2007 to the non-deemed beneficiaries along with a LIS application to assist the individual in reestablishing eligibility for 2008. Individuals who became eligible for the LIS for the first time between July 2007 and December 2007 were deemed eligible through December 31, 2008. In addition to a written communication from CMS, an annual notice of change was sent to all beneficiaries from their plan sponsors in 2007 that outlined changes to their benefit and indicated their deemed status.

Implications
Pharmacists should encourage beneficiaries to carefully read any information received from the government regarding their LIS status. Individuals who need to reapply for LIS should have done so in 2007 in order to receive extra financial help by the beginning of 2008. Beneficiaries who lose LIS status in 2008 can obtain information on reestablishing eligibility at www.ssa.gov or by calling the Social Security Administration (SSA) at 800.772.1213.

3. Why is CMS Re-assigning Some LIS Beneficiaries to New Part D Plans?

Each year, the average plan premium bid amounts are calculated for each prescription drug plan (PDP) region to determine the regional benchmark. Dual-eligible beneficiaries receive full-premium subsidy and are assigned by CMS to plans that are at or below the benchmark for the region they live in. Since the benchmark changes each year with the new bids and is difficult to predict, CMS allows some flexibility in an attempt to prevent member disruption. Plans that exceed the regional benchmark by $1 or less are considered to meet the de minimis amount and retain their current dual-eligible members but may not receive new auto-assignments. Plans that exceed the de minimis amount will lose their dual-eligible members who will be reassigned to plans at or below the regional benchmark for their region.

Implications
It is estimated that up to 1.6 million full-premium subsidy beneficiaries may need to be reassigned in 2008. Because benchmarks and plan premiums vary by region, some plans may meet the benchmark standard in 1 or more regions but not in others. Pharmacists can identify which plans in their region meet the benchmark by viewing the plan Landscape Source spreadsheet available from CMS. Although beneficiaries will receive notification of this change in the mail, some dual-eligibles may not be aware of their reassignment until they attempt to get their prescriptions filled in 2008. Pharmacists need to obtain new plan information from the beneficiary in order to successfully submit an electronic claim to the new plan for payment. If the beneficiary is unaware of this new plan information and is unable to locate it, the pharmacist may attempt to obtain this information via an electronic (“E1”) transaction. The pharmacy can submit some basic patient information (e.g., first name, last name, date of birth, zip code, etc.) in a real-time query through the pharmacy processing system to obtain eligibility and plan information. This information is obtained from a facilitator that is contracted by CMS. Eligibility information is provided to the facilitator by CMS and is updated nightly. Reassignment of LIS beneficiaries to new Part D plans can create additional work for pharmacists and contribute to potential delays in the pharmacy. If a dual-eligible beneficiary is not satisfied with the plan to which he or she has been reassigned, he or she can switch to another plan at any time during the year. Pharmacists should direct beneficiaries to www.medicare.gov or 800.MEDICARE for assistance.

4. What Marketing Activities Are Allowable for Pharmacists?

In 2007, CMS clarified the allowable marketing activities for providers, provider groups, and pharmacies. CMS emphasized consistent policy, which is that providers and pharmacies may not “market” to beneficiaries, defined as “steering, or attempting to steer, an undecided potential enrollee towards a plan, or limited number of plans, and for which the individual or entity performing marketing activities expects compensation directly or indirectly from the plan for such marketing activities.” However, CMS clarified that providers and pharmacies are free to assist in beneficiary enrollment based on the beneficiary’s needs, and beneficiary education. Furthermore, a Part D plan can use providers, provider groups, or pharmacies to distribute printed information comparing the benefits of different Part D plans as long as the providers or pharmacies display printed information comparing the benefits of different Part D plans with whom they contract. The providers or pharmacies are not obligated to accept or display any comparative information regarding those Part D plans with which they do not contract.

Implications
In the past, pharmacists may have refrained from assisting
beneficiaries with plan selection or sign-up because they thought those activities were considered marketing by CMS and, therefore, not allowable. Pharmacists play an important role in education and enrollment assistance, and this role is recognized as allowable by CMS as long as no steering occurs toward a specific plan that benefits the pharmacy. The clarification of allowable marketing activities for pharmacists gives them the assurance that they can assist beneficiaries with plan selection or sign-up, based on beneficiaries’ needs.

5. What if an Individual Enrolls in a Medicare Advantage Plan Based on Misleading or Incorrect Information?

CMS has established a special election period (SEP) to address situations where an individual has enrolled in a Medicare Advantage (MA) plan based on misleading or incorrect information provided by plan employees, agents, or brokers. CMS will decide, on a case-by-case basis, whether the individual is eligible for a “Medicare Marketing Misrepresentation SEP,” in which the beneficiary can select another MA plan, a Part D plan, or fee-for-service Medicare (Medicare A and B).

Implications

This guidance gives rapid recourse to beneficiaries who inadvertently signed up for an MA plan based on misleading information and who later find out that the plan is not right for them. Pharmacists can direct beneficiaries to the CMS help desk at 800.MEDICARE or to www.medicare.gov for assistance.

6. What Is the Member Transition Process for 2008?

There were minor changes to CMS guidance for 2008 regarding member transition to a new plan. CMS has devoted a significant portion of the Medicare Part D manual to this topic and requires plan sponsors to attest to their adherence to this policy on an annual basis. By developing standards for the transition process, CMS decreases the potential for member disruption and helps to facilitate a smooth transition of members from existing prescription coverage to a new plan.

A member transition process may apply to members new to a plan in any of the following scenarios:
1. Following the annual election period
2. Becoming a newly eligible Medicare beneficiary
3. Switching from one plan to another during the year
4. Residing in a long-term care (LTC) facility

The intent of the transition period is to prevent new members who are not yet familiar with their prescription formulary from being turned away from their pharmacy without medication on which they have been established. This transition period is a minimum of 90 days from the date when the beneficiary first becomes eligible in the new plan. Although the transition period is the first 90 days of eligibility, Part D plans are required only to provide up to a 30-day fill for ambulatory patients. That is because a member may have received a 90-day supply of medication prior to switching plans and may not need a refill until almost 90 days into the new plan. The 30-day temporary fill allows the member time to discuss formulary options with his or her physician or provide the time necessary to request a formulary exception.

LTC Transition Process

Based on the characteristics of LTC residents in which care is more intense due to complicated disease conditions and drug therapy regimens, special requirements have been instituted by CMS for transition of these members. As with the ambulatory patients, new LTC residents are also allowed a 90-day transition period; however, they are allowed multiple prescription fills for the entire 90-day transition period. These transition fills are allowed in a quantity up to a 31-day supply because many LTC pharmacies supply medications to nursing homes in blister packs based on a 31-day month. In addition to allowing multiple transition fills, plan sponsors are required to allow up to a 31-day emergency supply of medication for LTC residents who are outside of their initial 90-day period with a plan. What constitutes an “emergency” is not specifically defined by CMS but is generally interpreted by the health care providers as any prescription that a patient needs to satisfy an immediate medical need, and the prescriber cannot be reached during normal business hours or after hours or weekends.

This provision is intended to prevent a disruption in initiation of therapy until the physician can be consulted about covered formulary options or the plan can be contacted to request an exception to the plan’s formulary requirements. For example, an LTC facility contacts a physician because a resident has the symptoms of a urinary tract infection. The physician prescribes an antibiotic, and the LTC facility contacts its contracted pharmacy provider with the antibiotic prescription order. Once the pharmacy submits the claim, a rejection is received through the claims system that the antibiotic prescribed is non-formulary. At this point, the physician may no longer be available; also, the LTC pharmacy provider may have stated requirements or contractual requirements with the facility to deliver the acute medication within a specified amount of time, usually several hours. The emergency supply provision allows the pharmacy to receive a paid claim from the plan sponsor and provide the medication to the member expeditiously, preventing the LTC member from having a delay in delivery of an acute medication.

Medications Eligible for a Transition Fill

Medications that are eligible for a transition fill, regardless of patient setting, include drugs on the plan’s formulary that have utilization management restrictions such as prior authorization, step therapy, or quantity limits, or those Part D-eligible medications that are considered non-formulary.
Process for a Transition Fill

The beneficiary is charged cost-sharing for the prescription for the transition supply. LIS beneficiaries may not be charged more than the statutory maximum copayment amounts for which they qualify during that benefit year. Non-LIS beneficiaries are charged the cost-share amount based on the previously approved benefit design. The copayment or coinsurance is the same amount as if the patient had received a formulary exception for the medication.

All plan sponsors are required to mail a transition fill notice via U.S. first-class mail to the beneficiary within 3 business days of receiving a transition fill. This notice by U.S. mail is necessary despite electronic messaging at point of dispensing to the pharmacist to indicate that a particular fill was allowed because the message may not always be conveyed to the patient. Patients may receive their medications and not realize that further action is required on their part prior to the next fill. The minimum requirements for the transition fill notice, as defined by CMS, are as follows:

1. Explanation of the temporary nature of the transition supply an enrollee has received
2. Instructions for working with the plan sponsor and the enrollee's prescriber to identify appropriate therapeutic alternatives that are on the plan's formulary
3. Explanation of the enrollee's right to request a formulary exception
4. Description of the procedures for requesting a formulary exception (e.g., provide a customer service number for the patient to contact to initiate the process)

Plans are encouraged to enhance the notification sent by U.S. mail to the beneficiary. The enhancement may include the reason for a transition fill (e.g., the drug requires prior authorization), appropriate formulary alternatives, and prior authorization forms to help facilitate the process for the member.

The requirements outlined above are minimum requirements, and plans may have more robust transition policies and procedures. Since transition policies and procedures vary and may influence plan choice by beneficiaries, CMS requires plan sponsors to make their transition policies available in plan enrollment materials and Web sites.

Implications

Pharmacists should ensure they are familiar with the specific transition policies for all plans for which they process claims. There are significant differences between transition policies for ambulatory versus institutionalized beneficiaries, including the emergency supply requirement for LTC beneficiaries and the multiple-fill allowance (i.e., the patient may receive up to 3 separate 31-day fills or a larger number of fills for shorter days supply up the first 90 days of the patient’s eligibility for a beneficiary new to the plan). All patients, regardless of setting, should have a transition fill letter mailed to them within 3 business days of a transition fill. Pharmacists will undoubtedly receive questions regarding these letters and be asked for advice on how the patient should proceed.

7. How Should Part D Plans Use “Best Available Evidence” of LIS Status?

The best available evidence policy for LIS was developed by CMS in response to incorrect or lagging information of LIS status of members being passed on to the plan sponsors. The LIS status of a beneficiary is determined by either a state Medicaid agency or the SSA based on the information supplied to CMS on a monthly basis from the SSA and state Medicaid agencies. CMS then supplies this information to plan sponsors, which use this information to determine the appropriate cost-share amounts for LIS beneficiaries. If this information is not correct or is not supplied in a timely manner, some of the most vulnerable beneficiaries may be charged deductibles and copayments inappropriately and experience a lack of coverage of medication in the coverage gap or donut hole.

To assist beneficiaries in receiving the benefit to which they are entitled, CMS developed a best available evidence policy in 2006 and provided updates to this policy in 2007 for plans moving forward. As the name implies, plans are to work from the best available evidence they have to determine a beneficiary’s LIS status. Plans may act on evidence presented at the pharmacy to update a member’s LIS status; however, CMS notes that this evidence should be followed up with additional information and considered only when it is necessary to address urgent situations.

The type of documentation that CMS considers appropriate to allow a LIS update by plan sponsors includes 1 or more of the following: (1) copy of the member’s Medicaid card that includes the member’s name and eligibility date; (2) report of contact, including the date a verification call was made to the state Medicaid agency and the name, title, and telephone number of the state staff person who verified the Medicaid status; (3) copy of a state document that confirms active Medicaid status; (4) printout from the state electronic enrollment file showing Medicaid status; (5) screen print from the state’s Medicaid systems showing Medicaid status; or (6) other documentation provided by the state showing Medicaid status.

To establish that the beneficiary is institutionalized (e.g., LTC) and qualifies for a $0 cost-sharing level, the plan sponsor must furnish at least 1 of the following forms of proof: (1) remittance from the facility showing Medicaid payment for a full calendar month for that individual; (2) copy of a state document that confirms Medicaid payment to the facility for a full calendar month on behalf of the individual; or (3) screen print from the state’s Medicaid systems showing that individual’s institutional status based on at least a full calendar month stay for Medicaid payment purposes.

Once a plan has appropriate best available evidence, it may change the LIS status of a beneficiary for claims processing. On the basis of monthly file updates, CMS believes most of these
issues will resolve themselves without manual intervention. Plans are asked to wait 30 to 60 days to determine if the LIS is updated through the normal process. If there is no change, plans may make a LIS status correction request. Plan sponsors, or the business partner of plan sponsors, are required to maintain the records used to substantiate these requests for 10 years to satisfy the potential for government audits. Once a LIS determination has been made by CMS, the decision will be communicated to the plan’s contact of record, in a format that is not explicit in the guidance.

Implications
Plan sponsors need to ensure that they have an internal best available evidence policy for LIS determination and are able to follow this procedure when appropriate evidence is provided at the pharmacy to lower a patient’s cost-sharing at the point of dispensing. Although this situation can affect any LIS member regardless of patient setting, a large portion of LIS beneficiaries reside in the LTC setting. Unfortunately, LIS information is not always up to date or included in the eligibility information initially received by plan sponsors from CMS. LTC facilities will most likely act in good faith and not charge beneficiaries the higher copayments, anticipating an update to the LIS information.

8. How Has CMS Changed the Formulary Review Process?

Although changes related to formulary coverage requirements and the formulary review process are minimal for the 2008 benefit year, several are worth mentioning. First is the removal of the formulary key drug type (FKDT) inclusion criterion. The United States Pharmacopeia has developed a model formulary that contains therapeutic categories, pharmacologic classes, and FKDTs. For example, the renin inhibitor aliskiren, new to the U.S. market in March 2007, is in the therapeutic category of cardiovascular agents, the pharmacologic class of renin-angiotensin-aldosterone system inhibitors, and the FKDT of direct renin inhibitors. Plans in 2006 and 2007 were required to have at least 1 drug from each FKDT. Based on the FKDT requirement, plans would have been required to add aliskiren to their formularies. For 2008, CMS does not state that 1 drug from each of the USP formulary key drug types is required for a formulary to pass the approval process, but plan formularies will be compared against one another to identify outliers (defined as those plans that differ in FKDT inclusion from the majority of other Part D sponsors) that will be requested to make necessary enhancements to their formularies to receive approval. CMS also announced that the review process for formulary submissions in 2008 will be measured against an expanded list of treatment guidelines, but how this will be performed was not described in the guidance.

Another benchmark of comparison for formularies in 2008 will be the top 200 list of commonly prescribed medications in the Medicare/Medicaid population. This is a change from the previous comparison of 2006 and 2007 formularies against the top 100 list of commonly prescribed medications developed from the Medicare Discount Card program experience. This is an outlier test in which, again, CMS compares plans with their peers to determine if one plan formulary is substantially different from the majority of other plans. CMS does not provide a minimum number of top 200 drugs that must be covered to receive formulary approval but will develop expectations based on the averages determined by Part D sponsors in the marketplace.

