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Journal of Managed Care Pharmacy (ISSN 1083–4087) is published 9 times per year and is the official publication of the Academy of Managed Care Pharmacy (AMCP), 100 North Pitt St., Suite 400, Alexandria, VA 22314; 703.683.8416; 800.TAP.AMCP; 703.683.8417 (fax). The paper used by the Journal of Managed Care Pharmacy meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper) effective with Volume 7, Issue 5, 2001; prior to that issue, all paper was acid-free. Annual membership dues for AMCP include $60 allocated for the Journal of Managed Care Pharmacy. POSTMASTER: Send address changes to JMCP, 100 North Pitt St., Suite 400, Alexandria, VA 22314.
Cover Impressions

About our cover artist

Chair Daydreams (2006)  Jane Gottlieb

Color! Bold, bright, you-almost-need-sunglasses-to-look-at-it color is Jane Gottlieb’s artistic trademark. The Santa Barbara, California-based photographer has been perfecting her color-enhanced photography ever since she started using Cibachrome prints and colored dyes more than 25 years ago. One day in 1983, she was visiting her printer and saw him retouching a couple of her photographs with archival dyes. Gottlieb was immediately intrigued by the possibility of intensifying the colors in her photos. “I took it to the next level,” she says. “Adding vivid color to my photos was a huge breakthrough in my career.” Gottlieb’s altered pictures are slightly surreal and endlessly fascinating.

Encouraged to pursue her interest in painting and photography by family, friends, and teachers, Gottlieb enjoyed early success. In sixth grade, she held her first art exhibit in the hall outside her classroom at University Elementary School in Los Angeles. The school, located on the University of California-Los Angeles campus, is still considered to be a very progressive institution. Gottlieb also took art classes at UCLA during junior and senior high school. After attending the University of California, Berkeley, from 1964 to 1965, she spent a year studying art history in Florence, Italy, through Syracuse University’s study-abroad program. Gottlieb returned to Los Angeles to complete her undergraduate studies, and in 1968 she graduated from UCLA with a BA in painting and art history. “Photography became my first love when I started traveling after my college years,” she recalls. “By then, creating a painting had become too slow of a process for me.”

Moving to New York City in the late 1960s, Gottlieb excelled as an art director in fashion advertising. She was also involved in commercial photography, collaborating with major photographers such as Francesco Scavullo, Bill King, Neal Barr, and Sid Avery. Gottlieb moved back to Los Angeles in 1970, and became an art director at Warner Brothers Pictures where she helped to create movie advertisements and trailers for Klute, McCabe and Mrs. Miller, and Death in Venice, to name just a few. After several years at Warner Brothers, she decided to strike out on her own. Over the next decade, Gottlieb worked in various fields as a freelance art director, designer, and photographer. “I always had new challenges—I definitely learned on the job,” she says. Among her most memorable projects were the photo shoots that she did for “starchitect” Frank Gehry; she documented all of his postmodern and deconstructive buildings in the Los Angeles area.

Gottlieb continued to develop her signature style of colorful, hand-painted photographs during the ‘80s, and in 1988 she had her first solo exhibition at the Laguna Art Museum in Laguna Beach, California. Since then, she has shown her photos in exhibits around the world. Gottlieb is one of several photographers who were featured in a show this spring titled “In Focus” at the Carnegie Art Museum in Oxnard, California. In November and December 2008, she will have an exhibition at the Patty Look Lewis Gallery, a new gallery in Santa Barbara. Gottlieb’s work can also be seen on her Web site, www.janegottlieb.com. On the site’s biographical page she states, “I hope to create images that surprise and intrigue, drawing the viewer into my idyllic vision, ultimately uplifting them with vibrant color and evocative beauty.”

Gottlieb’s favorite photographic subjects are landscapes, old cars, and mysterious juxtapositions of objects. Her unique images have been featured in two books, Garden Tales: Classic Stories from Favorite Writers and Car Tales: Classic Stories About Dream Machines, as well as many museum catalogs, posters, and note cards.

The setting for Gottlieb’s beautiful Chair Daydreams photograph was an elegant hotel room in Sorrento, Italy, circa 1983. She used a Nikon 35mm camera equipped with a 50mm lens to capture the balcony overlooking the Gulf of Naples in the Tyrrhenian Sea. Then Gottlieb painted brilliant dyes onto the Cibachrome print to enliven the tranquil scene. In 2006, she utilized Adobe Photoshop to add more color to the photograph. Now the sea is an electric shade of blue, the sky is a fiery orange/yellow, and the drapes and French doors appear to be glowing in the sunlight. No objects were left untouched by the artist’s brush—even the chair cushion and floor have been enhanced with rich color.

Gottlieb has embraced digital technology for many years, and she especially appreciates it now that she has begun to scan and catalog the numerous photos taken throughout her career. She keeps up to date on technological advancements in photography with the help of her assistants from the Brooks Institute of Photography in Santa Barbara.

In addition to preparing for her show at the Patty Look Lewis Gallery, Gottlieb is currently working on a photograph titled Summer Solstice for the Santa Barbara Independent newspaper. In the near future, she will also launch a new version of her Web site, with larger images of her stunning photos.

Sheila Macho
Cover Editor

Cover Credit
Jane Gottlieb, Chair Daydreams, color-enhanced photograph. Santa Barbara, California. Copyright © 2006.

Sources
Interview with the artist.
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ABSTRACT

BACKGROUND: Ulcerative colitis (UC) is a chronic inflammatory disease with peak incidence in the third decade of life and a second peak in the sixth or seventh decade. While drug therapy can be used to control the inflammation and reduce symptoms, patients with UC may be treated surgically. There is little information in the published literature evaluating the all-cause health care costs of patients with UC according to age.

OBJECTIVE: To assess from administrative claims the direct all-cause (not disease-related) costs of care and resource utilization for patients with UC compared with members without UC by 3 age categories.

METHODS: A retrospective analysis was conducted using the PharMetrics database of patients with a diagnosis of UC (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 556.x) from January 1, 2000, through June 30, 2005. This database contains enrollment data and pharmacy and medical claims from more than 85 different managed care organizations and more than 55 million patients in the United States. Patients had to be continuously enrolled for 6 months before and 12 months after the initial UC diagnosis and have at least 2 distinct claims with a diagnosis code for UC. The mean per-patient health care resource utilization and costs were calculated for patients in the year following their initial UC diagnosis and compared with the same measures for a group of age- and gender-matched members (without UC claims) at a ratio of 4:1. Three age groups were analyzed: pediatric-adolescent (aged <18 years), adults (aged 18 to 64 years), and older adults (aged ≥65 years). Differences in the measures of all-cause health care resource utilization (claims and costs) between the UC and non-UC groups were tested for statistical significance using the Wilcoxon signed-rank test, a non-parametric alternative to the paired t test. Differences between the 3 age cohorts were tested using the Mann-Whitney U test.

RESULTS: Data were collected for 15,105 patients with UC and for 59,159 members in the comparator cohort without UC matched by age and gender. The average age for both cohorts was 44 years, and 54% were female. Mean ([SD], median) annual all-cause total health care costs in 2005 dollars for patients with UC were $13,233 ([$40,715], $5,190) versus $3,214 ([$12,741], $753) for the comparator group (P<0.001). For all UC patients, all-cause inpatient hospitalization costs constituted the largest component ($5,771, 43.6%) of the mean annual total costs, followed by prescription medications ($2,423, 18.3%); miscellaneous services, such as hospice, psychiatric facility, and nursing home care ($2,092, 15.8%); outpatient hospital visits ($1,310, 9.9%); physician office visits ($899, 6.8%); laboratory procedures ($470, 3.6%); and emergency department visits ($268, 2.0%). Resource utilization (e.g., physician visits, laboratory tests, pharmacy claims) was highest for older adults aged ≥65 years, followed by pediatric-adolescent patients and adults aged 18 to 64 years (all comparisons P<0.01). The mean ([SD], median) all-cause total health care costs were highest for pediatric-adolescent patients with UC (n=589, 3.9%) at $23,113 ([$70,999], $6,214), followed by older adults (n=650, 4.3%) at $15,811 ([$23,882], $6,886, P<0.001), while adults aged 18 to 64 years (n=13,866, 91.8%) incurred the lowest cost at $12,693 ([$39,505], $5,108, P<0.001).

What is already known about this subject

- Ulcerative colitis (UC) is a chronic disease that can affect patients of any age and lead to high direct costs, with hospitalizations and physician visits accounting for 59.9% and 19.3%, respectively, of all costs incurred by patients with UC.
- Distribution of total costs for UC patients is skewed, with the top 2% of high-cost patients accounting for 36% of total provider charges and 39% of health plan payments for UC.
- Among UC patients who were referred to a university hospital for treatment, 12% were hospitalized during the following 6 months, and 80% of those patients required surgery. In general, hospitalization costs account for 45% to 49% of the total disease-related costs of UC, estimated to be $1,488 per patient per year in 1990 dollars.

What this study adds

- Patients with 2 or more claims for UC had mean [median] all-cause (not disease-specific) health care costs in 12 months in 2005 dollars ($13,233 [$5,190]) that were more than 4 times higher than the mean [median] costs for members without these diagnosis codes ($3,214 [$753]).
- For UC patients, mean all-cause inpatient hospitalization costs accounted for 43.6% ($3,771) of total all-cause health care costs in 12 months after the index diagnosis, followed by outpatient prescription drugs ($2,423, 18.3%); miscellaneous services, such as psychiatric facility, nursing home, and hospice care ($2,092, 15.8%); outpatient hospital visits ($1,310, 9.9%); physician office visits ($899, 6.8%); laboratory procedures ($470, 3.6%); and emergency department visits ($268, 2.0%).
- Resource utilization as measured by visits and claims was highest for older adults aged ≥65 years, followed by pediatric-adolescent patients and adults aged 18 to 64 years (all comparisons P<0.01), but the mean [SD], median all-cause total health care costs were highest for pediatric-adolescent patients with UC ($23,113 [$70,999], $6,214), followed by older adults aged ≥65 years ($15,811 [$23,882], $6,886, P<0.001), and adults aged 18 to 64 years ($12,693 [$39,505], $5,108, P<0.001).
Ulcerative colitis (UC) is a chronic inflammatory disorder of unknown etiology, primarily involving the colonic mucosa. The inflammation is uniform and continuous with no intervening areas of normal mucosa and extends proximally from the rectum. The disease is characterized by a chronic course of unpredictable flares of intestinal inflammation, which result in diarrhea, abdominal pain, fecal urgency, and rectal bleeding. There is also an increased risk of colorectal cancer with UC. The incidence and prevalence of UC in North America have been estimated at 2.2-14.3/100,000 person years and 37.5-229 per 100,000 people, respectively.