Implications
Although there is no longer a requirement for at least 1 drug from each FKDT to be included in a plan’s formulary, little has changed in the formulary review process for 2008. There are few unique FKDTs (e.g., long-acting opioid analgesics) that are not included on plan formularies. The ones that are not included on plan formularies will most likely be consistently excluded across the majority of plans because they offer little clinical advantage over existing medications to treat the same condition. For example, aliskiren will most likely be excluded from formularies because they will already contain multiple angiotensin receptor blockers and angiotensin-converting enzyme inhibitors, which, although not in the same FKDT, do share the same therapeutic category and pharmacologic class. In addition, the CMS list of top 200 commonly prescribed medications contains many drugs that are available as generics. Based on these benchmarks, few plans will be considered outliers by CMS and asked to make substantial changes to their formularies.

9. How Has the Definition of Specialty Tier Changed?

The definition of a specialty-tier medication changed in 2008: the cost of the medication must on average exceed $600 for a 1-month supply to qualify for inclusion on a formulary’s specialty tier. This is a $100 increase over the 2007 threshold of $500. Cost is the only criterion that must be met for inclusion on this drug formulary tier. Therefore, any medication, whether brand or generic, oral or injectable, may receive specialty-tier placement if a plan chooses to do so.

Implications
One aspect of specialty-tier designation is that plans are not required to provide copayment-tier exceptions for these medications and, therefore, do not have to honor a request by a beneficiary to receive the medication at a lower cost-sharing tier. The change in dollar threshold for inclusion on a plan’s specialty tier will have minimal practical impact for 2008 because few drugs will end up falling off the specialty tier. Although a few medications may fall in the average price range of between $500 and $600 per month on average, the majority of medications that fall in this category easily exceed the new $600 minimum requirement limit. However, CMS is more closely scrutinizing which medications meet the qualifying criteria for specialty-tier...
inclusion and is asking plans to justify their specialty drug designations.

In certain circumstances, one strength of a particular drug may exceed the $600 cost threshold, yet the lower strengths do not. Plans will be allowed to have a higher strength of that particular drug on a specialty tier, but not the lower strengths of the same medication (e.g., erythropoietin 40,000 units per mL meets the criteria whereas erythropoietin 3,000 units per mL does not). This disparity may cause provider and patient confusion over the specialty tier.

10. How Is a Specialty-tier Medication Different From a Specialty Drug?

It is important to make the distinction between a specialty-tier medication and a “specialty drug.” What many in the health care industry refer to as a specialty drug, CMS refers to as a drug with limited distribution. CMS has taken the stance through previous guidance that plans may not restrict access to medications. However, CMS recognizes that a limited distribution network may be necessary for certain drugs such as lenalidomide, which requires special patient, physician, and pharmacist education. In 2008, plans are required to identify the medications that have a limited distribution network on their formulary flat file submissions through the CMS Web-based Health Plan Management System (HPMS). CMS expects health plans to restrict to a limited distribution network only those drugs that require extraordinary intervention (not defined) in handling, provider coordination, or patient education that could not be provided by the regular pharmacy network.

Implications

Part D sponsors have traditionally managed high-cost medications, in part by permitting dispensing only through a limited distribution network. The limited distribution pharmacy network provides patient education and case management and ensures that medication protocols are followed; there may also be a cost advantage for plan sponsors. The new requirement in 2008 for plan sponsors to identify the medications that are limited to a special distribution network will most likely lead to a type of outlier test as seen in other aspects of the program. Plan sponsors are allowed to continue this arrangement, but the list of drugs CMS allows through a limited distribution network will likely be smaller than what is currently used by commercial (non-Medicare) health plans.

11. Is There a New Formulary Reference File?

In March 2006, plan sponsors were introduced to the formulary reference file (FRF). This medication list, produced by CMS, contains representative National Drug Code (NDC) numbers for each strength and dosage form of Part D medications. For example, there is only one NDC number to represent amoxicillin 500 mg capsules, not every NDC number for this medication that is commercially available. This reference file was developed in an attempt to reduce the number of unique NDC numbers that were submitted by plans for the drugs on their formularies. The FRF decreases the work load for plans and makes the review process more efficient for CMS. CMS has been clear in its guidance that inclusion on the reference list does not necessarily make a medication a Part D drug, nor does exclusion from the list mean that it is not a Part D drug. All plans are required to make their own decisions as to the Part D status of medications. Although that may be the case, CMS will not accept submission of NDC numbers that are not found on the most current FRF.

CMS developed 2 different FRFs for 2007 and 2008, and each FRF pertains only to the respective year’s formulary submissions. There are many NDC numbers on the 2007 FRF that are not on the 2008 version. That is because CMS has become more thorough in its review of FRF drugs to ensure they have an approved application on file with the U.S. Food and Drug Administration (FDA). Drugs that do not have an approved application on file with the FDA have been excluded from the 2008 FRF. Plans need to determine what impact these exclusions have, if any, on their members, as the formulary changes in 2008. Until recently, CMS required that as soon as a reference NDC number was removed from the FRF, it was to be removed from the formulary submissions and would not be accepted through the prescription drug event files for reimbursement from that point forward. Although member notification of removal from the formulary was encouraged, it was not required.

DESI Drugs

In 2007, plans were challenged by the sudden change in Drug Efficacy Study Implementation (DESI) status of certain medications, such as the wound-healing ointment that has multiple formulations, including trypsin and balsam peru (e.g., Xenaderm). When these medications were reviewed by the FDA and determined to be less than effective DESI drugs, they no longer met the definition of a Part D medication. Plans often did not find this out until the reference file was updated. In addition, there was often a lag time before plan sponsors were able to operationalize a change in their adjudication systems. That resulted in plans paying for non-Part D drugs for a period of time, during which they did not receive reimbursement from CMS.

This situation changed on May 24, 2007. Since then, plans have been allowed to submit NDC numbers that were deleted from the FRF for 90 days after posting of the updated FRF. Although formulary submissions through the HPMS module are not allowed to have any NDC numbers that are not represented on the FRF, the plans’ adjudication system may continue to process these claims and submit them for reimbursement. CMS expects that when a negative change occurs due to a Part D status change of a drug—that is, when a drug is removed from the formulary—plans will provide affected members 60 days notice before the change goes into effect.
Implications
The FRF will continue to be a challenge for plan sponsors in 2008. Currently, the list is updated once a month. Some medications that are new to the market may be overlooked and may not be included for several monthly updates. Furthermore, inclusion on the list does not mean that a drug is a Part D drug, and exclusion does not mean that it is not a Part D drug. An FRF that is continuously updated (more than once a month) and that includes only drugs considered by CMS to be Part D drugs would be appreciated and well received by plan sponsors.

12. How Is Coverage Changing for Part D Vaccines?
The coverage of vaccines under Medicare Part D has been consistent since inception of the program; however, reimbursement for the administration component continues to evolve. In 2006, the guidance was clear that the administration of Medicare Part D-covered vaccines was not covered under the Part D or Part B benefit. The beneficiary was responsible for paying the administration fee, and because this fee fell outside of the Medicare benefit, none of it counted toward the patient’s true out-of-pocket (TrOOP) expenses. Whether the beneficiary had the standard benefit or was a LIS beneficiary who qualified for extra help, he or she could be charged directly for the administration fee.

In 2007, the CMS position changed to allow the administration fee of a Part D vaccine to be covered under the Part B benefit. This change came as a surprise to many plan sponsors, as guidance had been released in early December 2006 reiterating the policy that the administration fees fell outside of the Medicare benefit. In 2008, the policy has changed again to require the Part D plan sponsors to reimburse for both the vaccine and its administration.

Part D Vaccines
CMS has directed that starting in 2008, all Part D plans’ formularies must contain all commercially available vaccines (unless they are already covered under Part B). Medicare Part B covers pneumococcal pneumonia vaccine, influenza virus vaccine, hepatitis B vaccine for individuals at high or intermediate risk, and other vaccines (such as tetanus toxoid) when they are directly related to the treatment of an injury or direct exposure to a disease or condition. Part D covers zoster vaccine, human papillomavirus quadrivalent vaccine, and hepatitis B for beneficiaries who do not meet the intermediate- or high-risk coverage criteria. High-risk individuals include those who have end-stage renal disease, those with hemophilia who received Factor VIII or IX concentrates, clients of institutions for the mentally handicapped, persons who live in the same household as a hepatitis B virus carrier, homosexual men, and illicit injectable-drug abusers. Intermediate-risk groups include staff in institutions for the mentally handicapped and workers in health care professions who have frequent contact with blood or blood-derived body fluids during routine work.

Administration Fees
As of January 1, 2008, the administration fee associated with Medicare Part D-covered vaccines falls under the Part D benefit. This policy change is based on the fact that CMS views vaccines and their administration as having an “intrinsic relationship,” citing that one cannot exist without the other. The vaccine price, the dispensing fee, and the administration cost are collectively considered to be the vaccine price negotiated between the plan sponsor and the pharmacy. CMS expects that 1 claim will be submitted, whether received at an in-network pharmacy where the pharmacy dispenses and administers the vaccine or as an out-of-network claim where the physician supplies and administers the vaccine. Since the negotiated vaccine price contains all the components, beneficiaries are charged only 1 cost-share amount for the vaccine, the dispensing, and the administration. Whether the benefit design requires copayments or coinsurance, the entire price inclusive of all the components is applied to the specific coverage phase the patient is in.

Although CMS expects that vaccines and their administration are billed as 1 claim, they recognize that that may not be possible under all circumstances. There may be situations where a pharmacy dispenses the vaccination, but a physician or other qualified health care provider administers it. In this scenario, it is suggested that plan sponsors reimburse the pharmacy for the dispensing fee and the cost of the vaccine and reimburse the patient for the administration fee if he or she is billed for this service by the physician or other health care provider. CMS recognizes the potential “opportunity for both inappropriate and duplicate billing of administration fees.” For that reason, CMS prefers the single-claim method and requires plan sponsors to perform their due diligence through claims analysis to prevent fraudulent billing when allowing separate billing of the vaccine and its administration. It is suggested that when the vaccine is billed separately from the administration, plans should verify this one-to-one relationship. If one component is seen without the other, the plan sponsor should reach out to the beneficiary to ensure that the beneficiary did receive the vaccine and did not forget to submit a paper claim for reimbursement of 1 of the components.

CMS expects the National Council for Prescription Drug Programs (NCPDP) to develop standardized claim submission fields that will allow submission of Health Insurance Portability and Accountability Act-compliant transactions for the vaccine and its administration as 1 claim. In addition, CMS is adding a vaccine administration field to the PDE for submission. Plans are required to include the vaccine and the administration, whether submitted on the same PDE file or separately, in the case of separate billing, to assist in identifying the one-to-one relationship.

Reimbursement of Vaccine Administration Fee
Plan sponsors are permitted some flexibility in various aspects of the administration fee reimbursement. For example, they are allowed to negotiate the administration fee with network
pharmacies. This fee varies from the Part B vaccine administration fee, which is more clearly defined. Plans also have the ability to determine whether they will have 1 flat dispensing fee or varying administration reimbursements that can vary by provider type or difficulty of administration. In addition, plans can have utilization management on vaccines to verify safe and appropriate use in line with the Advisory Committee on Immunization Practices guidelines.\(^9\)

**Implications**

The inclusion of the administration fee in Part D is a service opportunity for pharmacists. CMS anticipates that “beneficiaries will consider receiving immunization of Part D vaccines in a pharmacy setting, given the real-time nature of the Part D benefit and the pharmacy’s ability to bill the Part D sponsor without the beneficiary having to pay upfront for the vaccine and its administration, as he or she might in the physician’s office.”\(^15\) Because of this new reimbursement structure for Part D vaccines, it may become standard practice for pharmacists to dispense and administer Part D vaccines such as zoster vaccine.

**Looking Ahead**

Medicare Part D is constantly evolving. The Children’s Health and Medicare Protection Act of 2007 passed the U.S. House of Representatives and the U.S. Senate but was vetoed by President George W. Bush in October 2007.\(^25\) The legislation proposed several beneficiary improvements to Medicare Part D, including (1) a SEP for beneficiaries in Part D plans that materially change their formulary to reduce coverage or increase cost-sharing for a drug that the beneficiary has been prescribed while enrolled in the plan, and (2) codification of the requirement that Part D plans cover all or substantially all drugs in 6 specific therapeutic classes of drugs (e.g., antiretrovirals, oral chemotherapy). The proposed legislation also allowed Part D coverage of benzodiazepines for the first time, simplified the application process for low-income beneficiaries, included costs incurred under AIDS Drug Assistance Programs and the Indian Health Service in TrOOP, and required consideration of factors such as pharmacy network and formulary when low-income beneficiaries are auto-assigned to a Part D plan. Although this legislation was vetoed, it is expected that similar changes may be addressed again in the 2008 legislative session. However, it is likely that any proposed changes to Medicare Part D during the 2008 election year will be administrative in nature.

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**Important Dates for 2008**

- January 1-March 31: Special enrollment period for managed care plans.
- October 1: Plans begin marketing for 2009 plan year.
- Mid-October: 2009 plan data and enhanced plan finder available.
- October 31: Annual notice of change and Medicare & You 2009 handbook must be in the mail to beneficiaries.
- November 15: Annual enrollment begins for 2009 plan year.
- December 8: Optimum date for early enrollment to ensure timely processing.
- December 31: Annual enrollment ends for 2009 plan year.

A pharmacist can find more assistance at the following sources:

- Call Medicare Pharmacists’ Help Line: 866.835.7595
- Call 800.MEDICARE (800.633.4227)
- TTY users should call 877.486.2048
- Visit www.medicare.gov/contacts/static/allStateContacts.asp for a list of local senior health insurance program organizations.
- Call Social Security Administration: 800.772.1213.
- Read Medicare & You (CMS Pub. No. 10112).

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**Authors**

RONNIE DEPUE, RPh, CGP, is corporate clinical pharmacy director, Medicare, Coventry Health Care, Glen Allen, Virginia; and JOANN STUBBINGS, RPh, MHCA, is manager, Research and Public Policy, Ambulatory Care Pharmacy Department, University of Illinois at Chicago College of Pharmacy.

AUTHOR CORRESPONDENCE: Ronnie DePue, RPh, CGP, Corporate Clinical Pharmacy Director, Medicare, Coventry Health Care, 4300 Cox Rd., Glen Allen, VA 23060. Tel.: 804.934.4242; E-mail: rjdepue@cvty.com
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The Search for Cost-Effective Treatment of Chronic Hepatitis B

Vanessa E. Smith, PharmD, BCPS, AE-C, and Christine J. Bruno, MD

Treatment of chronic hepatitis B remains challenging due to medication-resistant viral mutations, unanswered questions for initiation and duration of treatment, and risk for chronic liver complications. More than 400 million people worldwide are chronically infected with hepatitis B virus (HBV). Of those, an estimated 1 million die annually of HBV-related liver diseases. In the past decade, HBV-related hospitalizations, cancers, and deaths have more than doubled in the United States. Cirrhosis develops in 15%-20% of actively infected HBV patients within 5 years. For those patients, the incidence of hepatocellular carcinoma (HCC) is increased, with 70%-90% of HCC cases occurring in cirrhotics.

With the advent of telbivudine, the sixth medication approved for treatment of chronic hepatitis B by the U.S. Food and Drug Administration (FDA) in October 2006, treatment regimen complexity is predicted to increase due to HBV mutations leading to antiviral resistance. Combination therapies are being further explored, especially for treatment-experienced patients who face issues of resistance and adverse effects. Although vaccination to prevent hepatitis B became available in 1982, continued unawareness of modes of transmission and immigration from endemic areas are concerns for potential new exposures and development of costly chronic complications. Prevention is crucial to halt the increasing health care costs for hepatitis B, but current therapies have efficacy limitations for treatment-experienced patients. Further research to determine appropriate starting and ending treatment criteria is needed.

Hepatitis B treatment could reach the complexity of treatment of human immunodeficiency virus (HIV) with multiple medications in multiple classes. However, an increased ability to detect mutations may permit selection of the medication most likely to be effective for individual patients. For example, knowledge of the tyrosine-methionine-aspartate-aspartate (YMDD) mutation resulting from lamivudine therapy led to investigation of addition of therapy such as adefovir to decrease viral load and reduce resistance. Hepatitis B e antigen (HBeAg)-negative patients with lamivudine resistance who were treated for 3.5 years with adefovir plus lamivudine had less adefovir resistance (4.4%) than did patients treated with adefovir alone (33.3%).

The approval of tenofovir for treatment of chronic hepatitis B is expected within the next year, and other nucleoside analogues such as clevudine and emtricitabine remain in phase 3 trials. New advancements offer additional hope for treatment options for nonresponsive or resistant hepatitis B. A key to controlling the virus may lie in combination drug therapy.

To date, 8 genotypes for hepatitis B are known but are not routinely determined in patients outside of academic or clinical trial settings. Genotype determination may become standard in the near future and could increase the cost-effectiveness of treatment. One study demonstrated the positive predictive value for response in genotype A patients treated with interferon compared with genotypes B, C, and D. Another study showed that genotype B was more responsive than genotype C to interferon in HBeAg-positive patients. Knowledge of a patient’s genotype could also influence initial treatment decisions. Treating a patient with interferon injections for 16 to 32 weeks instead of prescribing lifelong oral medication could be cost saving, especially considering that immunomodulators such as peginterferon alfa-2a carry no risk for viral resistance. More data on the correct medication choice based on genotype are needed.

FDA approval of entecavir in 2005 substantially increased the ability to manage chronic hepatitis B. Lamivudine is no longer recommended as a first-line choice in treatment-naive patients. With a reportedly low incidence of adverse effects, entecavir therapy is well tolerated. Lamivudine’s reported resistance rate of 14% to 32% in the first year, increasing up to 20% each year thereafter, cannot compare with entecavir’s 0% reported resistance at 1 and 2 years for nucleoside-naive patients. Although the long-term resistance profile of entecavir is still unknown, 4-year data in a cohort of 120 nucleoside-naive patients showed that virologic rebound occurred in only 1 subject without evidence of genotypic or phenotypic resistance. As treatment benefits are obsolete once resistance develops and HBV DNA levels increase, maintenance of viral suppression is critical.

Telbivudine, the most recently approved oral medication for treatment of chronic hepatitis B, has a lower reported resistance compared with lamivudine, 21.6% for HBeAg-positive and 8.6% for HBeAg-negative patients at 92 weeks of treatment. Because of the higher rate of resistance for telbivudine compared with entecavir, telbivudine may eventually play the greater role in combination therapy. Adefovir and tenofovir are treatment options for telbivudine resistance. The PROACTIV Study is underway to evaluate continued therapy with (1) adefovir alone versus (2) telbivudine plus adefovir versus (3) telbivudine plus tenofovir.

Release of the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) trial results in 2006 precipitated the revision of national guidelines for the treatment of HBV to focus on viral levels versus the previous focus on alanine aminotransferase (ALT) elevations. More emphasis is now placed on suppressing viral loads. Data showed an increased risk of cirrhosis with HBV-DNA levels ≥10^4 copies per mL. Although an increased risk of progression to cirrhosis was associated with HBeAg-positive status and serum ALT elevations, the strongest predictor of future cirrhosis risk was elevated viral levels, providing evidence...
to heavily weight reduction of viral levels in making treatment decisions. The previous viral load cutoff for expected hepatitis B complications—100,000 copies per mL (20,000 IU per mL)—was decreased in the American Association for the Study of Liver Diseases (AASLD) practice guidelines in 2007 to 10,000 copies per mL (2,000 IU per mL) for HBeAg-negative patients with the goal of suppression to the lowest possible level.

While there are minor differences between the published treatment guidelines in AASLD versus Keeffe et al., there are substantial guideline changes common to both publications including (1) viral levels ≥20,000 IU per mL, (2) the measure of ALT elevated 2 times the upper limit of normal (ULN) for HBeAg-positive patients and viral levels ≥2,000 IU per mL for HBeAg-negative patients, and (3) the measure of ALT elevated 2 times ULN. Previous guideline criteria included (1) ALT levels alone to guide treatment for HBeAg-positive patients and (2) the degree of necroinflammatory changes and fibrosis on liver biopsy to guide treatment for HBeAg-negative patients, without mention of viral levels.

A potential cost-savings approach is to ensure that patients who meet recommendations for treatment receive proper medication and monitoring according to evidence-based guidelines. For example, initiation of antiviral therapy would be inappropriate for an HBeAg-negative patient with ALT 1.5 times ULN, HBV DNA 1,000 IU per mL, and a Metavir fibrosis score (an algorithm used to evaluate liver biopsy inflammation and fibrosis) of 0, the lowest possible score. Treatment outside of recommendations could result in patients starting costly therapy and potentially developing viral resistance sooner compared with monitoring and waiting until the evidence-supported starting point for treatment. Although guidelines do not always directly evaluate the cost-effectiveness of treatment, more evidence is building to guide initiation of hepatitis B treatment.

In the present issue of JMCP, Yuan et al. explore the cost-effectiveness of the previous first-line treatment, lamivudine, versus the newer therapy, entecavir. Although first-line use of entecavir is supported by national guidelines, third-party payers could be reluctant to cover entecavir as first-line treatment when a lower-cost alternative ($4,671 less per patient per year for lamivudine) is available. The REVEAL-HBV trial provides data to support a focus on decreasing viral levels by documenting prospectively a progression to cirrhosis ranging from 4.5% to 36.2% with increasing HBV-DNA levels in the absence of treatment. Despite applying mainly HBeAg-negative data to an HBeAg-positive population in the cost-effectiveness analysis, Yuan et al. proposed a model that is still useful in the overall picture of chronic hepatitis B treatment, considering that a 6.5 increased relative risk of cirrhosis was seen in REVEAL-HBV for the entire study population, including both HBeAg-positive and HBeAg-negative patients. However, more than 75% of cirrhosis complications, as well as HCC, occur after seroconversion from HBeAg-positive to anti-HBe. Therefore, the use of complication rates from a population in which 85% is HBeAg-negative may overestimate complication rates for an HBeAg-positive population. On the other hand, the cost savings of entecavir may be underestimated because the cost of liver transplantation for cases of HCC decompensation was not included in the model.

Also, it is unknown if extrapolation of results over a 10-year period is valid, given the unknown resistance pattern for entecavir. However, compared with lamivudine, entecavir is more attractive from the perspective of efficacy and prevention of hepatic complications. Additionally, there is the potential to discontinue treatment in HBeAg-positive patients as early as 6 months after seroconversion, possibly resulting in lower treatment costs compared with an HBeAg-negative population. As entecavir seroconversion rates range from 12% to 39% with increasing ALT levels, a number of HBeAg-positive patients may discontinue treatment before HBeAg-negative patients do.

A prior cost-utility analysis by Kanwal et al. in 2005 found that lamivudine and adefovir monotherapy strategies were more expensive and less effective than alternative treatment with interferon or step therapy with adefovir for patients who experience resistance to lamivudine. The authors concluded that this “salvage therapy,” in which adefovir is reserved for lamivudine-associated viral resistance, is likely to be highly cost-effective across most health care settings, regardless of HBeAg status of patients. However, interferon may still be preferred in health systems that focus on managing limited resources, particularly for populations with a high prevalence of HBeAg-negative HBV patients. In contrast to the analysis by Kanwal et al., the analysis by Yuan et al. did not consider the outcomes in HBeAg-positive versus HBeAg-negative patients.

However, using entecavir in lamivudine-resistant patients may increase the risk of resistance to entecavir, since genotypic HBV resistance to entecavir is 14% at year 2 of treatment in lamivudine-refractory patients. Using entecavir second line after lamivudine increases rates of resistance by 14% at 2 years of treatment. Although data from a Chinese population in the REVEAL-HBV trial may not be entirely applicable to a U.S. population that acquires hepatitis B mainly later in life, there is a direct correlation between increased viral level and risk of cirrhosis. Lowering HBV-DNA and therefore decreasing the risk for cirrhosis can prevent multiple complications, especially considering that the relative risk of developing HCC increases more than 100-fold in HBV-infected patients than in noninfected patients. However, use of lamivudine as a comparator with entecavir for estimating cost-effectiveness may not be the best choice when other comparators such as adefovir are available.

Medication cost may be a factor for nonadherence, especially for patients with Medicare Part D who reach the coverage gap or who lack medication coverage altogether. As the annual direct drug costs calculated by Yuan et al. based on annual wholesale acquisition cost (WAC) in 2006 were $7,365 for entecavir and $2,604 for lamivudine, postponing initiation of therapy might...
be a reasonable option until medication coverage is obtained, as an alternative to initiating therapy and then facing resistance associated with interruption of therapy.

One area in need of investigation is the cost-effectiveness of entecavir compared with adefovir for nucleos(t)ide treatment-naive patients. The costs of adefovir and entecavir are significant, with the average wholesale price (AWP) in 2007 of $8,720 for adefovir therapy and $9,742 for entecavir annually. Adefovir resistance is another factor to consider, with a reported incidence of approximately 30% at 5 years of treatment. Initial viral suppression is less potent with adefovir than with entecavir. However, adefovir is more closely matched with entecavir in efficacy compared with lamivudine.

As in so many areas in medicine, our need for information to guide decision making in patient care far outweighs the evidence available. Clinical trials of the complex array of treatment options in different patient subgroups (e.g., across different serum ALT and viral load levels, and HBsAg-positive vs. HBsAg-negative status) are needed. Chronic hepatitis B is the cause of 10%-20% of liver transplants. Chronic hepatitis B is the cause of 10%-20% of liver transplants.32

Our ability to treat HBV in a cost-effective way will depend on the quality of information available about prevention of complications in the array of patient subtypes seen in clinical practice. Only with such high-quality information can we decrease overall health care costs and increase quality of life in this complex patient population. The importance of HBV vaccination and screening in cost-effectiveness strategies should not be forgotten, especially considering that up to two thirds of the HBV chronically infected Asian and Pacific Islanders in the United States are unaware of their condition, increasing the potential to unknowingly transmit HBV to others and delay proper care and treatment.33

DISCLOSURES
The authors disclose no potential bias or conflict of interest relating to the subject of this commentary.

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Authors
VANESSA E. SMITH, PharmD, BCPS, AE-C, is an infectious disease clinical research specialist at Kaiser Permanente, Center for Health Research/Southeast, Atlanta, Georgia; and CHRISTINE J. BRUNO, MD, is a transplant hepatologist at Piedmont Hospital Transplant Services, Atlanta.

AUTHOR CORRESPONDENCE: Vanessa E. Smith, PharmD, Clinical Research Specialist, Kaiser Permanente, Center for Health Research/Southeast, Cumberland Medical Office, 2525 Cumberland Phwy., Atlanta, GA 30339. Tel.: 770.431.4247; Fax: 770.431.4124; E-mail: vanessa.c.smith@kp.org
The Search for Cost-Effective Treatment of Chronic Hepatitis B

Six products are approved in the United States for the treatment of chronic hepatitis B (CHB) viral infection: interferon alfa-2b, recombinant (Intron-A); peginterferon alfa-2a (Pegasys); lamivudine (Epivir HBV); adefovir dipivoxil (Hepsera); entecavir (Baraclude); and telbivudine (Tyzeka). In clinical trials, oral products administered up to 1 year to treat this chronic condition have demonstrated similar rates of hepatitis B e antigen (HBeAg) seroconversion from HBeAg-positive to HBeAg-negative status with the detection of hepatitis B e antibody (anti-HBe) ranging from 17% to 27% in adults. Costs, however, can vary widely. Factors affecting costs include the direct cost of the drug, length of treatment, and complications associated with continued therapy (e.g., development of resistance, intolerable adverse events). In addition, predictors and durability of response (pretreatment alanine aminotransferase [ALT] levels and serum hepatitis B virus [HBV] deoxyribonucleic acid [DNA] levels) may affect overall costs.

In this issue of JMCP, Yuan and colleagues attempt to estimate the long-term health and economic impact of treating patients with CHB from an overall cost perspective. The authors conclude that entecavir is more cost-effective than lamivudine in the long-term treatment of HBeAg-positive CHB virus patients. We applaud the efforts of the authors for the development and refinement of such a complicated and sophisticated model. However, the assumptions used for model development in this disease state (i.e., 10-year time horizon, difference in study populations, and epidemiology of the disease) create a double-edged sword. On one edge, using multiple variables allows an opportunity for greater accuracy for predictive modeling, and 10 years is an appropriate period to measure outcomes in a disease such as CHB since it typically takes 10 years or longer for the disease to manifest as adverse clinical outcomes. However, in a hypothetical population, if any of the assumptions used in creating the model are incorrect, the over- or underestimation of clinical utility will be magnified in proportion to the length of the time frame used in the model.

Lamivudine was the first oral nucleoside analog approved for the treatment of CHB and is now joined by 3 other oral agents. Since lamivudine’s entry into the marketplace, evidence of drug resistance to HBV has emerged, suggesting reduced susceptibility to lamivudine. Reported lamivudine resistance rates in CHB patients are 14% after 1 year of treatment and may increase to as high as 69% after 5 years of treatment. In light of lamivudine’s reported resistance patterns and the overall conclusion that entecavir given for up to 10 years is more cost-effective, the 10-year time horizon utilized in Yuan et al.‘s comparison of lamivudine with entecavir appears impractical. According to American Association for the Study of Liver Disease (AASLD) guidelines, lamivudine is preferred for short (undefined) courses of treatment.

In addition, this pharmacoeconomic (PE) model proposed by Yuan et al. begins with a hypothetical population of lamivudine treatment-naive individuals in the base-case model, and conclusions are drawn from the sensitivity analysis in which more than half of the patient population develops resistance to lamivudine within 10 years. This population is quite different from that of the Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD) study in which 2% of patients in the entecavir study group and 18% of patients in the lamivudine study group experienced virologic rebound during the first year of therapy. In the BEHoLD study, virologic rebound was used as a determinant to identify if resistance, defined as an increase in HBV DNA by at least 1 log_{10} copies per mL from the nadir, occurred during the treatment period. The continued use of lamivudine in treating lamivudine-resistant individuals has been associated with a diminished treatment response (i.e., higher pretreatment HBV DNA and ALT levels). The clinical significance of this observation, however, has not been fully elucidated.

The incidence and clinical course of CHB are different in developing countries than in the United States. In the United States, the risk of adults developing CHB from acute exposure to HBV is <5% while the incidence of CHB in endemic areas (e.g., Southeast Asia) can range from 25% to 30% in infants and children under the age of 5 years to as high as 90% in newborns of HBeAg-positive mothers.