UC can affect people of any age, but it generally follows a bimodal age distribution, with a peak incidence in the third decade of life followed by a second peak in the sixth or seventh decade. Some studies suggest that UC is more prevalent in men than women, while other research has found no gender predominance. A familial link has been observed. Approximately 5% to 10% of patients with UC have a first-degree relative who is also affected, and among children with UC, up to 40% have a relative with the disease. Many patients have long periods of complete remission; however, there is a 90% probability of having a relapse. Relapses are unpredictable, but 70% to 80% of patients with disease activity in the prior 2 years have disease activity the following year. In general, UC does not affect life expectancy, although an increased mortality rate has been associated with disease onset after the age of 50 and with severe disease.

Current treatment guidelines for UC emphasize the control of inflammation, reduction of symptoms, and healing of the mucosal lining in order to maintain remission. Surveillance procedures to check for pre-cancerous lesions are performed every 1 to 2 years in patients with long-standing disease. The specific treatments chosen depend on disease severity, location of inflammation, and associated complications of the disease. Some medications are used for the potential to lower the risk of cancer. Drug therapy options include aminosalicylates, corticosteroids, immunomodulators, and biologic agents. Many patients with UC require elective or emergency surgery, and the most common elective procedure is the ileal pouch-anal anastomosis (IPAA). While IPAA often results in an overall improvement in quality of life, there are several short-term and long-term complications of surgery for UC that vary according to the procedure. For all surgical procedures for UC, the most common early complications are small bowel obstruction, affecting 11% to 26% of patients, and sepsis, affecting 3% to 15% of patients. Pouchitis is the most common late complication of IPAA in patients with UC. A large study of 1,310 patients who had undergone IPAA with a J-shaped pouch found that the cumulative risk of pouchitis was 18% after 1 year and 48% at 10 years. Sepsis and pouchitis are leading causes of pouch failure, requiring pouch removal or an ileostomy. Other surgery-related complications include anal seepage, incontinence, fistulas, and a decrease in female fertility.

The lost time at work, hospitalizations, and other indirect costs to society contribute to the economic burden of UC. In 1990 dollars, the estimated per-patient annual disease-related health care cost of UC was $1,488, with an estimated $3,345 spent during the first year after diagnosis. The total direct cost of treating UC in the United States across all health care settings was estimated to be between $400 million and $600 million in 1990 dollars, with the largest costs incurred from hospitalizations (59.9%) and physician visits (19.3%). In addition, a small proportion of patients with UC account for a large proportion of cost; the top 2% of high-cost patients account for 36% of provider charges and 39% of health plan payments for UC. Hospitalizations and surgeries account for a large proportion of UC treatment costs. Of patients with UC who were referred to a university hospital, 12% required hospitalization within 6 months, and 80% of those patients required surgery. The hospitalization costs in that study made up 49% of the total treatment cost for UC, while the cost of drug treatment accounted for less than 25%. Another study found that, over a 10-year period, the cost of hospitalization was 45% of the total cost of UC treatment. Also, data from the Healthcare Cost and Utilization Project (HCUP) showed that the mean length of stay and the mean cost of hospitalization for inflammatory bowel diseases, including UC, were higher than for all conditions combined, using pooled data (6.1 days vs. 4.6 days and $9,200 vs. $7,700, respectively).

The present study sought to identify the total all-cause health care costs incurred by patients with UC, using a large database containing information from managed care plans in different regions of the United States, and to identify component cost categories for 3 age-stratified subgroups.

### Methods

A retrospective analysis of the PharMetrics Patient-Centric Database, evaluating patients with UC who were identified by health care claims containing International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 556.x from January 1, 2000, through June 30, 2005, was conducted (Table 1). The PharMetrics database contains enrollment data and pharmacy and medical claims from more than 85 different managed care organizations (MCOs), consisting of more than 55 million patients in the United States. The database is geographically diverse and is considered to be representative of the commercially insured population in the United States. New information from contributing plans is accepted as frequently as every month, and all data undergo quality assurance checks. Before inclusion, each new data submission is compared with expected values for the data fields, based on the complete production database. New data submissions with unexplained variances or identified problems are excluded from the database.

Eligible patients were continuously enrolled for 6 months prior to and 12 months after the index diagnosis date (date of...
the first claim with a UC diagnosis and had at least 2 distinct claims for UC during the study period (Figure 1). Health care resource utilization, including inpatient hospital, outpatient hospital, emergency department, physician, and laboratory services, and the mean and median health care costs paid by the health plans for services during the 12 months after the index diagnosis date were calculated. The type of service was obtained by applying an algorithm supported by PharMetrics that consisted of the use of a place-of-service variable, record type, Current Procedural Terminology code, Healthcare Common Procedure Coding System code, and revenue center code. A comparator group of members who did not have claims with a diagnosis code for UC was matched 4:1 to the study cohort based on age and gender to define a comparison group that was demographically similar to the UC patient group. Costs were defined as the amount paid by the health plan (i.e., after subtraction of member cost share) and were reported in 2005 dollars. Costs from other years were adjusted for inflation to 2005 dollars. In order to determine the factors that contributed the most to the total health care cost, subgroup analyses were conducted for 3 distinct age groups: pediatric-adolescent (aged <18 years), adults (aged 18 to 64 years), and older adults (aged ≥65 years).

Descriptive statistics were used to describe the cohorts. The variables included cost measures, including inpatient, outpatient, emergency department, physician office, laboratory, pharmacy, and total all-cause health care expenditures (which is the sum of the costs for each of the measures), and medical utilization measures, including the numbers of inpatient, outpatient hospital, emergency department, and physician office visits, and laboratory and pharmacy claims. Outcomes were calculated for all UC patients versus the comparator group and for each UC age group versus its own matched comparator cohort. Chi square tests with Yates correction were used to detect differences in the percentage of females in each of the cohorts. The Wilcoxon signed-rank test, a non-parametric alternative to the t test for paired samples, was used to test for differences between the mean costs and utilization rates for the UC and comparator groups. The Mann-Whitney U test, a non-parametric alternative to a t test for independent samples, was used to compare the 3 age groups. Comorbidity level was based on the Charlson Comorbidity Index (CCI) score, which is the sum of weights related to each condition for which the patient has claims. The CCI score was determined based on the ICD-9-CM codes during the 6 months before and 12 months after the index diagnosis date. The SAS statistical software package SAS 9 (9.1 TS1M2) was used for all analyses (SAS Institute, Inc., Cary, NC).

Results

The study included data from 15,105 patients with UC and 59,519 age- and gender-matched comparison members. Both the UC and comparator groups had a mean age of 44.4 years, and 54% were female. The UC group had a mean (standard deviation

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TABLE 1  ICD-9-CM Codes Used to Identify Ulcerative Colitis

<table>
<thead>
<tr>
<th>ICD-9-CM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>556.0</td>
<td>Ulcerative enterocolitis</td>
</tr>
<tr>
<td>556.1</td>
<td>Ulcerative ileocolitis</td>
</tr>
<tr>
<td>556.2</td>
<td>Ulcerative proctitis</td>
</tr>
<tr>
<td>556.3</td>
<td>Ulcerative proctosigmoiditis</td>
</tr>
<tr>
<td>556.4</td>
<td>Pseudopolyposis colon</td>
</tr>
<tr>
<td>556.5</td>
<td>Leftsided ulcerative colitis</td>
</tr>
<tr>
<td>556.6</td>
<td>Universal ulcerative colitis</td>
</tr>
<tr>
<td>556.8</td>
<td>Other ulcerative colitis</td>
</tr>
<tr>
<td>556.9</td>
<td>Ulcerative colitis, unspecified</td>
</tr>
</tbody>
</table>

TABLE 2
Characteristics and 12-Month All-Cause Resource Utilization and Costs for UC Patients Versus Age- and Gender-Matched Non-UC Members

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UC N = 15,105</th>
<th>Non-UC N = 59,519</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age—average [SD]</td>
<td>44.4 [14.1]</td>
<td>44.4 [13.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% females (number)</td>
<td>53.6 [8,097]</td>
<td>53.9 [32,051]</td>
<td>0.594</td>
</tr>
<tr>
<td>CCI score—mean [SD]</td>
<td>1.33 [1.98]</td>
<td>0.42 [1.10]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient hospitalizations</td>
<td>0 (0-15)</td>
<td>0 (0-9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.36 [0.92]</td>
<td>0.06 [0.32]</td>
<td></td>
</tr>
<tr>
<td>Inpatient hospital costs</td>
<td>0 (0-976,763)</td>
<td>0 (0-1,480,805)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>5,771 [28,378]</td>
<td>966 [10,024]</td>
<td></td>
</tr>
<tr>
<td>Physician visits</td>
<td>8.0 (0-154)</td>
<td>3 (0-158)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>10.87 [10.78]</td>
<td>4.90 [7.49]</td>
<td></td>
</tr>
<tr>
<td>Physician costs</td>
<td>522 (0-82,746)</td>
<td>170 (0-101,181)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>899 [1,663]</td>
<td>402 [1,082]</td>
<td></td>
</tr>
<tr>
<td>Laboratory claims</td>
<td>3.0 (0-110)</td>
<td>1 (0-87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>4.24 [5.01]</td>
<td>1.58 [2.74]</td>
<td></td>
</tr>
<tr>
<td>Laboratory costs</td>
<td>262 (0-24,342)</td>
<td>19 (0-55,445)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>470 [775]</td>
<td>123 [433]</td>
<td></td>
</tr>
<tr>
<td>Pharmacy claims</td>
<td>16.0 (0-331)</td>
<td>3 (0-352)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>23.29 [25.90]</td>
<td>10.27 [17.43]</td>
<td></td>
</tr>
<tr>
<td>Pharmacy costs</td>
<td>1,099 (0-2,762,952)c</td>
<td>65 (0-139,720)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2,423 [23,038]</td>
<td>593 [2,089]</td>
<td></td>
</tr>
<tr>
<td>Emergency department visits</td>
<td>0 (0-27)</td>
<td>0 (0-66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.38 [1.13]</td>
<td>0.17 [0.71]</td>
<td></td>
</tr>
<tr>
<td>Emergency department costs</td>
<td>0 (0-144,498)</td>
<td>0 (0-67,751)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>268 [1,599]</td>
<td>100 [617]</td>
<td></td>
</tr>
<tr>
<td>Other outpatient hospital visits</td>
<td>1 (0-95)</td>
<td>0 (0-150)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2.03 [4.17]</td>
<td>0.76 [2.62]</td>
<td></td>
</tr>
<tr>
<td>Other outpatient hospital costs</td>
<td>158 (0-209,988)</td>
<td>0 (0-186,665)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1,310 [4,199]</td>
<td>411 [2,298]</td>
<td></td>
</tr>
<tr>
<td>Total medical and facility visitsd</td>
<td>10 (0-204)</td>
<td>5 (0-184)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>13.65 [13.21]</td>
<td>5.91 [8.87]</td>
<td></td>
</tr>
<tr>
<td>Total medical and facility costsd</td>
<td>5,190 (0-2,770,192)</td>
<td>753 (0-1,543,378)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>13,233 [40,715]</td>
<td>3,214 [12,741]</td>
<td></td>
</tr>
</tbody>
</table>

a Costs are adjusted to 2005 dollars.

b The statistical tests were chi square with Yates correction for difference in % female and Wilcoxon signed-rank test for differences in the distributions of continuous variables (claims, visits, and costs) for the UC and comparator cohorts.

c One patient had a total pharmacy cost of $2,762,952 due to a large number of prescriptions from a specialty pharmacy. When this patient’s pharmacy claims were excluded from the analysis, the following values were obtained for pharmacy costs for the UC cohort: median = $1,098, minimum = $0, maximum = $200,130, mean = $2,240, standard deviation = $5,118. Thus, inclusion of the outlier did not influence study results.

d Total cost and utilization include miscellaneous services other than the main categories listed, such as nursing home or substance abuse treatment costs. These costs accounted for $2,092 and $619 of the total all-cause costs for UC patients and non-UC members, respectively.

CCI = Charlson Comorbidity Index; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; UC = ulcerative colitis.

[SD]) CCI score of 1.33 [1.98], compared with 0.42 [1.10] for the comparator group (P<0.001, Table 2).

The mean and median resource utilization and costs for the UC and comparator cohorts are reported in Table 2. The median annual total all-cause health care cost for all patients with UC was more than 5 times greater than that of the comparator group ($5,190 vs. $753, respectively). The mean [SD] costs were also substantially higher for the UC group ($13,233 [$40,715]) than for the comparator group ($3,214 [$12,741]). Inpatient hospitalization costs constituted the largest component of the mean total costs for both the UC cohort ($5,771, 43.6%; Table 2; Figure 2) and the comparator group ($966, 30.1%). The cost of
groups ($593, 18.5%). Not all health care costs and utilization cian, laboratory, pharmacy, emergency department, and other and included home health care, skilled nursing facility, hospice, psychiatric facility, substance abuse treatment center, and other similar treatment settings. This category accounted for 15.8% ($2,092) of costs for UC patients and 19.3% ($619) of costs for members without UC.

Subgroup analyses were conducted for each age group to determine the components that had the largest contribution to the total health care costs. The mean age of the pediatric-adolescent UC subgroup (n = 589) was 12.79 years, and the mean age of the pediatric-adolescent comparator group (n = 2,233) was 13.02 years (P = 0.321); 47.5% of the UC cohort and 47.1% of the comparator group were female (Table 3; Figure 2). Based on the mean CCI scores, the pediatric-adolescent UC cohort had significantly more comorbidities than did the comparator group (1.44 vs. 0.17, respectively, P < 0.001). The mean [SD] annual total all-cause cost for all pediatric-adolescent UC patients was $23,113 [$70,999], which was significantly higher than for the pediatric-adolescent comparator group, at $1,162 [$5,836], P < 0.001. Inpatient hospitalization costs constituted the largest component (65.0%) of the mean [SD] annual total all-cause cost for all pediatric-adolescent UC patients (Table 3; Figure 2) and were significantly higher than the inpatient costs for the pediatric-adolescent comparator group ($15,025 [$63,927] vs. $294 [$4,050], respectively, P < 0.001). Other mean [SD] costs for the pediatric-adolescent UC patients were prescription medications ($2,207 [$3,931], 9.5%), outpatient hospital visits ($1,413 [$3,502], 6.1%), physician office visits ($1,088 [$2,568], 4.7%), and laboratory procedures ($677 [$1,452], 2.9%) (Table 3).

The adult UC subgroup was the largest subgroup, comprising 13,886 patients matched to a comparator group of 55,186 non-UC members (Table 4). The mean ages of this patient cohort and the corresponding comparator group were 44.25 years and 44.46 years (P < 0.001), respectively, and 54% of each group was female. The adult UC group had a mean [SD] CCI score of 1.25 [1.91], compared with 0.39 [1.06] for the corresponding comparator group (P < 0.001), indicating a heavier comorbidity burden for the UC group. Cost and health care resource utilization trends among the adult UC group were similar to those of the pediatric-adolescent group. The mean [SD] annual total all-cause cost for adult patients with UC was $12,693 [$39,505], compared with $3,147 [$12,722] for the adult non-UC comparator group (P < 0.001). Again, inpatient hospitalization costs constituted the largest component (41.6%) of the annual total mean [SD] all-cause cost for adult patients with UC ($5,276 [$26,170]; Table 4; Figure 2) and were significantly higher than those for the corresponding comparator group ($903 [$10,024], P < 0.001; Table 4).

The subgroup of 650 older adult patients with UC had a mean age of 75.40 years, and 58.0% were female, a demographic profile that was similar to that of the comparator group (76.50 years, 58.6% female) (Table 5). The mean [SD] CCI score was 2.87 [2.84] and was significantly higher than the comparator group’s mean of 1.44 [1.95], P < 0.001. The mean [SD] annual total all-cause cost for older adult patients with UC ($15,811 [$23,882]) was significantly higher than for the comparator group ($7,171 [$17,060], P < 0.001), and mean total utilization (total medical plus facility visits) was also significantly higher (19.31 vs. 10.26 visits, respectively, P < 0.001). Inpatient hospitalization costs constituted the largest component ($7,926; 50.1%; Table 5; Figure 2) of the mean annual total all-cause cost for older adult patients with UC, followed by outpatient hospital costs ($1,941, 12.3%) and pharmacy costs ($1,641, 10.4%; Table 5).

In general, cost and utilization trends were similar among the UC cohorts, with the largest costs incurred from inpatient and outpatient hospital services, physician visits, and pharmacy claims for UC claimants in all 3 age groups (Table 6). Overall, the pediatric-adolescent UC group had the highest costs, followed by the older adult UC group and the adult UC group. However, the older adult UC group generally had higher utilization rates in key service categories (e.g., inpatient hospital stays, physician visits,
laboratory procedures, and pharmacy claims) than did the other UC groups.

**Discussion**

The expected cost of care for patients with chronic diseases such as UC is critical to MCOs. This study demonstrated that all-cause resource utilization was highest in the older adult population; however, the pediatric-adolescent patients with UC incurred the highest mean annual total all-cause cost, which was approximately twice the mean total all-cause cost for the other age groups. These high costs in the pediatric-adolescent UC group were largely due to inpatient hospitalizations. Previous research indicated an increased risk of surgery in pediatric-adolescent patients with severe UC, although it is unclear if any of the hospitalizations or possible surgeries in the present study's pediatric-adolescent patients were due to their UC diagnosis.32

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**TABLE 3** Characteristics and 12-Month All-Cause Resource Utilization and Costs for Pediatric-Adolescent (Aged < 18 Years) UC Patients Versus Age- and Gender-Matched Members Without UC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UC N = 589</th>
<th>Non-UC N = 2,233</th>
<th>P Valueb</th>
<th>Median (Range)</th>
<th>Mean [SD] (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% females (number)</td>
<td>47.5 (280)</td>
<td>47.1 (1,051)</td>
<td>0.882</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI score [SD]</td>
<td>1.44 [1.77]</td>
<td>0.17 [0.44]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient hospitalizations</td>
<td>0 (0-12)</td>
<td>0 (0-5)</td>
<td>&lt;0.001</td>
<td>0 (0-121,964)</td>
<td>294 [4,050]</td>
</tr>
<tr>
<td>Inpatient hospital costs</td>
<td>0 (0-976,763)</td>
<td>0 (0-121,964)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician visits</td>
<td>8 (0-154)</td>
<td>2 (0-90)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician costs</td>
<td>1,119 [12.13]</td>
<td>3.27 [5.26]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory claims</td>
<td>624 (0-45,559)</td>
<td>113 (0-14,072)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory costs</td>
<td>1,088 [2,568]</td>
<td>257 [585]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical claims</td>
<td>268 (0-24,342)</td>
<td>0 (0-5,767)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical costs</td>
<td>677 [1,452]</td>
<td>37 [186]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department visits</td>
<td>0 (0-12)</td>
<td>0 (0-6)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department costs</td>
<td>0 (0-13,939)</td>
<td>0 (0-10,650)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other outpatient hospital visits</td>
<td>1 (0-69)</td>
<td>0 (0-59)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other outpatient hospital costs</td>
<td>107 (0-53,915)</td>
<td>0 (0-18,546)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total medical and facility visitsc</td>
<td>1,184 (0-32,115)</td>
<td>3.92 (0-27,425)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total medical and facility costsc</td>
<td>2,207 [3,931]</td>
<td>169 [905]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a Costs are adjusted to 2005 dollars.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b The statistical tests were chi square with Yates correction for difference in % female and Wilcoxon signed-rank test for differences in the distributions of continuous variables (claims, visits, and costs) for the UC and comparator cohorts.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c Total cost and utilization include miscellaneous services other than the main categories listed, such as nursing home or substance abuse treatment costs. These costs accounted for $2,420 and $213 of the total all-cause costs for UC patients and non-UC members, respectively.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI = Charlson Comorbidity Index; UC = ulcerative colitis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Administrative Claims Analysis of All-Cause Annual Costs of Care 
and Resource Utilization by Age Category for Ulcerative Colitis Patients

Although the pediatric-adolescent cohort was the smallest cohort, the cost of long-term care for these patients will be significant. The average life expectancy of a person with UC is approximately 70 to 75 years, so the total cost of care for pediatric or adolescent patients over the course of a patient's lifetime could be substantial. 