Cohorts in studies describing the natural history of CHB can be categorized into 2 basic groups: (1) patients born in areas with high and intermediate prevalence rates for HBV and (2) patients in high-risk groups (e.g., intravenous drug users, homosexual men, inmates of correctional institutions, and individuals coinfected with hepatitis C virus or human immunodeficiency virus). This is an important consideration when evaluating drug therapy. Those who develop CHB early in life (i.e., acquired at birth from an infected mother or during early childhood) from an acute exposure experience disease progression and develop serious liver complications (i.e., compensated and decompensated cirrhosis and hepatocellular carcinoma) by the fourth decade of life due to the prolonged immune tolerance phase that is characterized by persistence of HBeAg, persistence of viremia for a longer duration, and normal ALT/aspartate aminotransferase (AST) levels. The prolonged immune tolerance phase is followed by a prolonged immune clearance phase (i.e., longer time to...
seroconversion of HBeAg and decrease in HBV DNA levels and more frequent bouts of disease activity constituted by hepatic flares.8,17-19

People of Asian descent born in areas endemic to hepatitis B typically acquire infections perinatally and thus fall into the immune tolerance phase. Conversely, adolescents and adults exposed to HBV that progresses to CHB immediately enter the immune clearance phase; the duration of the disease is usually shorter and becomes quiescent after seroconversion of HBeAg to anti-HBe. Individuals falling into this category are commonly referred to as healthy carriers of HBV and do not have active disease.8

Clinical trials have shown that clearance of HBeAg reduces the risk of hepatic decompensation and improves survival in patients with CHB.20,21 In the Risk Evaluation Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study, which was used by Yuan et al. to determine risks of complications for patients with differing levels of HBV viral load, most patients were from Taiwan and more likely to be in the immune tolerance phase; 85% of the REVEAL study patients were HBeAg-negative and 94% had normal (defined as <45 units per liter) ALT levels.22,23 In contrast, in the BEHoLD study, which was used by Yuan et al. to determine HBV DNA levels for patients treated with entecavir and lamivudine, 58% of the study subjects were of Asian descent and 40% were white. Also, at least 98% were HBeAg-positive in each BEHoLD study group, and 97% did not have antibodies to HBeAg. Hence, patients in the BEHoLD study group appeared to have active chronic disease, while individuals from the REVEAL study may have been carriers of HBV because the status of anti-HBe antibodies was not noted in the study.

In addition, the presence of HBeAg has been correlated with high levels of HBV DNA replication.24 In the REVEAL study, approximately 84% of HBeAg-positive individuals had HBV DNA levels > 1 million while 4% had HBV DNA levels <10,000 copies per mL.2 Because of the differences observed in these populations and the different disease etiologies in the 2 studies, it is difficult to interpret the applicability of the REVEAL study findings for Yuan et al.’s PE model for the treatment of hepatitis B in the United States. It is noteworthy that 86% of the patients in BEHoLD were from outside North America and 48% were from Asia and Australia. This PE model implies that the clinical course and progression of disease are similar for individuals with chronic disease versus carriers of HBV, an assumption that may or may not be correct.

PE models have advantages compared with clinical trials. For example, changes to the assumptions in the design or population can be made easily, and the vast amounts of time and resources required for a clinical study are not needed. However, the most useful study for payers of health care services would include real patients, stratified and randomized appropriately. The REVEAL study was a prospective cohort population-based study that evaluated the risk of liver complications based on HBV DNA viral load in treatment-naïve individuals. Because there is no direct correlation with HBV DNA viral load and complications in treated subjects, the reader is left to assume that this PE model mirrors the natural progression of CHB.

The current PE model proposed by Yuan et al. leaves the following 2 questions unanswered: (1) Does chronic administration with entecavir significantly reduce the risk of complications compared with the natural progression of the disease? (2) Does the amount of reduction in the risk of complications justify the additional costs in drug expenditure for entecavir? It is difficult to determine if the assumptions of the outcomes (compensated cirrhosis, decompensated cirrhosis, and hepatocellular cancer) based on the REVEAL and BEHoLD trials would come to fruition in an actual, long-term clinical trial. Additionally, a clinical trial would allow for more detailed analyses of the effects of race, gender, age, and other factors than is possible in a hypothetical model.

Another point not directly addressed in the Yuan et al. analysis is specification of the optimal regimen for treating HBV. Although this determination was not an objective of the study, it would have been interesting to see the analysis of the outcomes for an arm in which lamivudine was used first and patients were either converted to another agent upon treatment failure or intolerance of the product, or continued with add-on therapy. The model incorporates costs associated with add-on therapy with adefovir dipivoxil for study subjects who experienced virologic rebound with lamivudine and also included a sensitivity analysis of switching subjects from lamivudine to adefovir dipivoxil monotherapy. Both treatment scenarios may have varying degrees of impact on at least the HBV DNA viral load, with consequent influence on the associated costs of the model.

A few studies have shown improved outcomes in lamivudine-resistant patients as measured by virologic and serologic markers (i.e., HBV DNA viral load and ALT) associated with either adding adefovir dipivoxil to lamivudine in lamivudine-resistant patients or switching patients to adefovir monotherapy.25-27 Therefore, costs for a lamivudine-resistant patient treated with adefovir, either in monotherapy or in combination with lamivudine, may actually be lower than calculated by Yuan et al.’s model due to additional HBV DNA suppression. The PE model projects event probabilities of liver complications based on HBV DNA levels but does not appear to account for HBV DNA suppression that may occur with the addition of adefovir in lamivudine-resistant patients. Conversely, the addition of adefovir dipivoxil to lamivudine in lamivudine-resistant treated patients has also been associated with a higher risk of adefovir resistance.27,28 Accounting for this risk would increase the costs calculated by the Yuan et al. model.

Also unknown are the resistance patterns or mutations for entecavir. In the BEHoLD study, 2% of patients in the entecavir group and 18% of patients in the lamivudine group experienced
viral rebound during the first year of therapy. Although the genotypic analysis from this study did not reveal any substitutions in the isolates of subjects taking entecavir, the reason for virologic rebound is unknown. The PE model proposed by Yuan et al. does not provide enough information on viral rebound beyond 1 year for entecavir; thus, the validity of the assumptions is not readily apparent.

In addition, the correlation between lamivudine resistance and progression of disease is not clearly understood. It has been demonstrated that some patients seroconvert even in the presence of lamivudine-resistant hepatitis B viral mutants. At the end of 4 years, seroconversion occurred in up to 50% of patients treated with lamivudine. Thus, some experts favor continued treatment with lamivudine even in the presence of resistant variants. Therefore, the use of combination therapies would also need to be addressed in a more complete PE model.

Another uncertainty arises from the potentially invalid assumption that HBeAg seroconversion is equivalent to a positive clinical endpoint outcome. Although seroconversion is a valid measure of active disease, it is not a guarantee of clinical success. In the BEHoLD study, the HBeAg seroconversion rates for entecavir and lamivudine were similar in the 2 treatment groups (21% for entecavir vs. 18% for lamivudine, P = 0.33). Current clinical trials of drug therapy to treat CHB use a variety of biochemical, virologic, and histologic markers to determine disease progression and efficacy of drug therapies. It is not uncommon to see effectiveness defined by histologic score (e.g., Knodell or Ishak index score), biochemical score (e.g., ALT), virologic response (e.g., HBV DNA viral load, loss of HBeAg), HBsAg seroconversion, or presence of HBs or HBs antibodies. Unlike HBeAg status, which can denote if individuals have an acute or chronic infection, the presence of HBsAg indicates active infection.

Current diagnostic and treatment guidelines suggest that high-risk individuals and those living in areas with endemic HBV should be screened for HBsAg and HBsAg antibodies. Although HBeAg is a common biological marker used in clinical trials, its absence does not denote a true virologic cure of CHB. True cure is defined as (1) loss of HBsAg, (2) absence of detectable HBV DNA, (3) formation of anti-HBs antibodies, and (4) normalization of ALT levels. During the natural course of the disease, HBsAg average loss is <2% per year, similar to that seen with treatment with nucleoside/nucleotide analogs and 3% to 10% after 1 year of interferon therapy. HBeAg loss increases to 11% to 32% after 24 to 26 weeks of follow-up in those who initially respond to interferon therapy. Because of the complexity of these issues, it is difficult to determine the accuracy of the assumptions used in the PE model proposed by Yuan et al.

Also, the authors seem to imply that the treatment would be continuous; patients with CHB should be treated long-term with oral antiviral agents (in those eligible according to treatment guidelines) to maintain suppression of HBV DNA viral load. In clinical practice and in the BEHoLD trial, not all patients continue with therapy after an initial success. Studies from Asian and non-Asian populations have reported a sustained response following initial treatment of at least 52 weeks with lamivudine or 52 weeks with entecavir. It is interesting to note that of the patients in the BEHoLD trial who experienced a protocol-defined response (HBV DNA level <0.7 MEq per mL and HBeAg loss), 82% in the entecavir group and 73% in the lamivudine group had a sustained response 24 weeks after discontinuation of therapy; however, 41% in each group had undetectable HBV DNA levels and normalization of ALT. Thus, the results of this study show that the durability of response appears similar for the 2 agents.

Approximately 95% of primary infections in immunocompetent adults with HBV are self-limiting, with clearance of virus from blood and liver and subsequent development of lasting immunity to reinfection. CHB follows a dynamic history of progression. Current practice guidelines from 3 associations concerned with liver disease suggest that once a person achieves a healthy hepatitis B carrier state (i.e., seroconversion of HBeAg, presence of anti-HBe antibodies, and HBV DNA levels <10^5 copies per mL and normal ALT levels), treatment can be terminated. The debate, however, continues regarding the most appropriate duration of treatment, depending upon how early the patient contracted the infection.

The amount of viral replication has been suggested to play an important role in the development of cirrhosis and hepatocellular carcinoma. The magnitude of HBV DNA viral load is increasingly becoming a recognized independent risk factor that can be used to determine the risk of developing complications associated with CHB and to evaluate the efficacy of treatment regimens in treatment-naive patients and those who experience virologic rebound. Known factors affecting treatment outcome include viral load, ALT levels, and compliance with drug therapy.

More research is needed in tailoring therapy based on the diversity of disease progression and sustainability or durability of response, and determining the best treatment for failing regimens. Data are limited, and U.S. payers should be cautious in interpreting the results of this hypothetical model, particularly since the data inputs are not derived from populations in the United States. More studies are warranted to determine if long-term prophylaxis with entecavir will result in significant incremental cost savings and improved quality of life.

On the basis of current recommendations from the AASLD guidelines, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver, only 95% of primary infections in immunocompetent adults with HBV are self-limiting, with clearance of virus from blood and liver and subsequent development of lasting immunity to reinfection. CHB follows a dynamic history of progression. Current practice guidelines from 3 associations concerned with liver disease suggest that once a person achieves a healthy hepatitis B carrier state (i.e., seroconversion of HBeAg, presence of anti-HBe antibodies, and HBV DNA levels <10^5 copies per mL and normal ALT levels), treatment can be terminated. The debate, however, continues regarding the most appropriate duration of treatment, depending upon how early the patient contracted the infection.
or telbivudine) for a minimum of 1 year, followed by 6 months of additional therapy after HBeAg seroconversion. Patients should be treated until HBeAg seroconversion to anti-HBe, HBV DNA <20,000 IU per mL, and normalization of ALT levels.

Although 6 drugs are approved in the United States for the treatment of CHB, the Centers for Disease Control and Prevention (CDC) is moving to eliminate transmission of hepatitis B in the United States. From a societal perspective, the best course of action to decrease the risk of complications associated with CHB virus is through vaccination of high-risk individuals. Preliminary data from the CDC indicate that approximately 50% to 60% of adolescents aged 13 to 15 years are vaccinated against hepatitis B and that from 1990 to 2005, the incidence of acute hepatitis B in the United States declined by 78%. Data are also emerging to suggest that vaccination of individuals entering the United States from high-endemic areas may be cost-effective. The successful implementation of vaccination programs may truly reduce the economic burden of treating CHB and its complications.

**Authors**

MICHELLE L. HOLBROOK, PharmD, is a clinical pharmacy services specialist at Highmark Blue Shield, Pittsburgh, Pennsylvania; and ERIC J. CULLEY, PharmD, is the clinical pharmacy services manager at Highmark Blue Shield. Culley is a member of the JMCP Editorial Advisory Board.

**AUTHOR CORRESPONDENCE:** Michelle L. Holbrook, PharmD, Clinical Pharmacy Services Specialist, Highmark Blue Shield, 120 Fifth Ave., Suite 1812, Pittsburgh, PA 15222. Tel.: 412.544.6018; Fax: 412.544.4527; E-mail: michelle.holbrook@highmark.com

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The Future of Prescription Drug Cost-Sharing: Real Progress or Dropped Opportunity?

Kathleen A. Fairman, MA

It was October 25, 1986. Game 6 of the World Series between the New York Mets and the Boston Red Sox was tied in the bottom of the 10th inning, with 2 outs and 1 runner on base. The Mets' Mookie Wilson hit a routine grounder in the direction of first baseman Bill Buckner, who bent down to scoop it up. But in one of the most infamous incidents in sports history, the ball sailed past Buckner's outstretched glove and rolled through his legs into right field. The Mets scored, won the ball game, and eventually took the Series title. The Sox did not make another trip to the World Series until 2004. Their critical moment of opportunity had been lost.1

Managed care pharmacy currently faces a critical moment of opportunity as it considers the future of cost-sharing for prescription drugs. Nearly every serious observer of health care outcomes research understands that decisions about patient out-of-pocket (OOP) cost should be based on evidence. But what is less universally recognized is the importance of catching the right evidence to avoid dropping the ball in today's cost-sharing game. The key to understanding our industry's challenge (and opportunity) lies in recognizing that a paradigm transition is underway in both business and academic sectors of health care policymaking. A once almost universally held view, that generic/brand cost-share differentials and increases in cost-sharing to keep pace with inflation are the best tools to align consumer behavior with desired clinical and economic outcomes, is gradually being challenged by a new model of patient incentives. According to this new model, reduction or elimination in cost-sharing for prescription drugs has the potential to cure ills ranging from patient non-compliance to rising costs for medical services.2 As an industry, we can either respond to the paradigm shift to ensure that our bases are covered or risk dropping the ball.