Across all age groups, hospitalization accounted for the largest proportion of the mean annual total all-cause costs incurred by the UC cohort (43.6% overall, 65.0% for pediatric-adolescent patients, 41.6% for adult patients, and 50.1% for older adult patients). These results underscore the opportunity for future therapies to reduce the need for hospitalization and

TABLE 4 Characteristics and 12-Month All-Cause Resource Utilization and Costs for Adult [Aged 18-64 Years] UC Patients Versus Age- and Gender-Matched Members Without UC a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UC (N = 13,866)</th>
<th>Non-UC (N = 55,186)</th>
<th>P Value b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (Range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean [SD]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong>—mean [SD]</td>
<td>44.25 [11.23]</td>
<td>44.46 [10.99]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>% females (number)</strong></td>
<td>53.7 (7,440)</td>
<td>53.9 (29,770)</td>
<td>0.549</td>
</tr>
<tr>
<td><strong>CCI score [SD]</strong></td>
<td>1.25 [1.91]</td>
<td>0.39 [1.06]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Inpatient hospitalizations</strong></td>
<td>0 (0-15)</td>
<td>0 (0-9)</td>
<td></td>
</tr>
<tr>
<td><strong>Inpatient hospital costs</strong></td>
<td>0 (0-828,630)</td>
<td>0 (0-1,480,805)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Physician visits</strong></td>
<td>7 (0-143)</td>
<td>2 (0-158)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Physician costs</strong></td>
<td>508 (0-82,746)</td>
<td>167 (0-101,181)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Laboratory claims</strong></td>
<td>3 (0-95)</td>
<td>1 (0-87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Laboratory costs</strong></td>
<td>265 (0-18,718)</td>
<td>20 (0-55,445)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pharmacy claims</strong></td>
<td>16 (0-331)</td>
<td>3 (0-352)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pharmacy costs</strong></td>
<td>1,117 (0-2,762,952)c</td>
<td>68 (0-139,726)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Emergency department visits</strong></td>
<td>0 (0-27)</td>
<td>0 (0-66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Emergency department costs</strong></td>
<td>0 (0-144,498)</td>
<td>0 (0-67,751)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Other outpatient hospital visits</strong></td>
<td>1 (0-95)</td>
<td>0 (0-116)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Other outpatient hospital costs</strong></td>
<td>143 (0-209,988)</td>
<td>0 (0-186,665)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Total medical and facility visits</strong></td>
<td>9 (0-204)</td>
<td>3 (0-163)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Total medical and facility costs</strong></td>
<td>5,108 (0-2,770,192)</td>
<td>755 (0-1,543,378)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a Costs are adjusted to 2005 dollars.
b The statistical tests were chi square with Yates correction for difference in % female and Wilcoxon signed-rank test for differences in the distributions of continuous variables (claims, visits, and costs) for the UC and comparator cohorts.
c One patient had a total pharmacy cost of $2,762,952 due to a large number of prescriptions from a specialty pharmacy. When this patient's pharmacy claims were excluded from the analysis, the following values were obtained for pharmacy costs for the UC cohort: median = $1,098, minimum = $0, maximum = $200,130, mean = $2,240; standard deviation = $5,118. Thus, inclusion of the outlier did not influence study results.
d Total cost and utilization include miscellaneous services other than the main categories listed, such as nursing home or substance abuse treatment costs. These costs accounted for $2,857 and $614 of the total all-cause costs for UC patients and non-UC members, respectively.
CCI = Charlson Comorbidity Index; UC = ulcerative colitis.
surgery and perhaps decrease the total health care costs for patients with UC.

To further assess the economic impact of UC on patients, studies that incorporate indirect costs, such as lost school and work days, lost earnings, and out-of-pocket expenditures, should be conducted. The direct impact of therapy options on health care costs for patients with UC should be examined to determine the cost-effectiveness of these options.

**Limitations**

Foremost among the study limitations was that we analyzed all-cause health care costs. The degree to which these costs are attributable to UC is unknown. Second, because this analysis was based on claims data, the contribution of UC to the CCI score and the cause of the comorbidities (UC or other) could not be determined. Third, the comparison group in the present study comprised members who may not have had any medical

| TABLE 5 | Characteristics and 12-Month All-Cause Resource Utilization and Costs for Older Adult [Aged ≥65 Years] UC Patients Versus Age- and Gender-Matched Members Without UC a |
|---|---|---|---|
| Median (Range) | UC N = 650 | Non-UC N = 2,100 | P Value b |
| Mean [SD] | | | |
| Age—mean [SD] | 75.40 [6.98] | 76.50 [7.18] | 0.178 |
| % females (number) | 58.0 (377) | 58.6 (1,230) | 0.832 |
| CCI score [SD] | 2.87 [2.84] | 1.44 [1.95] | <0.001 |
| Inpatient hospitalizations | 0 (0-8) | 0 (0-6) | <0.001 |
| Inpatient hospital costs | 0 (0-138,032) | 0 (0-209,903) | <0.001 |
| Physician visits | 12 (0-91) | 6 (0-64) | <0.001 |
| Physician costs | 725 (0-15,756) | 382 (0-26,115) | <0.001 |
| Laboratory claims | 4 (0-86) | 2 (0-44) | <0.001 |
| Laboratory costs | 218 (0-16,922) | 69 (0-5,084) | <0.001 |
| Pharmacy claims | 21 (0-201) | 10 (0-158) | <0.001 |
| Pharmacy costs | 730 (0-75,116) | 205 (0-35,711) | <0.001 |
| Emergency department visits | 0 (0-8) | 0 (0-7) | <0.001 |
| Emergency department costs | 0 (0-8,694) | 0 (0-10,580) | <0.001 |
| Other outpatient hospital visits | 1 (0-58) | 0 (0-150) | <0.001 |
| Other outpatient hospital costs | 692 (0-112,877) | 0 (0-64,246) | <0.001 |
| Total medical and facility visits c | 16 (0-114) | 7 (0-184) | <0.001 |
| Total medical and facility costs c | 6,886 (100-165,685) | 2,131 (0-245,169) | <0.001 |
| a Costs are adjusted to 2005 dollars. |
| b The statistical tests were chi square with Yates correction for difference in % female and Wilcoxon signed-rank test for differences in the distributions of continuous variables (claims, visits, and costs) for the UC and comparator cohorts. |
| c Total cost and utilization include miscellaneous services other than the main categories listed, such as nursing home or substance abuse treatment costs. These costs accounted for $2,562 and $1,146 of the total all-cause costs for UC patients and non-UC members, respectively. |

CCI = Charlson Comorbidity Index; UC = ulcerative colitis.
### TABLE 6
Comparison of All-Cause Resource Utilization and Costs for Pediatric-Adolescent, Adult, and Older Adult Patients With UC a

<table>
<thead>
<tr>
<th></th>
<th>Pediatric-Adolescent (Aged &lt; 18 Years)</th>
<th>Adult (Aged 18-64 Years)</th>
<th>Older Adult (Aged ≥ 65 Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean [SD] (Median)</td>
<td>Mean [SD] (Median)</td>
<td>Mean [SD] (Median)</td>
</tr>
<tr>
<td>Inpatient hospitalizations</td>
<td>N = 589</td>
<td>N = 13,866</td>
<td>N = 650</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent b</td>
<td>0.58 [1.18] (0)</td>
<td>0.33 [0.88] (0)</td>
<td>0.75 [1.27] (0)</td>
</tr>
<tr>
<td>P value versus adult b</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient hospital costs</td>
<td>15,025 [63,927] (0)</td>
<td>5,276 [26,170] (0)</td>
<td>7,926 [17,868] (0)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>0.75 [1.27] (0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physician costs</td>
<td>1,088 [2,568] (624)</td>
<td>884 [1,629] (508)</td>
<td>1,052 [2,929] (725)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>14.74 [11.37] (12)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laboratory claims</td>
<td>4.95 [6.87] (3)</td>
<td>4.12 [4.73] (3)</td>
<td>5.98 [7.70] (4)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>0.032</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laboratory costs</td>
<td>677 [1,452] (268)</td>
<td>467 [730] (265)</td>
<td>357 [799] (218)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>0.153</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>18.64 [18.08] (15)</td>
<td>23.26 [26.01] (16)</td>
<td>28.21 [28.59] (21)</td>
</tr>
<tr>
<td>Pharmacy claims</td>
<td>1,088 [2,568] (624)</td>
<td>884 [1,629] (508)</td>
<td>1,052 [2,929] (725)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>14.74 [11.37] (12)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pharmacy costs</td>
<td>2,207 [3,931] (1,184)</td>
<td>2,469 [24,015] (1,117)</td>
<td>1,641 [4,143] (730)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>0.805</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergency department visits</td>
<td>0.50 [1.11] (0)</td>
<td>0.38 [1.14] (0)</td>
<td>0.48 [1.06] (0)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergency department costs</td>
<td>283 [911] (0)</td>
<td>264 [1,643] (0)</td>
<td>332 [1,005] (0)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Other outpatient hospital visits</td>
<td>2.53 [6.48] (1)</td>
<td>1.95 [3.94] (1)</td>
<td>3.33 [5.77] (1)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>0.523</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other outpatient hospital costs</td>
<td>1,413 [3,502] (107)</td>
<td>1,276 [4,158] (143)</td>
<td>1,941 [5,428] (692)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>0.635</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>1.941 [5,428] (692)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>19.31 [14.57] (16)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total medical and facility costs a</td>
<td>23,113 [70,999] (6,214)</td>
<td>12,693 [39,505] (5,108)</td>
<td>15,811 [23,882] (6,886)</td>
</tr>
<tr>
<td>P value versus pediatric-adolescent</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value versus adult</td>
<td>15,811 [23,882] (6,886)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a Costs are adjusted to 2005 dollars.

b P values determined using Mann-Whitney U test.

c Total cost and utilization include miscellaneous services other than the main categories listed, such as nursing home or substance abuse treatment costs.

UC = ulcerative colitis.
claims; in other words, the comparison group comprised health plan members without medical claims as well as patients with medical claims.

Fourth, previous research has shown that UC is an episodic disease with long periods of remission in some patients: 5% to 17% of patients in clinical trials experience spontaneous remission. Therefore, our examination of total health care costs for only 12 months following diagnosis of UC may not predict longer-term costs, and studies beyond 12 months are needed. Fifth, the cost analysis was based on the amount paid and, therefore, excludes member costs and indirect costs. Sixth, the PharMetric database is considered representative of the commercially insured population in the United States but may not be representative of Medicare and Medicaid patients, the uninsured, or populations outside the United States. Although this analysis controlled for the effects of age and comorbidities, regional differences in health care costs or the differences in amounts paid according to health plan type were not analyzed.

**Conclusion**

All-cause health care costs for patients with 2 or more claims with a diagnosis of UC were more than 4 times that of a comparator group of members without UC. Total all-cause costs were highest in the pediatric-adolescent UC group, while resource utilization as measured by visits and claims was greatest in the older adult UC groups.

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**DISCLOSURES**

This study was funded by Centocor, Inc., Ortho Biotech Services, LLC, Horsham, Pennsylvania. Four of the authors (Heidi C. Waters, Omar Dabbous, Boxiong Tang, and Mirza I. Rahman) are or were employed by Centocor at the time this study was conducted and own stock in Johnson & Johnson, of which Centocor Ortho Biotech Services, LLC, is a subsidiary. Stephen J. Bickston reported work for Centocor, Abbott, and UCB as a faculty speaker and as a principal investigator in clinical trials for Otsuka, Berlex, and Centocor.

All authors except Tang contributed to the study concept and design. Data collection was primarily the work of Dabbous, with assistance from Tang and Waters. All authors contributed to data interpretation. The manuscript was written primarily by Bickston, with assistance from Waters, Dabbous, and Rahman. All authors except Dabbous contributed to revision of the manuscript.

**ACKNOWLEDGMENTS**

The authors thank Brian Meissner, PharmD, PhD, of Xcenda for statistical support and Rebecca E. Clemente, PhD, of Centocor, Inc., for editorial support that included revision of the manuscript.

**REFERENCES**

Managed Care Perspective on Three New Agents for Type 2 Diabetes

Shawna VanDeKoppel, PharmD; Hae Mi Choe, PharmD, CDE; and Burgunda V. Sweet, PharmD, FASHP

ABSTRACT

BACKGROUND: Despite effective monotherapy for diabetes, approximately 50% of patients require additional medications after 3 years to achieve target glycated hemoglobin (A1C) <7%. Three new agents, each the first in its therapeutic class with a unique mechanism of action, have been approved for the treatment of type 2 diabetes by the U.S. Food and Drug Administration: pramlintide in March 2005, exenatide in April 2005, and sitagliptin in October 2006.

OBJECTIVE: To review the efficacy and safety of 3 new agents for type 2 diabetes (exenatide and pramlintide by subcutaneous injection and sitagliptin by oral administration) and to define their place in therapy given their relatively high cost and unknown long-term safety and efficacy.

METHODS: A MEDLINE search (1950 to June 2007) for English-language articles of studies in human subjects was conducted using these search terms: type 2 diabetes, exenatide, pramlintide, and sitagliptin. This database was supplemented by systematic reviews and meta-analyses through December 2007 and reference citations from the articles identified in the MEDLINE search.

RESULTS: Exenatide, pramlintide, and sitagliptin have all shown to have a modest effect on reducing A1C. In several relatively short-term trials (generally 15-30 weeks in duration), exenatide injection has been shown to be safe and effective for patients with type 2 diabetes who are either at the maximum doses of or cannot tolerate metformin, sulfonylurea, and/or thiazolidinedione therapy and need to further decrease A1C by at least 0.5% to 1%. While weight loss of 1.5 kg to 2.5 kg associated with exenatide is modest, this effect is of obvious value in many patients with type 2 diabetes. Nausea is the most notable side effect with exenatide, occurring in up to 50% of patients within the first 8 weeks of therapy but decreasing to 5% to 10% by week 24. In addition, the risk for hypoglycemia increases 4- to 5-fold when used in combination with sulfonylureas. Like exenatide, pramlintide injection reduces A1C by approximately 0.5% to 1%, carries the advantage of modest weight loss (1.5 kg over 1 year), and has a high incidence of nausea. Pramlintide can also result in severe hypoglycemia because of its ability to enhance the effects of insulin, a concern given that it is only indicated for use in combination with insulin. Sitagliptin is an oral agent that can be used alone or in combination with other oral hypoglycemic agents and has been shown to reduce A1C by 0.5% to 0.7%. It has only been studied in short-term studies, to date, so the long-term safety and efficacy are unknown. There is potential for severe allergic and dermatologic reactions with sitagliptin.

CONCLUSIONS: The 3 new agents for the management of type 2 diabetes have been shown to reduce A1C by no more than 1.0%, modest by comparison with insulin and the older oral agents. The 3 newer agents have either modest positive effects on body weight or are weight neutral. The long-term safety and efficacy of the 3 newer agents are unknown, and their cost is considerably higher than the first-line agents, metformin and sulfonylureas, which are available by generic name. The newer agents offer treatment options in select patients, although their use should be reserved for patients who are not adequately managed by agents with known long-term efficacy and safety, which are often available at a lower cost.

J Manag Care Pharm. 2008;14(4):363-80

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diabetes, to summarize the data for agents (exenatide, pramlintide, and sitagliptin) that have recently become available, and to help the clinician identify clinical situations in which the new agents should be considered in the treatment algorithm.

Glucose Homeostasis and Pathophysiology of Type 2 Diabetes

Normal glucose metabolism involves a balancing act between insulin and glucagon. When glucose is consumed, beta cells in the pancreas are stimulated to release insulin and suppress glucagon. Insulin is typically secreted in 2 phases: a quick, immediate increase in response to glucose intake followed by a slower, sustained release. Insulin allows for cellular uptake of glucose, the energy source for the cell. It also inhibits any cellular production of glucose.2 Glucagon, another regulatory hormone, reacts in response to low plasma glucose levels. It stimulates the production of glucose via gluconeogenesis, ketogenesis, and hepatic breakdown of glycogen.

Other hormones have also been found to play key roles in regulating glucose homeostasis. Incretin hormones are released from the gut after a meal. One of these incretin hormones, glucagon-like peptide-1 (GLP-1), binds to the beta-cell membrane in the pancreas, thereby stimulating insulin secretion by the beta cell. GLP-1 is not activated when glucose concentrations are below a certain threshold, thereby preventing glucose levels from becoming too low. Studies have shown that GLP-1 also appears to increase cell glucose sensitivity and aids in insulin synthesis and beta-cell function.3-6

Amylin, a neuroendocrine hormone, has also been found to be important for glucose metabolism. Amylin is released from the beta cells of the pancreas in conjunction with insulin secretion. It binds to receptors in the brain to aid in the regulation of glucose by inhibiting glucagon secretion. This allows the body to use glucose recently ingested instead of glucose via gluconeogenesis.7,9

In type 2 diabetes, regulation of glucose utilization is impaired because of decreased pancreatic beta-cell function, which causes decreased insulin and amylin secretion. The result is decreased blood glucose utilization and over-expression of glucagon. Unopposed glucagon will subsequently increase glucose production from endogenous sources and promote glycogen breakdown. Incretin hormone secretion, including GLP-1, is also decreased in type 2 diabetes, further impeding insulin production by and secretion from beta cells. The net result is hyperglycemia and perpetuation of the unregulated cycle.2,3,9

Management of Type 2 Diabetes

In order to prevent the complications of diabetes, the American Diabetes Association (ADA) recommends glycated hemoglobin (A1C) <7%. Lifestyle interventions, such as good nutrition and exercise, are an important component of managing type 2 diabetes. However, for many patients, diet and exercise alone are inadequate to maintain optimal blood glucose control. As such, the current ADA guidelines recommend initiation of metformin at the time of diagnosis and consider metformin to be the only drug for diabetes prevention.10

The ADA and the American Association of Clinical Endocrinologists (AACE) provide an overview of the treatment options for glycemic management.10,11 The different classes of agents available for the management of diabetes are shown in Table 1. Treatment is usually initiated with oral metformin monotherapy; a sulfonylurea should be considered in patients in whom metformin is not an option (i.e., those with reduced renal function).10,14 Despite optimal monotherapy, approximately 50% of patients with diabetes will require additional medications after 3 years to achieve an A1C <7%.14 A second oral agent is often added at this point. If a patient is receiving the maximum dose of metformin, a sulfonylurea is typically added.10,12,14,15 If a patient is unable to tolerate or has a contraindication to metformin or sulfonylurea therapy, a thiazolidinedione or bedtime insulin may be added to aid in further reducing A1C.10,12,16,17 Insulin may be favored over a thiazolidinedione if levels of glycaemia are high (≥8.5%) or if a patient cannot tolerate a thiazolidinedione. Despite the variety of treatment options available, combination therapy with or without insulin may still be inadequate to achieve glycemic control.

Bolen et al. conducted a systematic review outlining the comparative efficacy and safety of the oral medications (excluding sitagliptin) for type 2 diabetes.18 In recent years, compounds that mimic the actions of the natural endocrine hormones GLP-1 and amylin have been isolated and are now available for the treatment of type 2 diabetes. Two of these agents, exenatide and pramlintide, are available for subcutaneous use only. Sitagliptin is a new oral agent that inhibits the metabolism of GLP-1. The availability of new agents with differing mechanisms of action for a disease state whose incidence has increased by 54% in the past 7 years in the United States is generally viewed as favorable. However, there are concerns with the routine use of newer agents given the lack of long-term efficacy data, their high cost, and ongoing reports through post-marketing data regarding overall safety.10

Clinical Studies

Exenatide

Exenatide (Byetta, Amylin Pharmaceuticals), is an incretin mimetic similar to GLP-1 that was originally discovered in Gila monster saliva. Exenatide was approved by the U.S. Food and Drug Administration (FDA) in April 2005 and is labeled for adjunctive therapy to improve glycemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, or a thiazolidinedione, either alone or in combination.19 Exenatide binds to the GLP-1 receptor in the gut, but it has increased potency and a longer duration of action than endogenous GLP-1.19,20 It has been shown to potentiate insulin secretion, decrease glucagon secretion, decrease gastric emptying time, and enhance satiety.
It may also promote beta-cell synthesis and proliferation. In an in vitro trial using human pancreatic islet cells, Chen et al. demonstrated that exenatide reduced apoptotic factors and maintained beta-cell function. Fineman et al. also showed a possible improvement in beta-cell function with exenatide therapy.