**An Early Paradigm: Increasing Out-of-Pocket Cost Without Adverse Consequences**

The classic and best-designed study of the effects of cost-sharing, the RAND Health Insurance Experiment (HIE), randomized 2,750 families to receive medical care (1) free of charge, (2) at a 25%, 50%, or 95% coinsurance rate for all services, or (3) at a 95% coinsurance rate for outpatient services with free hospital inpatient care. Maximum annual OOP cost was indexed to family income, and all families received a lump sum payment equal to their worst-case OOP outlays to ensure that no family was financially harmed by participation in the experiment.3,4

HIE researchers found that as OOP cost increased, health care expense decreased. For example, annual total health care expenses in 1984 dollars were 45% higher for enrollees in the free-care plan ($749 per member per year [PMPY]) than for enrollees who were charged 95% coinsurance for all services ($518 PMPY) and 18% higher than for enrollees in the 25% coinsurance group ($634 PMPY).3 Annual prescription drug expenses in 1983 dollars were 60% higher in the free plan ($54.41 PMPY) than in the 95% coinsurance plan ($33.95 PMPY).3 The savings observed for the higher cost-sharing group were derived from lower utilization (e.g., number of physician visits and hospitalizations, number of prescriptions filled) rather than from reductions in cost per service. Notably, researchers posited that lower prescription drug expenditures were attributable to a smaller number of medical contacts (e.g., office visits) rather than to substitution of lower-cost for higher-cost medications, since neither cost per prescription nor generic fill rate was affected by cost-sharing.5

The decreased health care expense attributable to cost-sharing in the HIE study was not associated with negative health consequences. Although enrollees subjected to cost-sharing used fewer services, their health outcomes did not differ from those of enrollees who received free care.3,4 The only exceptions were observed in the group of enrollees at or below the lowest 20th income percentile. For this low-income group, free care was associated with lower blood pressure among patients with hypertension, modestly better vision among patients with vision problems, and improvement in 2 measures of dental health.3,4 Satisfaction with coverage was generally high and unaffected by the amount of cost-sharing, and enrollees in higher cost-sharing plans were less likely to worry about their health and had fewer restricted-activity days (including time spent in medical care) than those receiving free care.4

Because the HIE’s findings supported the use of cost-sharing for most enrollees with the exception of low-income persons, the HIE’s authors later speculated that their findings had encouraged an industry-wide move away from first-dollar health insurance coverage beginning in the early 1980s. If so, the HIE’s authors argued, the investment of $80 million in research costs to conduct the HIE had yielded savings of $7 billion in reduced hospital expenditures from 1982 to 1984.3

**The Early Cost-Sharing Paradigm Applied to Prescription Drugs**

The Kaiser Family Foundation estimates that from 2000 to 2006, mean prescription drug copayments under U.S. employer-sponsored health plans increased from $7 to $11 (about a $0.67 average annual increase) for generics, from $13 to $24 (about a $1.83 average annual increase) for preferred brands, and from $17 to $38 (about a $3.50 average annual increase) for non-preferred
brands. The largest average copayment increase occurred between 2001 and 2002, when the mean non-preferred brand copayment changed from $20 to $25. Increases in cost-sharing at point of sale had been advocated by proponents of managed competition, who argued that without sufficient financial responsibility for their preferences (e.g., for advertised brand-name medications instead of generic drugs, for richer versus more basic insurance benefits), consumers would have no “direct personal interest in economical medical care” and thus would not accept any cost consciousness in the health care system. Yet the need to measure the outcomes of copayment increase was widely recognized; the prevailing concern was whether higher OOP cost outlays would prompt or even force patients to reduce use of essential medication.

Consistent with the prevailing paradigm, most drug benefits research conducted since the mid-1980s has measured the impact of cost-sharing increase, usually applied to flat copayment amounts, on a variety of outcomes including utilization, cost, and medication adherence. Several studies employing strong quasi-experimental (pre-post with comparison group) designs examined modest copayment increases (i.e., change amounts ranging from $5 to $13 for brand medications). These amounts are greater than the annual average changes from 2000 to 2006 as reported in the Kaiser Family Foundation data but are typical of changes implemented in commercially insured populations at any single point in time.

These quasi-experimental studies found that modest copayment increases produced savings, particularly to net payer cost after subtracting member cost-share amount, without affecting adherence to chronic medication therapy or utilization of medical services, including hospitalizations, emergency room visits, and physician office visits. Controlled assessments of formulary compliance have similarly found that modest increases in patient cost-sharing are associated with increased utilization of preferred brands or generics.

Landsman et al.’s more recent quasi-experimental study of response to higher copayment amount increases (increases of up to $25 for non-preferred brand medications) in commercially insured populations assessed price elasticity, the ratio of change in quantity to change in price, which is a standard measure of price sensitivity. Study findings demonstrated price inelasticity (i.e., insensitivity to price change) among recent users (2 or more pharmacy claims in the therapy class within the 3 months prior to the copayment change) of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and HMG-CoA reductase inhibitors (statins). Price elasticity was moderate for cyclo-oxygenase-2 inhibitors, nonsteroidal anti-inflammatory drugs, 5-hydroxytryptamine receptor agonists (triptans), and selective serotonin reuptake inhibitors (SSRIs).

In a separate analysis of the same study sample, the authors documented higher “discontinuation” rates for patients subject to copayment increases than for a comparison group in several drug classes, including ACEIs, ARBs, statins, SSRIs, and tricyclic antidepressants. However, in the “discontinuation” analysis, the authors included patients whose most recent use of the drug class was more than 3 months prior to the copayment change and defined switches from ARBs to ACEIs, or from ACEIs to ARBs, as discontinuations. Thus, the price elasticity analysis was likely a better measure of response to price change than was the discontinuation analysis. Notably, in both analyses Landsman et al. excluded 20% of the potential sample of patients because of copayment discrepancy (i.e., at least 1 copayment actually paid by the patient did not match the copayment that should have been paid according to the benefit design), a decision that had the effect of removing from the sample all patients whose first prescription filled under the higher copayment system was “grandfathered” in (provided at the lower copay). Because “grandfathering” is a commonly used mechanism to ease patients’ transition into higher copayment designs, excluding the “grandfathered” patients likely biased Landsman et al.’s analyses in favor of finding higher discontinuation rates for the copayment change group.

One exception to the general rule of inelastic consumer response to a cost-sharing increase is the situation, more common in publicly funded coverage than in commercial insurance, in which members are enrolled in plans with atypical benefit designs (e.g., single-tier, very low or $0 copay) prior to the benefit design change. Huskamp et al.’s quasi-experimental analysis of discontinuation rates in 3 classes of chronic medications (ACEIs, proton pump inhibitors [PPIs], and statins) showed that users of non-preferred brand drugs in a copayment intervention group, who experienced a $12 increase in the highest copayment tier at the community pharmacy (from a 2-copayment tier at $6/$12 [generic/brand] to a 3-copayment tier at $6/$12/$24 [generic/preferred brand/non-preferred brand]), did not discontinue therapy at greater rates than did non-preferred brand users in a comparison group, who experienced no copayment change to a $6/$12 (brand/generic) structure. In fact, in that analysis, discontinuation rates for ACEIs were actually lower for the intervention group (8.3%) than for the comparison group (15.8%). However, non-preferred brand drug users who experienced a simultaneous $23 copayment increase and major tier-structure change (from a $7 single-copayment tier to an $8/$15/$30 3-copayment tier structure) discontinued therapy at higher rates than did non-preferred brand drug users who experienced no copayment change (16% vs. 6% for ACEIs, 21% vs. 11% for statins, and 32% vs. 19% for PPIs).

As Curtiss pointed out in a January/February 2004 editorial critical of Huskamp et al.’s work, the finding of a higher discontinuation rate for the group experiencing a $23 copayment increase was suspect. The comparison group in that analysis had a 2-tier $8/$15 (brand/generic) copayment design, not at all comparable with the intervention group’s $7 single-tier copayment design in the pre-intervention period.
because of the plan's formulary, the number of tier 3 statin users was extremely small, and the difference between the 21% (intervention) and 11% (comparison) statin discontinuation rates represented only 8 people. Nonetheless, Huskamp et al.'s results at least suggested the possibility that drastic copayment changes negatively affect adherence.

Roblin et al.'s study of oral hypoglycemic use in 5 managed care organizations produced a similar result using a time series with comparison group design.26 Although cost-sharing increases of $1 to $10 were found to be unrelated to average daily dose of oral hypoglycemic drugs, increases of more than $10 were associated with a decline of 2.6% per month in average daily dose. However, less than 2% of the study sample experienced a copayment change of more than $10, and of that group 69% of patients had received their medication either free of charge or for a copayment of <$5 per month prior to the copayment change. Thus, only large and atypical increases in beneficiary cost-share, not smaller and much more typical increases, were associated with declines in utilization.

Even among those accustomed to free medication, the effects of introducing a cost-sharing increase do not appear to be uniform. Dormuth et al. and Schneeweiss et al. conducted several studies of elderly (aged ≥65 years) beneficiaries in British Columbia's public health care system, examining the effects of sequential changes.19-21 Beneficiary cost-share changed first from free medication to a flat copayment of either $10 or $25, and then from the copayment design to 25% coinsurance with an income-based deductible. Results were inconsistent across therapeutic classes and disease states. Adherence (defined as percentage of days covered [PDC] >80%) to newly initiated statin therapy and use rates for inhaled steroids, inhaled anticholinergics, and inhaled beta-2 agonists were significantly lower under cost-sharing.19,20 However, adherence to beta-blocker therapy was only marginally related to cost-sharing (difference of 0.8 to 1.3 percentage points),21 and initiation rates for a beta-blocker or a statin following hospitalization for an acute myocardial infarction were unrelated to cost-sharing change.

Consistent with the RAND HIE's finding of increased vulnerability to cost-sharing among lower-income persons, additional exceptions to the general rule of consumer price insensitivity to prescription drug cost-sharing increases include low-income enrollees and patients with serious mental illness.3,4,22-25 Tamblyn et al.'s study of low-income and elderly persons in Quebec found that a change from $0 to $2 copayments to 25% coinsurance with income-indexed OOP maximums was followed by reductions in essential drug use by 9% for the elderly and by 14% for low-income persons; however, that study lacked a comparison group.22 A better-designed quasi-experimental study of veterans with schizophrenia, conducted by Zeber et al., found that patients subject to a $5 drug copayment increase (from $2 to $7) reduced use of psychotropic medications by nearly 25%; a slight increase in psychiatric admissions and total inpatient days occurred as well.23 That study's patient population was particularly vulnerable to the effects of a cost-sharing increase since, as the authors pointed out, 95% of veterans with schizophrenia earn less than $26,000 per year.

### Consumer-Driven Health Care: The Paradigm of Cost-Sharing Increase at Its Peak

Buoyed by research evidence that desired outcomes of cost-sharing change (generally inelastic consumer response, increased use of preferred brands and generics, overall cost savings) were being achieved in commercial populations, policy analysts began to speculate that asking consumers to pay a higher portion of total cost could be a potential, if partial, solution to the problem of balancing the sustainability of the health care insurance system against consumer preferences. Advocates of higher cost-sharing argued that members could freely choose among different options available (e.g., when selecting health care coverage or providers or requesting specific prescription drugs from their physicians) but should bear some financial responsibility for their choices.29

The higher cost-sharing paradigm appeared to reach its peak in market-based models, particularly in consumer-driven health care (CDHC), a financing approach that typically combines a high-deductible health plan with tax-advantaged accounts that can be used by enrollees to pay expenses for medical services and prescription drugs. Typical consumer-driven health plan (CDHP) features also include lower monthly premiums and greater consumer choice of services and providers, although these features are not universal.28 As RAND Health researchers have pointed out, CDHPs' cost-sharing features are similar to the design used in the HIE's 95% coinsurance plan.4 Among CDHC advocates, expectations for its potential to transform the health care delivery system are high. "Armed with money in hand and information they can act on, U.S. consumers can be an impatient and demanding bunch," one CDHC proponent wrote in 2005. "This is where the revolution really begins: in the impact such informed buyers will have on the rest of the health care system."29 In this view, consumers' ready willingness to reject "goods and services that no longer meet their needs" will "impose a level of discipline and accountability on health care that has long been missing."29

Whether consumers have the ability to determine which services meet their needs is open to question. The HIE found that enrollees in higher cost-sharing arrangements reduced their use of effective and less effective medical care by approximately equal amounts.4 However, a much more recent quasi-experimental (pre-post with comparison group) study suggested that CDHP enrollees distinguish between necessary and unnecessary services. That study found that in the 12 months following an insurance enrollment process in which beneficiaries were given no choice of plans, new enrollees of a high-deductible health plan (HDHP, n=8,724) were more likely than a comparison group of traditional insurance enrollees (n=59,557) to reduce use of repeat emergency department visits for conditions of low severity.
(e.g., upper respiratory tract infections, neck and back pain, headache, nausea) and indeterminate severity (e.g., abdominal pain; open wounds of extremities, head, neck, and trunk; nonspecific chest pain; superficial injury). For low-severity conditions, repeat emergency department visit rates per 1,000 members for the 12-month baseline and follow-up periods, respectively, were 142.5 and 92.1 for the HDHP members versus 128.0 and 132.5 for the traditional insurance members. Notably, neither initial emergency department use nor visits for high-severity conditions were significantly related to HDHP enrollment.30

Despite questions about consumers’ ability to make good health care choices, CDHP availability and enrollment have increased rapidly in the past few years. A recent nationwide survey of employer-sponsored health plans estimated that from 2005 to 2006, the percentage of large companies (20,000 or more employees) offering a CDHP increased from 22% to 37%. For smaller companies (10 to 499 employees), the percentage increased from 2% to 5%.31

### Opposition to Cost-Sharing Increases: Support for a Paradigm Shift

In about 2003, opposition to higher cost-sharing began to emerge from 2 camps that can best be described as “strange bedfellows.” In one camp, political advocates of universal health care coverage began arguing against market-based approaches to health care delivery, claiming that CDHC’s high OOP requirements prompt patients to curtail or cease use of necessary and cost-effective medical services. One claim was made by Commonwealth Fund president Karen Davis on the NewsHour with Jim Lehrer in February 2006. When asked by NewsHour host Ray Suarez what effects Davis believed would result from widespread implementation of CDHC, she answered that the Commonwealth Fund had “supported a survey … about people who had these high-deductible plans with health savings accounts and they do report that they go without needed care, they don’t fill a prescription where they really should be taking their prescription to control a chronic condition.”32 Davis argued that, ultimately, higher overall medical cost would result from lower adherence.