**Efficacy of Exenatide**

Several studies have been conducted that evaluated the safety and efficacy of exenatide. Overall, twice-daily subcutaneous dosing of exenatide was able to decrease A1C and fasting plasma glucose while also reducing weight in patients with type 2 diabetes. These effects were initially shown in a 28-day trial comparing twice-daily administration of placebo or exenatide 2.5 mcg, 5 mcg, 7.5 mcg, or 10 mcg. All exenatide treatment groups displayed significant decreases in A1C, with the absolute decrease being dose-dependent. There was also a dose-related decrease in weight compared with baseline by day 28 with all exenatide doses compared with no change in weight in subjects receiving placebo. Only the exenatide 7.5 mcg and 10 mcg groups experienced significant weight loss compared with baseline (-1.4 kg and -1.7 kg, respectively; *P*<0.010). In another 28-day trial, 109 patients were randomized to receive placebo or 1 of

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**TABLE 1** Pharmacological Agents Used for the Treatment of Type 2 Diabetes in Order of Effect on A1C[^10,19,55]

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>% A1C Reduction</th>
<th>Medication</th>
<th>Dosage Form</th>
<th>Usual Dose</th>
<th>Drug Cost ($) (per month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulins</td>
<td>• Provides exogenous insulin</td>
<td>&gt;2.5%</td>
<td>Insulin glargine</td>
<td>100 u/mL, 10 mL vials</td>
<td>Various</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>• Provides exogenous insulin</td>
<td></td>
<td>Insulin lispro</td>
<td></td>
<td></td>
<td>150-225</td>
</tr>
<tr>
<td></td>
<td>• Provides exogenous insulin</td>
<td></td>
<td>Insulin human isophane</td>
<td></td>
<td></td>
<td>90-120</td>
</tr>
<tr>
<td></td>
<td>• Decreases endogenous glucose synthesis</td>
<td></td>
<td>Metformin</td>
<td>500/750/850/1,000 mg tablets</td>
<td>1,000 mg BID</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>• Decreases intestinal absorption of glucose</td>
<td>1.5%</td>
<td>Metformin ER</td>
<td>500/750/1,000 mg tablets</td>
<td>1,000 mg daily</td>
<td>40</td>
</tr>
<tr>
<td>Biguanides</td>
<td>• Increases insulin sensitivity</td>
<td></td>
<td>Glipizide</td>
<td>5/10 mg tablets</td>
<td>5 mg BID</td>
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<tr>
<td></td>
<td>• Decreases endogenous glucose synthesis</td>
<td></td>
<td>Glipizide XL</td>
<td>2.5/5/10 mg tablets</td>
<td>5 mg daily</td>
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<tr>
<td></td>
<td>• Decreases intestinal absorption of glucose</td>
<td></td>
<td>Glimepiride</td>
<td>1/2/4 mg tablets</td>
<td>2 mg daily</td>
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<tr>
<td></td>
<td>• Decreases endogenous glucose synthesis</td>
<td></td>
<td>Glyburide</td>
<td>1.25/2/5/5 mg tablets</td>
<td>5 mg daily</td>
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<tr>
<td>Sulfonylureas</td>
<td>• Stimulates insulin release</td>
<td>1.5%</td>
<td>Nateglinide</td>
<td>60/120 mg tablets</td>
<td>60-120 mg AC</td>
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<tr>
<td></td>
<td>• Stimulates insulin release</td>
<td></td>
<td>Repaglinide</td>
<td>0.5/1/2 mg tablets</td>
<td>0.5-4 mg AC</td>
<td>150-240</td>
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<tr>
<td>Glinides</td>
<td>• Stimulates insulin release</td>
<td>1.0%-1.5%</td>
<td>Pioglitazone</td>
<td>15/30/45 mg tablets</td>
<td>30 mg daily</td>
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<td></td>
<td>• Stimulates insulin release</td>
<td></td>
<td>Pioglitazone/metformin</td>
<td>15/500; 15/850 mg tablets</td>
<td>1 tablet BID</td>
<td>192</td>
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<tr>
<td></td>
<td>• Stimulates insulin release</td>
<td></td>
<td>Rosiglitazone</td>
<td>2/4/8 mg tablets</td>
<td>4-8 mg daily</td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>• Stimulates insulin release</td>
<td></td>
<td>Rosiglitazone/metformin</td>
<td>2/500; 4/500; 2/1,000; 4/1,000 mg tablets</td>
<td>1 tablet BID</td>
<td>130-226</td>
</tr>
<tr>
<td>Incretin mimetics</td>
<td>• Potentiates insulin secretion</td>
<td>0.5%-1.0%</td>
<td>Exenatide</td>
<td>Pre-filled subcutaneous pen</td>
<td>5-10 mcg BID</td>
<td>213-230</td>
</tr>
<tr>
<td></td>
<td>• Decreases glucagon secretion</td>
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<td></td>
<td>(5 mcg and 10 mcg)</td>
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<td>Amylinomimetics</td>
<td>• Decreases post-prandial glucagon secretion</td>
<td>0.5%-1.0%</td>
<td>Pramlintide</td>
<td>5 ml vial (600 mcg/mL)</td>
<td>60-120 mcg TID</td>
<td>232-440</td>
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<td></td>
<td>• Slows gastric emptying</td>
<td></td>
<td></td>
<td>Pre-filled subcutaneous pen</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>• Increases satiety</td>
<td></td>
<td></td>
<td>(60 mcg and 120 mcg)</td>
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<td></td>
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<tr>
<td>Alpha¬-glycosidase inhibitors</td>
<td>• Decreases digestion of polysaccharides</td>
<td>0.5%-0.8%</td>
<td>Acarbose</td>
<td>25/50/100 mg tablets</td>
<td>25 mg TID</td>
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<td></td>
<td>• Decreases post-prandial glucose</td>
<td></td>
<td>Miglitol</td>
<td>25/50/100 mg tablets</td>
<td>25 mg TID</td>
<td>80</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>• Inhibits incretin hormone metabolism</td>
<td>0.5%-0.9%</td>
<td>Sitagliptin</td>
<td>25/50/100 mg tablets</td>
<td>100 mg daily</td>
<td>171</td>
</tr>
</tbody>
</table>

*Products available as a generic formulations are shown in bold.*


AC = before meals; BID = twice daily; DPP-4 = dipeptidyl peptidase-4; ER = extended release; TID = 3 times daily.
3 exenatide 0.08 mcg per kg regimens (twice-daily, breakfast/dinner; twice-daily, breakfast/bedtime; or 3-times-daily). There was a significant decrease in A1C compared with placebo for the twice-daily (breakfast/dinner) and 3-times-daily regimens (-1.1% and -1.0% versus -0.3%, P<0.001) and for the twice-daily (breakfast/bedtime) regimen (-0.7% versus -0.3%, P=0.006). There was no difference in fasting plasma glucose, body weight, or lipid levels between any of the treatment groups.

Hypoglycemia occurred in 15% of patients overall (active and placebo groups) and was reported to only be seen in patients who were also receiving a sulfonylurea. Unfortunately, no specific data on the incidence of hypoglycemia, either overall or in the subgroup of patients receiving a sulfonylurea, were reported. Nausea was the most commonly reported adverse effect, with exenatide therapy occurring in 31% of patients overall. However, this declined to 13% by day 28. This study demonstrated that short-term therapy with exenatide is effective in combination with a sulfonylurea and/or metformin. However, it suggested that the risk for hypoglycemia is higher in patients receiving concomitant sulfonylurea therapy, although no specific data were provided to assess this risk. In addition, this study was limited by its short duration.

The long-term studies evaluating the safety and efficacy of exenatide therapy for type 2 diabetes are summarized in Table 2. Buse et al. conducted a blinded, placebo-controlled, randomized study of 377 patients with type 2 diabetes who were not controlled on the maximum dose of a sulfonylurea. Baseline characteristics of all treatment groups were similar, with an average A1C of 8.6%, mean age of 55 years, and an average body mass index (BMI) of 33 kg/m². Patients were randomized to receive placebo or exenatide 5 mcg or 10 mcg subcutaneously twice daily for 30 weeks. All patients who were to receive exenatide were initiated at 5 mcg twice daily for 4 weeks to improve tolerability. The high-dose group then had their dose increased to 10 mcg twice daily. Exenatide significantly decreased A1C in both treatment groups, with mean decreases of 0.46% and 0.86% in the 5 mcg and 10 mcg groups, respectively, compared with a 0.12% increase in the placebo group. There were no differences in fasting plasma glucose seen between exenatide 5 mcg twice daily and placebo, but there was a significant decrease when exenatide 10 mcg twice daily was compared with placebo (-0.6 mmol per L vs. 0.4 mmol per L, P<0.050).

There was a reduction in the proinsulin:insulin ratio in the exenatide 10 mcg group at week 30 when compared with placebo. There was also a significant decrease in fasting plasma insulin in patients receiving exenatide (both doses) versus those receiving placebo. At week 30, only the exenatide 10 mcg group showed a significant weight loss (-1.6 kg) compared with placebo (-0.6 kg). Nausea, the most common side effect reported, was seen in 51% of those receiving exenatide 10 mcg, 39% of those receiving exenatide 5 mcg, and 7% of those receiving placebo. Nausea was most prevalent within the first 4 to 8 weeks of therapy, with the incidence decreasing to 5% to 10% by week 24 of therapy.

Mild to moderate hypoglycemia was reported at in 36%, 14%, and 3% of subjects in the 10 mcg, 5 mcg, and placebo groups, respectively. Other common adverse events with exenatide therapy included dizziness, feeling jittery, vomiting, diarrhea, and upper respiratory infection. This study demonstrated that adding exenatide to patients not adequately controlled on sulfonylurea therapy can improve A1C control in patients with type 2 diabetes. Exenatide 10 mcg subcutaneously twice daily provided additional improvement in fasting plasma glucose, proinsulin:insulin ratio, and weight loss.