Davis did not mention that the response rate to the survey was only 6.5%,33 that the degree to which its Web-based respondent pool represented insured persons in the United States was questionable, or that the CDHC-related medical care reductions were actually proportionally larger for higher-income than for lower-income enrollees.34 Notably, compared with traditional insurance respondents to the Commonwealth Fund survey, CDHP-enrolled respondents reported similar medical utilization (e.g., office visit rates) and significantly better health; yet they indicated greater unmet health care needs.34 The obvious methodological and logical weakness of this evidence was typical of early studies of high-deductible plans; an October 2006 review of early experience with CDHC noted that the “evidence needed to draw firm conclusions about CDHC’s overall effects” was nonexistent.35

From another camp at about the same time (beginning in about 2002), numerous studies, many sponsored by pharmaceutical manufacturers, began documenting cross-sectional associations between higher prescription drug cost-sharing amounts and lower rates of medication utilization and adherence.36-43 The change in research methodology from strong quasi-experimental designs to cross-sectional analyses was seminal. Cross-sectional analyses compare different groups at the same points in time. They do not directly assess response to a change or intervention; they simply document statistical associations (e.g., between cost-sharing category and outcomes) that might or might not be causal.44,45

A marked shift in the findings of cost-sharing research reflects the magnitude of the methodological change. An early cross-sectional study conducted by Joyce et al. of RAND Health investigated employer-based coverage provided through 25 large companies. Study authors used medical and pharmacy claims data to compare prescription drug expenditures under various benefit designs. Statistical modeling controlled for demographic characteristics, including age, gender, work status, and median household income in the enrollee’s ZIP code; clinical characteristics, including comorbidities; and health plan characteristics, including cost-sharing for physician office visits. The model predicted that average PMYP prescription drug spending was $725 for a 1-tier plan with a $5 copayment, $678 for a 2-tier plan with $5/$10 copayments, $666 for a 3-tier plan with $5/$10/$15 copayments, and $436 for a 3-tier plan with $10/$20/$30 copayments.38 Thus in sharp contrast to the very modest utilization effects documented in quasi-experimental work,12,13,15 these cross-sectional results indicated that, for example, utilization was a dramatic 35% lower in a $10/$20/$30 benefit than in a $5/$10/$15 benefit.38 Another study conducted by Taira et al., again using a cross-sectional methodology, found that compliance (medication possession ratio [MPR] >80%) with antihypertensive medication was 24% lower for medications with a $20 copayment compared with a $5 copayment.39

In discussions of the findings of this cross-sectional work, claims going far beyond the available data have been remarkably and unfortunately common. For example, Goldman et al. asserted that they had documented “significant price responsiveness” among health care consumers, even though their study’s design had not actually measured price change at all (only an association between utilization measures and higher versus lower prices, supplemented by a mathematical simulation of how consumers behave when prices change).37 Similarly, in reporting results of a study that included no measures of medical costs or utilization at all, Joyce et al. concluded that “pharmacy benefit managers and their sponsors may be designing prescription benefit packages that reduce the costs of pharmaceuticals but increase overall medical costs.”38 Although knowledgeable observers at the time pointed out the lack of methodological rigor in cross-sectional work compared with stronger quasi-experimental designs,45,46
the body of cross-sectional work remains influential and is often cited as a key factor underlying the new “lower-is-better” view of cost-sharing.\(^2,47,48\)

The association between pharmaceutical manufacturer support (funding and/or personnel) and the results of cost-sharing research should not go unnoticed. Of pharma-supported studies of the relationship between patient outcomes and cost-sharing in commercially insured populations,\(^{14,16-18,36,37,39,43}\) most have produced at least 1 major finding critical of cost-sharing.\(^{14,18,36,37,39,43}\) In contrast, of studies that were not pharma-supported,\(^{12,13,15,26,38,42}\) few have produced findings clearly critical of cost-sharing.\(^{38,42}\) Notably, 2 quasi-experimental studies that produced findings critical of cost-sharing were pharma-supported\(^{14,18}\) and both employed study methodologies that were unusual or questionable. The use of unusual methodology in producing findings critical of cost-sharing was highlighted by Curtiss in 2004, when he pointed out that the headline press attention to the findings of the Huskamp et al. study\(^{14}\) ignored important ambiguities in its methods and findings.\(^{27}\) Curtiss reminded us that “like many things in life, the truth and wisdom” of cost-sharing research “are in the details.”\(^{27}\)

### A New Paradigm for Cost-Sharing: Copayment Reductions to Improve Outcomes

Not surprisingly, given the change in the direction of research findings, a new paradigm that had first been mentioned in 2001 began to gain substantial traction beginning in about 2004.\(^{31,42,47-52}\) Policy analysts began to describe associations between higher patient OOP costs and lower prescription drug utilization in a different way—this time emphasizing the association between lower OOP cost and higher utilization. Instead of asking how much patient OOP cost could be increased without damaging outcomes, policy analysts began asking how much OOP cost should be decreased to encourage adherence to prescription drug therapy and improve outcomes.\(^{31,42,47-52}\)

For example, Ellis et al. in 2004 found an association between higher copayments and lower statin adherence rates and asked whether copayment levels should be targeted, with lower copayments for patients “with the most to gain” from statin therapy.\(^{31}\) The authors argued that “coincidence alone cannot explain” why rates of discontinuation are lower in clinical trials (“where study medication is almost always provided free of charge to study subjects”) than in routine clinical practice. The authors suggested that providing lower-cost or no-cost medications to patients in routine clinical practice would improve medication adherence.\(^{31}\) Goldman et al.’s statistical simulation in 2006, based on cross-sectional analysis of medical and prescription claims data, produced a similar result. After finding associations between lower statin copayments and higher MPRs, and between higher MPRs and lower medical costs (but without actually measuring the relationship between prescription drug cost-sharing and medical costs), the authors concluded that “varying copayments for [cholesterol-lowering] therapy by therapeutic need would reduce hospitalizations and [emergency department] use.”\(^{42}\)

By 2007, the new concept that reducing OOP cost would yield big medical cost savings had taken hold in a small but growing share of the commercial insurance market. Large employers, including Procter & Gamble, Eastman Chemical, Pitney Bowes, and the Marriott Corporation, began reducing or eliminating copayments for chronic medications.\(^2,48,50\) For Pitney Bowes, the copayment reductions were part of a larger strategy that included elimination of all deductibles and provision of free preventive care, enhanced wellness programs, access to free clinics and fitness centers, and healthier snacks in the company cafeteria.\(^{47,49}\) Large insurers, including Humana, Aetna, and Cigna, began offering designs in which copayments were lowered or eliminated for medications that offer greater clinical benefits.\(^2,48\)

A Wall Street Journal article announced in May 2007 that payers “desperate for ways to curb soaring health-care costs” could find relief in copayment reduction. The policy of “shifting costs onto workers and encouraging them to use lower-cost generics” was the subject of an “about-face,” the article said, because “the new model” of copayment reduction for chronic illness “makes better medical sense.”\(^{48}\) Benefits designers began offering cost modeling tools to assist clients in offsetting copayment changes in different therapeutic classes (e.g., lowering copayments in essential medication classes but increasing copayments for less essential drugs).\(^53\) Despite the typically long-term and progressive nature of chronic illness, proponents even began to hint that short-term savings could be achieved from copayment reduction, albeit without supporting evidence: “Employers worry about the cost of this design,” commented one of its proponents, “[but] I tell them that reducing the costs of these drugs means their employees will be working instead of in a hospital.”\(^2\)

### State of the Art: Cost-Sharing Research Today

Articles recently published in JMCP provide additional lessons in the strengths and weaknesses of cost-sharing research today. In the October 2007 issue of JMCP, Zhang et al. reported the results of a study of patients newly initiating therapy with a single-agent angiotensin system blocker.\(^{51}\) Their analyses assessed the relationship between copayment for the first prescription fill and several measures of medication adherence during the first 6 months of treatment, statistically controlling for numerous variables representing predisposing factors (age, gender, previous use of antihypertensive medications other than angiotensin system blockers, and race measured at ZIP code level); enabling factors (urban vs. rural residence, whether pharmacy benefit included an OOP maximum, and several measures of medical and prescription drug utilization); and need factors (hypertension, cardiac conditions, diabetes, and dyslipidemia). The authors reported that every $1 of additional patient OOP cost for a 30-day supply of the initial prescription was associated with a 1.9% increase in total number of days without angiotensin...
system blocker medication, a 2.8% increase in the odds of having a PDC < 80%, and a 1.0% increase in the risk of having a treatment gap of more than 30 days.53

Zhang et al. advanced the cost-sharing debate by examining several different measures of medication adherence, focusing on the first 6 months of treatment and evaluating a wide range of cost-sharing amounts ranging from $0 to $128 per 30-day supply. However, the value of Zhang et al.'s study, like that of all other cross-sectional analyses of cost-sharing, was limited by the potential effect of unmeasured factors on study outcomes. Higher cost-sharing levels could be associated with unmeasured tangible factors (e.g., utilization management programs as step therapy or prior authorization, formulary differences, or scope of pharmacy and physician networks) and intangible factors (e.g., organizational culture, patient educational efforts that could have taken place years before, or local practice patterns). These factors, not the cost-sharing levels themselves, could be largely responsible for the differences observed between higher and lower cost-sharing groups.53,54

Because of the extreme vulnerability of cross-sectional design to the effects of confounding factors, overall measures of quality of statistical models (e.g., measures of percentage of variance explained such as R-squared and pseudo-R-squared or predictive accuracy measures such as area under the Receiver Operating Characteristic curve) are particularly critical when using this design. These overall quality measures demonstrate the degree to which the models have accurately accounted for confounding factors in comparing outcomes across cross-sectional groups. For this reason, the current tendency among authors of cross-sectional studies to fail to report accepted measures of quality for their statistical models is unfortunate.36-43 Although Zhang et al. are to be commended for reporting goodness-of-fit measures for their models, they indicate that the percentage of variance explained by their PDC model was only 9%. Thus, 91% of the variance in their measure of adherence was explained by unmeasured factors.53

In the November/December 2007 issue of JMCP, Klepser et al. provided a rare look at the outcomes of a change from a 3-tier copayment structure ($10/$25/$40 for generic/preferred brand/non-preferred brand) to a 25% coinsurance pharmacy benefit design with minimum and maximum OOP outlays per prescription.54 Beneficiaries who experienced no change in the 3-tier copayment levels served as a comparison group. Using a difference-in-difference analysis, Klepser et al. found that from the pre-intervention to post-intervention period, total spending increased 6.3% in the intervention group and 9.5% in the comparison group for a relative difference of $1.30 per member per month (PMPM). However, overall prescription drug utilization (number of claims) did not differ significantly across intervention and comparison groups. From the pre-intervention to the post-intervention period, utilization per patient per month (PPPM) in 3 essential drug classes (antihypertensives, antidepressants, and statins) increased 4.1% in the intervention group versus 9.0% in the comparison group (P=0.004), and total expenditures in the 3 classes for the intervention and comparison groups increased by 8.2% ($5.07 PMPM) and 13.3% ($7.80 PMPM), respectively (P=0.003). However, the increases in employer cost for the 3 essential drug classes in the intervention group (7.5%, $2.86 PMPM) and comparison group (16.1%, $5.67 PMPM) did not differ (P=0.057).54

Klepser et al. advanced the cost-sharing debate by using a strong quasi-experimental (pre-period to post-period with comparison group) research design to assess an extremely understudied benefit structure and by explaining the potential impact of specific minimum and maximum OOP outlays per prescription on the outcomes assessed by their study. However, the coinsurance group assessed by Klepser et al.'s study did not experience a change in overall cost-share relative to the comparison group; increases in beneficiary cost from the pre-intervention to post-intervention periods were not significantly different for the intervention (7.5%) and comparison (3.0%) groups (P=0.983). Thus, the Klepser et al. study does not shed light on the effect of simultaneous benefit design change and an increase in the overall magnitude of beneficiary cost-share.

Protecting Home Plate: What Must We Do Now?

As Klepser et al. suggest, comparisons of different types of cost-sharing changes are needed. Changes from a 3-tier copayment plan to coinsurance structures with various amounts of cost-sharing increase are unstudied. Also unexplored in the peer-reviewed research literature is whether different forms of cost-sharing increase that achieve the same overall cost-sharing increase (e.g., increasing copayments in a 3-tier plan vs. increasing coinsurance rates) produce different outcomes; for example, prescription drug and medical utilization and cost, adherence to chronic medication therapy, or use of expensive services such as hospitalizations and emergency department visits.

Well-designed studies that directly measure the effect of cost-sharing decreases represent a more urgent need. Under the early cost-sharing paradigm, controlled studies of cost-sharing increases were the most appropriate way to inform the constantly evolving pharmacy benefit design process; these studies directly assessed the question of how consumers respond to rising prices for prescription medications. Conversely, under the new cost-reduction paradigm, we need controlled (at least quasi-experimental, preferably randomized) studies to document how consumers behave when their OOP outlays decline. Until the results of high-quality investigations of cost-sharing reductions become available to inform policymaking in this critical area, we risk the loss of the well-documented gains made in cost-sharing design over the past several decades (Table). Decision makers who reduce prescription drug copayments in hopes of better adherence and lower medical costs do so without the benefit of research evidence about how patients

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actually respond to OOP cost reductions, making it especially important to monitor the clinical and economic outcomes of these reductions.

The Center for Value-Based Insurance Design (VBID), whose founders oppose CDHC and have long advocated determination of copayment levels based on medical need (e.g., reducing statin copayments for patients with higher cardiac risk), is currently involved in several research projects assessing VBID’s impact on quality and cost.55 Aetna, whose subsidiary ActiveHealth helps clients identify high-risk members for interventions (e.g., reduced copayments), plans a randomized trial of the effect of providing free medication in specified therapeutic classes (e.g., beta-blockers, statins) to patients who have had a myocardial infarction; a control group of patients will receive usual coverage and services.2

Meanwhile, the very limited evidence available to date does not support the view that reducing or eliminating prescription drug OOP cost will produce desired behavioral changes and even suggests that conclusions based on cross-sectional work may be incorrect. Karter et al.’s independent (not pharma-supported) quasi-experimental study of patients with diabetes mellitus assessed the effects of cost-sharing policy changes for glucose testing strips.36 Under a policy of charging copayments for the test strips, Karter et al. documented a cross-sectional association between copayment amount and lower levels of test strip utilization. However, a new policy providing test strips free of charge did not increase test strip utilization, even among those with higher cost-sharing amounts prior to the change. The authors concluded that providing the free test strips had “shifted costs from patient to health plan, without improving adherence.”36

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<td>RAND Health Insurance Experiment team35</td>
<td>Experimental. Numerous outcomes. Key outcomes were total expenditures for health care and prescription drugs and a variety of health outcomes measures.</td>
<td>2,750 families randomized to 1 of 5 cost-sharing plans: (1) free of charge, (2) at a 25%, 50%, or 95% coinsurance rate for all services, or (3) at 95% coinsurance for outpatient services with free hospital inpatient care. Maximum annual OOP cost was indexed to family income; families received lump-sum payments for participation.</td>
<td>• Expenditures decreased at higher cost-sharing levels; health care costs and prescription drug costs were 57% higher and 60% higher, respectively, for free care than for 95% coinsurance enrollees. • Free-care enrollees used more medical care than did enrollees in higher cost-sharing arrangements, but did not have better outcomes. The only exceptions were low-income enrollees with certain chronic conditions. • Satisfaction with health care was generally high and unrelated to cost-sharing amount. • Enrollees in higher cost-sharing arrangements were less likely to worry about their health and had fewer restricted-activity days (including time spent in medical care) than did those receiving free care.</td>
<td>U.S. Department of Health and Human Services</td>
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<td>Mootheral and Fairman (Express Scripts)33</td>
<td>Pseudo-experimental (pre-post with comparison group); compared 12-month periods before and after implementation of copayment change. Outcomes were total drug cost, net insurer cost, number of prescription drug claims, rates of continuation with chronic medication therapy, use of antibiotics following a diagnosis of otitis media, and medical utilization (office visits, ER visits, and inpatient hospitalizations).</td>
<td>Intervention group whose employer switched from a 2-tier ($7/$12) to 3-tier ($8/$15/$25) structure (n = 8,881) in 1998. Comparison group whose employer retained a 2-tier ($7/$12) structure (n = 13,279).</td>
<td>• From the pre-implementation period through the first year post-implementation, payer’s cost net of member copay grew by 3% in the intervention group and by 24% in the comparison group. • In the first year post-implementation, non-formulary medication use declined in the intervention group. Growth in total prescription claims was modestly lower in the intervention group than in the comparison group. • Study groups did not significantly differ in medication continuation rates for oral contraceptives, antihypertensives, or antihyperlipidemics. Continuation rates for estrogen were lower in the intervention group than in the comparison group at 6 months (91% vs. 87%) and at 11 months (84% vs. 76%), but discontinuation could not be linked to non-formulary drug use. • Study groups did not differ in use of antibiotics for otitis media. • Study groups did not significantly differ in use of any medical services measured.</td>
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<td>Mather and Henderson (University of Arizona and Express Scripts)</td>
<td>Quasi-experimental (pre-post with comparison); compared periods 6 months before and 6 months after copayment change. Outcomes were measures of (1) prescription drug utilization and expenditures; (2) continuation with chronic medication; and (3) outcomes by medication type.</td>
<td>Age- and gender-matched samples of intervention (change from either $4/$10 to $5/$15 or $5/$10 to $7/$15) and comparison ($5/$10) plans; n = 1,112 adults (age ≥ 18 years) in both groups.</td>
<td>• In the 6 months following the copayment change, total drug expense declined by $18 PMPM in the intervention group and increased by $31 PMPM in the comparison group.</td>
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### STUDIES PUBLISHED IN 2002

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<td>Joyce et al. (RAND Health)</td>
<td>Cross-sectional, statistical controls.</td>
<td>Outcomes were drug costs, overall and for generic, single-source brand and multisource brand; costs for payers and OOP beneficiary cost.</td>
<td>420,786 beneficiaries aged 18-64 years enrolled at any time from 1997 to 1999 (claims database, 25 employers).</td>
<td>Predicted (statistically adjusted) PMPY drug spending was $725 for a single-tier plan with a $5 copayment, $678 for a 2-tier plan with $5/$10 copayments, $666 for a 3-tier plan with $5/$10/$15 copayments, and $436 for a 3-tier plan with $10/$20/$30 copayments.</td>
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<td>Fairman et al. (Express Scripts)</td>
<td>Pseudo-experimental (pre-post with comparison group); analyses compared 12-month pre-implementation period with 30-month post-implementation follow-up. Outcomes were total drug cost, net insurer cost, number of prescription drug claims, rates of continuation with chronic medication therapy, and medical utilization (office visits, ER visits, and inpatient hospitalizations).</td>
<td>Intervention group whose employer switched from a 2-tier ($7/$12) to a 3-tier ($8/$15/$25) structure on (n = 3,577) in 1998. Comparison group whose employer retained a 2-tier ($7/$12) structure (n = 4,132).</td>
<td>• From the pre-implementation period through the second year post-implementation, payer’s cost net of member copay grew by 30% in the intervention group and 57% in the comparison group.</td>
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<td>• In the first year post-implementation, non-formulary medication use declined in the intervention group. Growth in total prescription claims was modestly lower in the intervention group than in the comparison group.</td>
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<td>• Study groups did not significantly differ in medication continuation rates for estrogens, antihypertensives, or antihyperlipidemics. Continuation rates for oral contraceptives were lower in the intervention group (66%) than in the comparison group (79%) at 6 months but not at any other time during follow-up.</td>
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<td>• Study groups did not significantly differ in use of any medical services measured.</td>
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<td>Huskamp et al. (Harvard Medical School, Brigham and Women’s Hospital, Medco Health Solutions [Merck &amp; Co.])</td>
<td>Quasi-experimental (pre-post with comparison group); analyses compared pre-implementation and post-implementation periods that were each “more than one year” in duration. Outcomes were probability of use, total spending, rates of discontinuation, and rates of switching for 3 drug classes.</td>
<td>Users of PPIs, statins, and ACEIs in 2 employer groups. Employer 1 changed from a single-tier ($7) to a 3-tier ($8/$15/$30) benefit. Employer 2 changed from a 2-tier ($6/$12) to a 3-tier ($6/$12/$24) benefit. Comparison groups for Employers 1 and 2 made no copayment changes to designs of $8/$15 and $6/$12, respectively.</td>
<td>• Probability of use was lower for the copayment change group than for the comparison group for Employer 1 (dramatic copayment change) but not for Employer 2 (modest copayment change).</td>
<td>Robert Wood Johnson Foundation, National Institute of Mental Health, AHRQ</td>
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• Probability of use was lower for the copayment change group than for the comparison group for Employer 1 (dramatic copayment change) but not for Employer 2 (modest copayment change).
• The plan’s drug expenditures dropped and enrollee expenditures increased for both employers, but these trends were more pronounced for Employer 1.
• Users of non-preferred (tier 3) drugs subject to a $12 copayment change (Employer 2) were more likely to switch to preferred drugs but were not more likely to discontinue therapy than were comparison patients in the 6 months following the change.
• Users of non-preferred (tier 3) drugs subject to a $23 copayment change were more likely to discontinue therapy than were comparison patients in the 6 months following the change.

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<td>Nair et al. (University of Colorado, Wolfe Statistical Consulting, University of Iowa, Anthem Blue Cross Blue Shield of Colorado)</td>
<td>Quasi-experimental (pre-post with comparison); analyses compared 7 month pre-change versus 7 month post-change period. Mean prescriptions PPPM, generic use rate, formulary compliance rate, MPR, discontinuation of non-formulary medication (whether patient discontinued therapy or switched to a formulary medication was not measured).</td>
<td>8,132 patients who filled prescriptions for ≥ 1 of 5 disease states (hypertension, dyslipidemia, arthritis, diabetes, gastrointestinal reflux disease) during the 5 months prior to a copayment change. Intervention group changed from a 2-tier to a 3-tier benefit (n = 5,710). Comparison groups remained 2-tier (n = 715) or remained 3-tier (n = 1,707).</td>
<td>• Formulary compliance rate increased by 5.6% for the copayment change group but did not significantly increase for the comparison group. • Generic fill rate increased for all 3 study groups—4.9 percentage points for the copayment change group, 4.8 percentage points for the 2-tier comparison group, and 3.3 percentage points for the 3-tier comparison group. • Rates of discontinuation of non-formulary medications were higher for copayment change groups than for comparison groups (odds ratios 1.76 vs. 2-tier comparison group and 1.49 vs. 3-tier comparison group); however, authors noted that predictive ability of logistic regression model was poor (c-statistic = 0.57).</td>
<td>Merck &amp; Co.</td>
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<td>Rector et al. (UnitedHealth Group, Wharton School)</td>
<td>Longitudinal with comparison groups (tiered vs. non-tiered); however, the point in time at which tiered copayment was instituted was not measured, making it difficult to assess effects of change. Change from 1998 to 1999 in percentage of prescriptions that were for preferred brand products.</td>
<td>Prescriptions for medications in selected classes (ACEIs, PPIs, statins) in 4 health plans (188 employers) using the same formulary; some groups instituted tiered copayments at unmeasured points in time (for an unknown number, this change occurred before the start of the study period), while other groups did not have tiered copayments.</td>
<td>• Between-group (tiered vs. non-tiered) differences in percentage change amounts for ACEIs, PPIs, and statins were 17.3%, 8.4%, and 12.7%, respectively. • Logistic regression analyses estimated increases in the probability of preferred brand use associated with tiered copayments; estimated increases were 13.3, 8.9, and 6.0 percentage points for ACEIs, PPIs, and statins, respectively. • Logistic regression analyses explained only 1.4%-3.6% of the variance in preferred brand use.</td>
<td>AstraZeneca Pharmaceuticals</td>
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<td>Briesacher et al. (University of Maryland, Novartis, AstraZeneca, Merck &amp; Co., TAP)</td>
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The Future of Prescription Drug Cost-Sharing: Real Progress or Dropped Opportunity?

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<td>Quasi-experimental (pre-post with comparison); compared periods 12 months pre-change with 12 months post-change. Outcome measures were MPRs, rates of switching to lower-copayment products, discontinuation rates, and price elasticity. Users of 9 commonly used therapeutic classes enrolled in plans that (1) changed from $5/10 to $5/$25 ($n = 30,000); (2) changed from $10/$20 to $10/$40 ($n = 400,000); (3) changed from $5/$10 to $5/$20/$35 ($n = 200,000); and (4) made no change to a $10/$20 structure ($n = 1,000,000). Authors excluded 20% of potential sample for copayment discrepancies, including “grandfathering” of initial post-implementation fill. MPRs declined in the intervention group by “statistically significant but modest” amounts (largest change was –6.8% for NSAIDs) but remained more than 80% for all cardiovascular medication classes. Drug switch rates were higher for intervention than for comparison patients among users of calcium channel blockers, statins, NSAIDs, and triptans, but not among users of ACEIs, ARBs, COX-2 inhibitors, SSRIs, or TCAs. Discontinuation rates were significantly higher for intervention group patients than for comparison group patients among users of ACEIs, ARBs, statins, SSRIs, and TCAs; however, this analysis counted switches from ACEIs to ARBs and from ARBs to ACEIs as discontinuations and included patients whose most recent claim was &gt;3 months prior to the copayment change. For the subset of patients with ≥2 claims within the 3 months prior to the change, prescription-filling behavior was inelastic (not price sensitive).</td>
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| Gibson et al. (Thomson MedStat, Pfizer)<sup>26</sup> | Cross-sectional time series (unit of analysis was the person-month), statistical modeling. Outcome was MPR for statins. New (n = 142,341) and continuing (n = 92,344) statin users identified during 2000-2003 (MarketScan Database). Enrollment of 5 managed care organizations aged ≥19 years, with ≥4 months of OH use during the 6 months pre-change and >1 filled OH prescription for the same OH medication during the 6 months post-change; 12-month episodes were split by cost-sharing increase levels: $1-$6 (n = 11,975), $7-$10 (n = 904), and >$10 (n = 231). Cost-sharing increases of $1-$10 were unrelated to ADD of OH. Increases of >$10 were associated with a decline of 2.6% per month in ADD. For episodes with a cost-sharing increase of >$10, at 6 months after the increase, OH ADD was 18.5% less than expected based on pre-change trend. However, <2% of the study sample experienced a copayment change of >$10, and of that group 69% had received OH medication either free of charge or for <$5 per month prior to the change. Higher copayments were associated with lower statin adherence rates. A 100% change in index copayment was associated with a 2.6 percentage point decline in adherence among new users and a 1.1 percentage point decline among continuing users. | AHRQ |

| Goldman et al. (RAND Health)<sup>26</sup> | Cross-sectional, statistical modeling. Outcomes were (1) MPR for cholesterol-lowering (CL) therapy in the first year and (2) use of hospitalizations and ER visits in subsequent years. 62,274 patients aged ≥20 years who initiated CL therapy (no use of CL therapy in prior 6 months) from 1997 to 2001 (claims database, 88 health plans, 25 employers). Higher copayment levels were associated with reduced adherence; mean compliance rates were 5 percentage points lower when copayments were $10 higher. The modeled full compliance percentage was 6-10 percentage points lower for patients with ≥2 copayments than for patients with ≥10 copayments. For each 1,000 patients classified as “high risk” based on age, sex, and comorbid conditions, modeled hospitalization counts were 643 for fully compliant patients and 1,000 for partially compliant patients. A simulated policy eliminating copayments for high- and medium-risk patients and raising copayments for low-risk patients would “avert” 79,837 hospitalizations and 31,411 ER visits annually, assuming 6.3 million U.S. adults on CL therapy. | National Institute on Aging and UCLA Claude D. Pepper Older Americans Independence Center |

| Taira et al. (Hawaii Medical Service Association, Novartis)<sup>26</sup> | Cross-sectional; statistical controls. Outcome was MPR; compliance was defined as MPR ≥80%. 114,232 patients who had ≥1 medical claim with a diagnosis of hypertension and filled ≥1 antihypertensive medication prescription between January 1999 and June 2004 (managed care organization with 650,000 lives). Patients were grouped by tier (tier 1 = $5, tier 2 = $20, tier 3 = difference between preferred and nonpreferred [range $20-$165]). Patients who switched tiers were counted in multiple tier categories. MPRs were 66.8% for tier 1 (n = 58,809), 66.1% for tier 2 (n = 66,486), and 53.6% for tier 3 (n = 60,553). Adjusted odds ratios for compliance were 0.76 for medications in tier 2 and 0.48 for medications in tier 3 (reference category was medications in tier 1). | Novartis |

<sup>STUDIES PUBLISHED IN 2005</sup>

<sup>STUDIES PUBLISHED IN 2006</sup>

<sup>Continued on next page</sup>
As this article was going to press, a purportedly controlled analysis, co-sponsored by 2 pharmaceutical manufacturers, showed improved adherence (MPR increase of ≤4 percentage points for ACEIs and ARBs, beta-blockers, statins, and diabetes drugs) for a large employer that reduced OOP costs compared with another employer that made no OOP cost reduction. However, the study report did not disclose key baseline utilization measures for the intervention and comparison employer groups, whose mean ages differed by >6 years (37.4 vs. 43.9, respectively) and whose copayment structures appeared markedly different even prior to the change (e.g. for generics $5 flat copayment vs. $16.22 average, respectively). Clearly this research is in its nascent stage; randomized studies or analyses of more comparable groups are urgently needed.

**Our Challenge Today**

This is a moment of opportunity, in which the health insurance industry will choose to base its decisions about cost-sharing on evidence directly linked to proposed policies or implement unproven designs based on a hoped-for but untested “home run” improvement to the cost-sharing paradigm. Policymakers will do well to understand that in cost-sharing benefit designs, the future of prescription drug cost-sharing: real progress or dropped opportunity? (January/February 2008)
credence to studies that directly measure the effect of a similar change. For example, if a cost-sharing decrease is being considered, the best and most informative research is a controlled study (i.e., a design that includes a control or comparison group) of a cost-sharing decrease, preferably in a similar population (e.g., same type of insurance, similar age and gender profile, similar industry). Much less weight should be accorded to studies that measure only associations between cost-sharing levels and patient outcomes. Studies that report statistically controlled associations but fail to report key measures of the adequacy of those statistical controls should be given little or no consideration.

It took the Red Sox 18 years to recover the opportunity that was lost in 1986, and in 2004 the team finally won a World Series title. Yet in the health care field, massive system-wide changes to health care financing and delivery are being proposed at a pace that should give pause to advocates of evidence-based decisions. These changes have the potential to affect not only outcomes for individual patients, but also the viability of the health care financing system—whether publicly or privately funded—to sustain affordable coverage for necessary services in the years to come. Like the Boston Red Sox, the health insurance industry may take far too many years to make up for our error if we miss the opportunity to measure the impact of these cost-sharing and benefit design proposals now.

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The Future of Prescription Drug Cost-Sharing: Real Progress or Dropped Opportunity?


It’s Only a Pharmacoeconomic Model—Believe It or Not

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

Several years ago at a national meeting, when Fairman et al. first presented their attempt to validate the assumptions and findings of 2 frequently cited pharmacoeconomic (PE) models,1 reaction was mixed. Although some audience members welcomed the concept of model validation, others expressed concern and even irritation with the work. In the lively discussion that followed, one man, who identified himself as the employee of a pharmaceutical manufacturer, expressed his view: “Your work seems to assume that models are supposed to represent real life,” he said. “They aren’t. It doesn’t make sense to validate a model. It’s not real life; it’s only a model.”

In early 2004, Fairman and Motheral were judged to have contributed the most important article to managed care pharmacy published in JMCP in 2003.2 The 2003 JMCP Award for Excellence was bestowed on these authors for their work in applying actual health plan data to the assumptions used in PE decision-analytic models; specifically, 2 widely cited models of the medical and drug costs associated with combination regimens of antimicrobial and antisecretory drugs to eradicate Helicobacter pylori (H. pylori) infection.3 Study evidence suggested that the H. pylori treatment models had overstated the cost-effectiveness of brand drug combination regimens such as a proton pump inhibitor with clarithromycin (PPI-C) and had understated the cost-effectiveness of generic drug combinations such as bismuth with metronidazole and tetracycline (BMT). For example, the findings of one model had indicated that costs per successfully treated patient were $1,001 for BMT and $980 for PPI-C. After Fairman and Motheral empirically adjusted that model for actual health plan utilization, costs per successfully treated patient were $852 for BMT and $1,118 for PPI-C.

Two months after the publication of the work by Fairman and Motheral, Cox et al. performed a similar analysis to assess the validity of a PE model of the use of cyclooxygenase-2 (COX-2) inhibitors.4 Like Fairman and Motheral, Cox et al. found that the proposed PE model was inaccurate. When the model’s assumed use rates for gastroprotective agents (e.g., PPIs, histamine-2 receptor antagonists, misoprostol) were replaced with actual utilization data, the cost per year of life saved for a patient taking a COX-2 inhibitor increased from $18,614 in the original model to $106,192 in the empirically adjusted model.