DeFronzo et al. conducted a similar blinded, placebo-controlled, randomized study in 336 patients with type 2 diabetes who were not adequately controlled on metformin (1,500 mg per day). All patients (treatment and placebo groups combined) had similar baseline characteristics (A1C 8.2%, mean age 53 years, and average BMI 34 kg/m²). Patients were randomized to receive placebo or exenatide (5 mcg or 10 mcg twice daily) for 30 weeks. Exenatide 5 mcg and 10 mcg twice daily decreased A1C significantly compared with placebo (-0.4% and -0.8% vs. 0.1%, P<0.001). Fasting plasma glucose, post-prandial plasma glucose, and body weight were all significantly decreased when both exenatide doses were compared with placebo. Nausea was the most common adverse effect; it was reported most often in the exenatide 10 mcg group (45%) compared with the exenatide 5 mcg group (36%) or the placebo group (23%), suggesting a dose-related effect. It was noted more in the first 8 weeks of therapy and declined thereafter. Hypoglycemia (5%) was similar across all groups when exenatide was administered with metformin. This study showed that exenatide 5 mcg and 10 mcg subcutaneously twice daily in combination with metformin significantly decreased A1C, fasting plasma glucose, post-prandial plasma glucose, and body weight compared with placebo in patients with type 2 diabetes.

Exenatide was also studied in 733 patients not adequately controlled with a sulfonylurea, metformin, or a combination of both in a double-blind, placebo-controlled trial. Patients were randomized to receive placebo or exenatide 5 mcg or 10 mcg subcutaneously twice daily for 30 weeks. Patients had similar baseline characteristics: A1C of 8.5%, mean age of 55 years, and an average BMI of 33.6 kg/m². Similar results were seen, as in the previous trials, with decreases in A1C, fasting plasma glucose, post-prandial glucose, and body weight when exenatide 5 mcg or 10 mcg twice daily were compared with placebo. Nausea was again the most commonly reported adverse event, with the highest incidence seen with exenatide 10 mcg (48.5%) and exenatide 5 mcg (39.2%) compared with placebo (20.6%). Tolerance to nausea developed several weeks after initiation of treatment. In this study, the incidence of hypoglycemia was 4- and 5-fold greater in both treatment groups (5 mcg: 19.2%, 10 mcg: 27.8%) compared with the study by DeFronzo et al. (4.5% and 5.3%, respectively). This is likely because patients were receiving a sulfonylurea...
Efficacy and Safety of Exenatide for the Treatment of Type 2 Diabetes

**Authors and Study Design**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Dose (No. Patients)</th>
<th>Study Parameters</th>
<th>Efficacy Results</th>
<th>Tolerability Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buse et al. (2004)²⁷</td>
<td>Exenatide 5 mcg BID (n = 125) Exenatide 10 mcg BID (n = 129) Placebo BID (n=123) Total: 30 weeks Patients continued sulfonylurea therapy</td>
<td>Primary: • A1C Secondary: • FPG • Body weight</td>
<td>At week 30:</td>
<td>Most common (% for 10 mcg dose vs. placebo):</td>
</tr>
<tr>
<td>R, TB, PC, MC</td>
<td></td>
<td></td>
<td>A1C change</td>
<td>FPG</td>
</tr>
<tr>
<td>DeFronzo et al. (2005)²⁸</td>
<td>Exenatide 5 mcg BID (n = 110) Exenatide 10 mcg BID (n = 113) Placebo (n = 113) Total: 30 weeks Patients continued sulfonylurea therapy</td>
<td>Primary: • A1C Secondary: • A1C ≤ 7% • FPG • PPG • Body weight</td>
<td>At week 30:</td>
<td>Most common (% for 10 mcg dose vs. placebo):</td>
</tr>
<tr>
<td>R, TB, PC, MC</td>
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<td></td>
<td>A1C change</td>
<td>A1C ≤ 7%</td>
</tr>
<tr>
<td>Patients with type 2 diabetes not controlled with maximum doses of metformin (≥1,500 mg per day)</td>
<td></td>
<td></td>
<td>5 mcg</td>
<td>10 mcg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+0.12%</td>
<td>+0.4 mmol per L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>aP≤0.001; bP&lt;0.050. For subjects with baseline A1C &gt;7%, 41.3% of those receiving exenatide 10 mcg and 32.6% of those receiving exenatide 5 mcg reached an A1C ≤ 7%, significantly greater than those receiving placebo (8.8%).</td>
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<tr>
<td>Kendall et al. (2005)²⁹</td>
<td>Exenatide 5 mcg BID (n = 245) Exenatide 10 mcg BID (n = 241) Placebo (n = 247) Total: 30 weeks Patients continued existing oral regimen</td>
<td>Primary: • A1C Secondary: • A1C ≤ 7% • FPG • Body weight</td>
<td>At week 30:</td>
<td>Most common (% for 10 mcg dose vs. placebo):</td>
</tr>
<tr>
<td>R, DB, PC, MC</td>
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<td></td>
<td>A1C change</td>
<td>A1C ≤ 7%</td>
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<tr>
<td>Patients with type 2 diabetes not controlled with a sulfonylurea and/or metformin therapy</td>
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<td></td>
<td>5 mcg</td>
<td>10 mcg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>aP=0.006; bP&lt;0.050; cP&lt;0.001.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Both doses of exenatide resulted in a significant decrease in body weight (-1.6 kg) compared with placebo (-0.9 kg).</td>
<td></td>
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</table>

A1C = glycosylated hemoglobin; BID = twice daily; BW = body weight; DB = double blind; FPG = fasting plasma glucose; HOMA = homeostasis model assessment; MC = multicenter; PC = placebo controlled; PPG = post-prandial plasma glucose; R = randomized; TB = triple blind.

Continued on next page.

**TABLE 2**

in addition to metformin. The incidence of hypoglycemia in patients receiving placebo was also higher than that seen in the DeFronzo trial (12.6% vs. 5.3%).²⁸ Other common adverse events with exenatide included feeling jittery, vomiting, diarrhea, upper respiratory infection, and headache. Despite the increased risk of hypoglycemia, this study showed that the addition of exenatide to patients not adequately controlled with their current regimen, including combination therapy, is effective and well tolerated. Zinman et al. conducted a double-blind, placebo-controlled trial in 233 patients with type 2 diabetes who were stable on a
### Authors and Study Design

<table>
<thead>
<tr>
<th>Study Parameters</th>
<th>Efficacy Results</th>
<th>Tolerability Results</th>
</tr>
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<tbody>
<tr>
<td><strong>Exenatide 10 mcg twice daily (n = 121)</strong></td>
<td></td>
<td>Most common with exenatide vs. placebo:</td>
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<tr>
<td><strong>Placebo twice daily (n = 112)</strong></td>
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<td>Nausea (39.7% vs. 15.2%)</td>
</tr>
<tr>
<td><strong>Patients continued on existing oral regimen</strong></td>
<td></td>
<td>Nasopharyngitis (13.2% vs. 8.0%)</td>
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<tr>
<td><strong>Total: 16 weeks</strong></td>
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<td>Vomiting (13.2% vs. 0.9%)</td>
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<tr>
<td><strong>Primary:</strong></td>
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<td>Hypoglycemia (10.7% vs. 7.1%)</td>
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<td><strong>A1C</strong></td>
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<tr>
<td><strong>Secondary:</strong></td>
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<td><strong>FPG</strong></td>
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<td><strong>Daily self-monitored glucose</strong></td>
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<td><strong>PPG</strong></td>
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<tr>
<td><strong>HOMA β-cell function</strong></td>
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<td><strong>Body weight</strong></td>
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### Heine et al. (2005)¶

<table>
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<tr>
<td><strong>Exenatide 10 mcg BID (n = 282)</strong></td>
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<td>Most common with exenatide vs. insulin glargine:</td>
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<td><strong>Insulin glargine titrated to FPG &lt; 100 mg per dL (n = 267)</strong></td>
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<td>Nausea (37.1% vs. 8.6%)</td>
</tr>
<tr>
<td><strong>Total: 26 weeks</strong></td>
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<td>Vomiting (17.4% vs. 3.7%)</td>
</tr>
<tr>
<td><strong>Primary:</strong></td>
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<td>Headache (8.9% vs. 8.6%)</td>
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<td><strong>A1C</strong></td>
<td></td>
<td>Diarrhea (8.5% vs. 3.0%)</td>
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<tr>
<td><strong>Secondary:</strong></td>
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<tr>
<td><strong>FPG</strong></td>
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<td><strong>Body weight</strong></td>
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### Kim et al. (2007)¶

<table>
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<tr>
<td><strong>Exenatide LAR 0.8 mg weekly (n=16)</strong></td>
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<td>Most common with exenatide LAR 2 mg dose vs. placebo:</td>
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<td><strong>Exenatide LAR 2 mg weekly (n = 15)</strong></td>
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<td>Nausea (27% vs. 15%)</td>
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<tr>
<td><strong>Placebo (n = 14)</strong></td>
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<td>Gastroenteritis (13% vs. 0%)</td>
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<tr>
<td><strong>Total: 15 weeks</strong></td>
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<td><strong>Safety</strong></td>
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<td><strong>Plasma concentration</strong></td>
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<td><strong>FPG</strong></td>
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<td></td>
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<tr>
<td><strong>Body weight</strong></td>
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A1C = glycosylated hemoglobin; BID = twice daily; BW = body weight; DB = double blind; FPG = fasting plasma glucose; HOMA = homeostasis model assessment; LAR = long-acting release; MC = multicenter; OL = open label; PC = placebo controlled; PPG = post-prandial plasma glucose; R = randomized, TB = triple blind.
thiazolidinedione (rosiglitazone ≥ 4 mg per day or pioglitazone ≥ 30 mg per day), with or without metformin. Patients were randomized to receive either placebo or exenatide (5 mcg twice daily for 4 weeks, then increased to 10 mcg twice daily for 12 weeks). Baseline characteristics were similar between groups, with a mean A1C of 7.9%, age of 56 years, and BMI of 34 kg per m². At week 16, there was a decrease in A1C with exenatide compared with an increase in the placebo group (-0.89% vs. +0.09%, or a mean between-group difference of -0.98, 95% confidence interval [CI], -1.21 to -0.74). Exenatide also significantly decreased fasting plasma glucose, daily self-monitored glucose levels, post-prandial glucose, and body weight when compared with placebo. There was no difference in outcomes between patients who were receiving a thiazolidinedione alone compared with those receiving a thiazolidinedione with metformin. Not surprisingly, nausea was the most commonly reported adverse event compared with placebo (39.7% vs. 15.2%). Similar rates of hypoglycemia were seen in patients receiving exenatide and placebo (10.7% vs. 7.1%).