It is often forgotten that the follow-up analysis of actual pharmacy and medical claims data to test the assumptions in predictive modeling is a fundamental principle in the use of PE modeling results in drug formulary decision making by pharmacy and therapeutics (P&T) committees. Early in 2003, the Task Force on Good Research Practices of the International Society for Pharmacoeconomics and Outcomes Research advised that PE models should only aid decision making and not be represented as “statements of scientific fact,” and should be “continually assessed against data, and models should be revised accordingly.”5 At the time that the Fairman and Motheral article was published in JMCP in September-October 2003, this research was groundbreaking, with no other similar work (application of actual health plan data to the assumptions contained in a PE model) published in the peer-reviewed literature. Today, these 2 studies by Fairman and Motheral and Cox et al. are the only published research in validation of PE models using actual medical and pharmacy claims; 1 German study published in 2006 used data from cancer registries to test a decision-analytic model for cervical cancer screening in Germany.6

In an editorial that accompanied the Fairman and Motheral critical analysis of model assumptions in H. pylori eradication, Hakim opined that all PE models produce results at a given point in time that are expected to be wrong at a future point in time, and that it is more important to focus on the interaction between assumptions and outcomes in a PE model rather than on specific results.7 To understand that interaction clearly, Hakim argued, model transparency is critical. For the same reason, Hakim advocated use of simple rather than complex models when possible, because simple models facilitate replication and validation. A very different view of modeling was put forth 3 years later by Eddy. He argued that since the point of a model is to get the correct answer, a complex model that is not well understood but that closely simulates real-life processes is preferable to a simpler transparent model that produces a less accurate result.8 To assess model accuracy, Eddy advocated use of complex mathematical simulations of clinical trials, performed using technology that encompasses object-oriented (“virtual world”) programming and systems of differential equations.9 Such an approach seems to ignore the problem of markedly flawed input data, which even the most sophisticated mathematical procedure cannot overcome and which was the chief problem uncovered in the 2 analyses performed by Fairman and Motheral and Cox et al. Also overlooked is the difficulty that health plans would encounter in attempting to validate or modify the assumptions and findings of complicated (and proprietary) mathematical models in their own populations.

Healthy skepticism in viewing the results of PE models extends beyond the need for applying real-world outcomes data to the assumptions. Previously, Curtiss described some of the fruit harvested from examining closely the methods used to derive the inputs for PE analyses of self-injectable drugs used for treating multiple sclerosis.10 For example, he cited 4 “methodological inaccuracies” in the clinical trials of these drugs plus 2 characteristics of the results available from clinical studies that reduce PE analyses of these data to exercises in frustration:
(1) failure to report treatment side effects and adverse events after 2 years of follow-up, and (2) no information reported on the impact of treatment, including side effects, on the quality of life of patients. These omissions have particular importance in the PE analysis of these drugs because patient interviews revealed that treatment side effects were the most common reason for discontinuation of therapy, cited by 52% of patients.11

In the current issue of JMCP, Yuan et al.12 base their PE model primarily on 2 data sources: (1) the Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD) clinical trial, in which 709 patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) were assigned to treatment with entecavir (n = 354) or lamivudine (n = 355);13 and (2) the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL–HBV) longitudinal (mean follow-up time 11.4 years) cohort analysis of CHB-infected Taiwanese community residents, of whom 85% were HBeAg-negative.14 Model estimates of total treatment costs associated with entecavir and lamivudine were based on calculations of liver disease (hepatocellular carcinoma and cirrhosis) rates expected over a 10-year time horizon. To calculate these expected rates, Yuan et al. applied post-treatment viral load (HBV DNA) levels from the BEHoLD trial to the REVEAL study’s observed liver disease rates, stratified by viral load categories. For example, in the REVEAL study, after statistical adjustment for age, gender, cigarette smoking, and alcohol consumption, adjusted hazard ratios for hepatocellular carcinoma were 1.2, 2.9, 9.5, and 15.2 for serum HBV DNA levels of 300–9,999, 10,000–99,999, 100,000–999,999, and ≥1 million copies per mL, respectively, compared with the reference category, undetectable viral load (<300 copies per mL). Because 69.1% of entecavir-treated patients in the BEHoLD trial were treated to an undetectable viral load, the model assumed a hazard ratio of 1.0 (baseline risk only) for 69.1% of the hypothetical cohort of patients treated with entecavir in clinical practice. For lamivudine-treated patients, the percentage treated to undetectable viral load was 39.8%.

Feld and Ghany recently summarized eloquently the limitations of the clinical trials of the drugs used to treat CHB, including the use of surrogate endpoints that poorly predict long-term remission of CHB.15 Two commentaries in this issue of JMCP describe numerous limitations of the PE model proposed by Yuan et al.16,17 Two of these limitations deserve special attention. First, in the REVEAL study, only 1.4% (n = 8) of HBeAg-positive patients had an undetectable viral load, and no HBeAg-positive patients had a viral load of 300–9,999 copies per mL. Thus, REVEAL’s mathematical relationship between viral load level and liver disease rates was based almost entirely on HBeAg-negative patients, yet REVEAL’s hazard ratios were applied to a population consisting entirely of HBeAg-positive patients. Second, Yuan et al.’s model assumes that a patient who is treated to an undetectable viral load level in a clinical trial with a minimum viral load level of 3 million copies per mL for study entry (BEHoLD) has the same liver disease risk as a community resident in a cancer screening program who enters a cohort study with an undetectable viral load (REVEAL). In future years, will validations of the Yuan et al. model demonstrate that it accurately predicted liver disease rates for patients treated with entecavir and lamivudine or will it, like the models studied by Fairman and Mohterl and by Cox et al., be largely refuted by empirical evidence?

While we await the answer to that question, information about actual histologic improvement for BEHoLD subjects may represent the best “rubber-meets-the-road” assessment of the model that we currently have, especially since the BEHoLD study authors describe histologic improvement as the study’s “primary efficacy end point.” The BEHoLD trial report indicates a higher rate of “histologic improvement” with entecavir (72%; 226/314) than with lamivudine (62%; 195/314). However, that comparison included in the denominator all study patients with baseline biopsy specimens and did not exclude patients with missing follow-up biopsies. It is only in a footnote to their primary data table for histologic improvement that the authors identify the counts for “adequate pairs of biopsy specimens” as 292 for entecavir and 269 for lamivudine. Using those denominators, the percentages of cases with histologic improvement are 77% for entecavir (226/292) and 72% for lamivudine (195/269), yielding a nonsignificant P value of 0.204 for the comparison (Fisher’s exact test); that is, there was no significant difference in the primary efficacy endpoint of histologic improvement for entecavir versus lamivudine when only the cases with evaluable liver biopsies are compared.

Given all of these sources of uncertainty created by the application of epidemiological data (REVEAL) to clinical trial data (BEHoLD) and the apparent lack of difference between entecavir and lamivudine in the primary endpoint of histologic improvement in BEHoLD, the model proposed by Yuan et al. may reveal less about the cost-effective treatment of CHB than it does about the current state of the art in PE modeling. If we are concerned about the accuracy of answers produced by PE models, we are not alone. Skepticism about model results is common, with some observers arguing that models are so obtuse and difficult to scrutinize that authors should be required to submit electronic versions as part of peer review to enable verification by journal editors and reviewers.18–22 Inadequacies in economic models submitted as part of product dossiers using AMCP Format for Formulary Submissions have been reported.23,24 In a review of PE analyses contained in dossiers submitted to one health plan between 2002 and 2005, only 43% contained sensitivity analysis, 38% described the study perspective, 20% described assumptions clearly, and 18% described caveats to study conclusions.

For some observers, lack of confidence in PE model results is amplified by pharmaceutical manufacturer sponsorship. For example, in 1994 the New England Journal of Medicine established

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a conflict of interest policy for PE models similar to its existing policy for review articles: PE models would be “excluded from consideration” if any author had “a personal financial conflict of interest” in model results. Such policies, although well intentioned, may be insufficient to address the problem of potentially biased or incorrect model assumptions when results of a sponsored clinical trial are applied to a model developed and published at a later date. Only a careful reader of the BEHoLD clinical trial report, published in the New England Journal of Medicine in 2006, will find the following statement contained well within the methods section and NOT in the disclosures at the end of the article: “The sponsor collected the data, monitored the conduct of the study, performed the statistical analyses, and coordinated the writing of the manuscript with all authors.”

The credibility gap in PE modeling is longstanding among pharmacy and medical directors involved in P&T decision making and is unlikely to be resolved by increasingly complex mathematical solutions, no matter how theoretically accurate or sophisticated. Authors of PE models might do better by focusing on basic face validity and on careful documentation and support of model assumptions. Otherwise, readers of PE models might just decide that the man who raised the point years ago was right—a model is not real life; it’s only a model.

Authors

KATHLEEN A. FAIRMAN, MA, is associate editor and senior methodology reviewer of the Journal of Managed Care Pharmacy; FREDERIC R. CURTISS, PhD, RPh, CEBS, is editor-in-chief of the Journal of Managed Care Pharmacy.

AUTHOR CORRESPONDENCE: Kathleen A. Fairman, MA, Kathleen Fairman LTD, PO Box 31278, Phoenix, AZ 85046, Tel.: 602.867.1343, E-mail: kathleenfairman@qwest.net

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PSTAC Survey in 2006 Was Instrumental in Obtaining Permanent (Category I) CPT Codes for MTM Services Performed by Pharmacists

To the Editor:
The Pharmacy Services Technical Advisory Coalition (PSTAC) was formed in 2002 to improve the coding infrastructure necessary to support billing for pharmacists’ professional services. PSTAC is a coalition of 7 national pharmacy organizations whose principal goal was to establish Current Procedure Terminology (CPT) codes for pharmacist-delivered medication therapy management (MTM) services. PSTAC petitioned the CPT Editorial Panel in February 2005 at the Newport Beach, California, meeting to establish CPT codes for MTM services. MTM services were described as face-to-face patient assessment and intervention by a pharmacist to optimize the patient response to medications or to manage treatment-related medication interactions or complications. In July 2005, the CPT Editorial Panel assigned Category III (temporary) status to 3 CPT codes for MTM services:

- 0115T—the first 15 minutes of MTM service(s) provided for the initial encounter
- 0116T—the first 15 minutes of a subsequent encounter
- 0117T—each additional 15 minutes (used in conjunction with 0115T, 0116T)

The CPT Editorial Panel voted to approve Category III (temporary) status until there was evidence of widespread availability and delivery of MTM services. PSTAC subsequently developed a 9-item survey instrument for pharmacy providers in consultation with the CPT Editorial Panel members, advisors, and staff. The pharmacy provider survey gathered information to document and determine the availability of MTM services provided by pharmacists. A 14-item survey instrument was developed for payers to gather information on the compensation of MTM services.

Providers and payers were surveyed from August 2006 through October 2006 and were asked to report data for the preceding 2-year period. PSTAC asked payers and providers to report the characteristics of practice sites, including geographic location, type and location of practice, number of years providing MTM services, and number of documented face-to-face MTM encounters. Participants were invited to participate in this survey via 3 methods: (1) direct contact of specific practice sites known by the members and staff of the PSTAC Steering Committee to provide MTM services, (2) broadcast e-mail invitation of members of the national organizations constituting PSTAC, and (3) direct invitation of pharmacy leadership within the U.S. Department of Veterans Affairs (VA), Veterans Health Administration.

A total of 240 practice sites, not including the VA, responded to the pharmacy provider survey. The practice sites reported a collective 858,405 face-to-face MTM encounters over a 2-year period; 86% of the responses originated from ambulatory care practice sites, including community pharmacies, clinic and physician office practices, outpatient pharmacies, work sites, and home and hospice care locations. These data have been reported previously.

A total of 14 payers responded to the payer survey. These payers covered MTM services provided to patients in all 50 states and the District of Columbia and Puerto Rico. The payers reported that 88% of the pharmacists delivered MTM services, described as comprehensive medication review, including identification and resolution of drug therapy problems. Of the 8 payers that responded to the survey item regarding the method of MTM delivery, 7 reported more than 75% of the encounters were face to face, meeting the CPT panel’s definition of how MTM services should be delivered.

These survey results provided PSTAC with the evidence necessary to demonstrate the widespread availability of MTM services for justifying Category I (permanent) CPT codes. In February 2007, the PSTAC presented these findings to the CPT Editorial Panel in a petition to convert the temporary codes to Category I codes. The code proposal included components of the consensus document developed by 11 national pharmacy organizations in 2004, including description of pharmacists performing a face-to-face comprehensive medication review and assessment to identify, resolve, and prevent drug therapy problems; formulation of a medication treatment plan to achieve patients’ goals of therapy; and monitoring and evaluation of patient outcomes of therapy.

In October 2007, 3 Category I CPT codes were established for MTM services performed by a pharmacist in face-to-face encounters with assessment and interventions:

- 99605—initial 15 minutes for MTM services for a new patient
- 99606—initial 15 minutes, established patient
- 99607—each additional 15 minutes (used in conjunction with 99605 or 99606)

We believe that establishing Category I CPT codes for MTM services provides pharmacists an incentive to deliver, document, and bill for these services with the greater likelihood of payers providing compensation for their professional services. The subsequent outcome is greater availability and access for our patients and the opportunity for pharmacists to provide services intended to improve medication therapy outcomes.

The results gathered from the PSTAC survey of providers and payers showed that MTM services are being provided, these services are widely available to patients, and these services are being billed and reimbursed by payers. The survey data extrapolates to nearly 2.8 million MTM encounters in the United States, including the VA, over a 2-year period from mid-2004 through mid-2006. The next step for PSTAC is establishing the value of MTM services using a relative value scale similar to the Resource-Based Relative Value Scale established for physicians under Medicare Part B. This relative value scale will look at the
complexity of MTM services, the time associated with MTM delivery, and the technical skill to provide these services.

We would like to thank all entities that participated in the survey, providing PSTAC with the data needed to convince the CPT Editorial Panel to establish Category I CPT codes and recognize the professional services delivered by pharmacists through MTM services.

Elizabeth Brusig, PharmD
PSTAC Steering Committee, AMCP Representative
ELBRUSIG@sentara.com

William Davies, RPh, MS
PSTAC Steering Committee, AMCP Representative
wdavies@cox.net

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Letters to the Editor

JMCP welcomes letters that serve to clarify subjects published in previous issues of the Journal or regarding subject matter of interest to managed care pharmacists. Letters in JMCP are not peer reviewed but are subjected to editorial review. Letters should be prepared in a word processing program, preferably Microsoft Word, and submitted electronically at jmcp.msubmit.net. See www.amcp.org for details.

ERRATUM

The following article was printed with the second line of 3 author names inadvertently obscured. The online version has been corrected to show all 6 authors: Eric Q. Wu, PhD; Howard G. Birnbaum, PhD; Huabin F. Zhang, MD, MPH; Jasmina I. Ivanova, MA; Elaine Yang, PhD; and David Mallet, MBA. Health Care Costs of Adults Treated for Attention-Deficit/Hyperactivity Disorder Who Received Alternative Drug Therapies. J Manag Care Pharm. 2007 Sep;13(7):561-69. Available at: www.amcp.org/data/jmcp/JMCPMaga_Sept%2007_561-569.pdf.
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