The efficacy of exenatide has also been compared with insulin, another agent frequently prescribed for managing type 2 diabetes.2 Heine et al. compared 26 weeks of therapy with either exenatide or insulin glargine in 549 patients who were taking maximum doses of metformin and a sulfonylurea in a randomized, open-label trial.31 Patients were randomized to receive either exenatide (5 mcg twice daily for 4 weeks, then increased to 10 mcg twice daily for the remainder of the study) or insulin glargine (initiated at 10 units/day and titrated as necessary to achieve a fasting blood glucose of <100 mg per dL) for 26 weeks. A1C decreased comparably in both treatment groups. Insulin glargine decreased fasting plasma glucose to a greater extent than exenatide (-51.5 mg per dL vs. -25.7 mg per dL, P < 0.001). Patients receiving exenatide had more constant blood glucose levels throughout the day compared with those receiving insulin glargine, an interesting finding since insulin glargine is thought to be a peakless insulin product. Nausea was reported approximately 6 times more with exenatide (57.1%) compared with insulin glargine (8.6%), most notably in the first few months of therapy. Patients receiving insulin glargine had an increase in body weight (+1.8 kg) compared with a loss seen in patients receiving exenatide (-2.3 kg). There were similar rates of hypoglycemia between insulin glargine and exenatide. Other common adverse events with exenatide therapy included constipation and dyspepsia.

A long-acting release (LAR) exenatide formulation is currently being studied but is not yet approved by the FDA. In a randomized, placebo-controlled, phase 2 study, Kim et al. evaluated 45 patients with type 2 diabetes managing their disease with diet plus exercise and/or metformin.32 At baseline, patients had an average A1C of 8.5% and weight of 106 kg. Subjects were randomized to receive either exenatide LAR (0.8 mg or 2 mg) or placebo as weekly subcutaneous injections for 15 weeks. At week 15, A1C was significantly decreased in both the exenatide LAR 0.8-mg and 2-mg groups versus placebo (-1.4% and -1.7% vs. +0.4%, respectively, P < 0.001). Fasting plasma glucose was also decreased by -2.4 mmol per L (exenatide LAR 0.8-mg group) and -2.2 mmol per L (exenatide LAR 2-mg group) compared with +1.0 mmol per L in the placebo group (P < 0.001). Body weight was significantly decreased in the exenatide LAR 2-mg group (-3.8 kg compared with no change in both the exenatide LAR 0.8-mg and placebo groups, P < 0.05). The most common adverse effects reported were nausea, gastroenteritis, and hypoglycemia. This study shows the potential efficacy for a long-acting formulation of exenatide, which would be a novel treatment approach for this disease state.

Amori et al. recently (2007) described a meta-analysis evaluating the efficacy and safety of incretin therapy.33 Based on pooled analysis of the data from placebo-controlled trials, there was a significant reduction in A1C with exenatide therapy (-0.97%; 95% CI, -1.13% to -0.81%). Patients receiving exenatide were also more likely to achieve an A1C < 7% compared with those receiving placebo. Significant but modest weight loss occurred with exenatide therapy (weighted mean difference, -2.37 kg; 95% CI, -3.95 to -0.78), which was progressive, dose-dependent, and did not plateau by week 30. Severe hypoglycemia was rare; mild to moderate hypoglycemia occurred more often with exenatide than placebo (16% vs. 7%, respectively), particularly in patients receiving concomitant sulfonylurea therapy. Based on their analysis, the authors considered exenatide therapy to be an option for the treatment of non-pregnant adults with type 2 diabetes, particularly in patients with adequate beta-cell function who are at risk for developing hypoglycemia and who would benefit from weight loss.

Safety of Exenatide

Nausea is the most common side effect seen with exenatide therapy, with the incidence increasing with increasing dose. The incidence of nausea is about 44% with exenatide compared with 18% with placebo. Patients can expect to develop a tolerance to nausea within the first 2 months as exenatide use continues.20 Exenatide does not cause hypoglycemia. However, when studied as adjunctive therapy to sulfonylureas, the incidence of hypoglycemia was 4 to 5 times higher than when used in combination with other treatment options. For this reason, it is recommended to decrease the sulfonylurea dose by 50% when a patient initiates exenatide therapy.20 Studies have shown that it is not necessary to adjust metformin dosing due to any concern for hypoglycemia.25,28 Other potential adverse events that patients may experience include diarrhea (13%), feeling jittery (9%), dizziness (9%), headache (9%), and dyspepsia (6%).20 The FDA recently issued a warning to health care professionals about the potential for exenatide to cause acute pancreatitis, an event seen in 30 patients through post-marketing reports. Twenty-one of these reports required hospitalization, with 5 of these having serious complications. Based on these reports, patients should...
discontinue exenatide therapy if any symptoms of pancreatitis develop.34

To date, no studies have demonstrated major drug interactions with exenatide. Recent post-marketing reports suggest that concomitant use of warfarin and exenatide may result in an increased International Normalized Ratio (INR).20 Patients who are taking both warfarin and exenatide should be monitored for bleeding. Because exenatide decreases gastrointestinal emptying, medications that require rapid absorption (e.g., pain medications) should be taken at least 1 hour before or 2 hours after exenatide administration to ensure adequate absorption.20

Exenatide is not approved for, nor are there published trials evaluating its safety and efficacy, in pediatric patients. It is pregnancy category C because it has been shown to cause reduced fetal and neonatal growth in animals. It is not known whether exenatide is excreted in human breast milk. Therefore, exenatide should be used cautiously, if at all, in nursing women.20

**Dosage and Administration of Exenatide**

Exenatide is available as pre-filled pens that deliver 60 doses of medication (either 5 mcg or 10 mcg per dose). Pre-filled pens should be kept refrigerated but should not be frozen. Unopened pens are good until the expiration date on the carton. Opened pens can be kept at room temperature and should be discarded 30 days after they are first used, even if some drug remains in the pen.20

Like insulin, exenatide is administered by subcutaneous injection. However, it is dosed in micrograms rather than units. Exenatide therapy should be initiated at 5 mcg twice daily, administered within the 60-minute period before the 2 largest meals of the day (at least 6 hours apart). It should not be administered after a meal. If a patient is able to tolerate exenatide 5 mcg twice daily after 1 month, and additional blood glucose lowering is needed, the dose may be increased to 10 mcg twice daily. Tolerance to nausea should develop over time. If a patient is currently receiving a sulfonylurea, the sulfonylurea dose should be decreased by 50% when exenatide is initiated, and the patient should be counseled on the signs and symptoms of hypoglycemia. No dose adjustment is needed for patients receiving concomitant metformin therapy or for elderly or heptatically impaired patients.20 No dosage adjustment is necessary in patients with mild to moderate renal impairment, but its use should be avoided in patients with severe renal disease (creatinine clearance < 30 mL per minute) or end-stage renal disease because clearance is significantly reduced.

**Summary for Exenatide**

Exenatide is a new treatment option for the management of type 2 diabetes that works by a novel mechanism of action. In short-term trials, it has been shown to be safe and effective for patients with type 2 diabetes who are either at the maximum doses of or cannot tolerate metformin, sulfonylurea, and/or thiazolidinedione therapy and still need to decrease their A1C by at least 0.5% to 1.0%. It may also be a good choice for those patients concerned with weight gain from other antidiabetic medications or in those needing to lose weight to improve glycemic control since it has been shown to lead to weight loss. While clinical trials published to date have shown promising results, the trials primarily studied patients who were relatively healthy with no serious comorbidities. Post-marketing studies will provide a better picture of the long-term efficacy and safety profile of exenatide. While exenatide is a viable option for adjunctive therapy, it requires 2 injections daily, has a moderate effect on A1C relative to insulin, and is quite costly. Compliance should be closely assessed, particularly given the nausea seen early on in treatment.

**Pramlintide**

Pramlintide (Symlin, Amylin Pharmaceuticals) is an analog of the neuroendocrine hormone, amylin, which appears to be at least as potent as endogenous amylin.9,35 It decreases post-prandial glucagon secretion, slows gastric emptying, and increases satiety. Because amylin dysfunction occurs in patients with diabetes, providing exogenous amylin could attenuate the issues of satiety and increased glucagon secretion, which affects patients with type 2 diabetes.

Pramlintide was approved by the FDA in March 2005; it is labeled to be given at meal times for type 1 and type 2 diabetes in patients who use meal-time insulin therapy and who have failed to achieve the desired glucose control despite optimal insulin therapy.35 Patients with type 2 diabetes may or may not also be receiving concurrent treatment with a sulfonylurea and/or metformin. The data evaluating the use of pramlintide for patients with type 2 diabetes are summarized below.

**Efficacy of Pramlintide**

There are 2 pivotal phase 3 trials evaluating the safety and efficacy of pramlintide in type 2 diabetes (Table 3). Both were randomized, placebo-controlled, double-blind trials that analyzed subjects for a total 52 weeks.36,37 Patients were already stable on insulin and may or may not have also been receiving metformin and/or a sulfonylurea. The baseline characteristics of subjects in both trials in all treatment groups were comparable (average age of 56 years, primarily white, average A1C of 9.1%).

Ratner et al. randomized 538 patients to receive either placebo or pramlintide 30 mcg, 75 mcg, or 150 mcg 3 times daily for 52 weeks.36 At 13 weeks, there was a 1% decrease in A1C in the pramlintide 75-mcg and 150-mcg groups. By week 52, there was no significant difference between the pramlintide 75-mcg and placebo groups. The pramlintide 150-mcg group remained significantly better than placebo at week 52, but the difference went from a 1.0% decrease at week 13 to a 0.6% difference at week 52. The effect of pramlintide on body weight was significantly different than placebo for all 3 pramlintide doses and remained constant through week 52, with the most dramatic weight loss occurring within the first month. While insulin use increased
among all groups, placebo and treatment alike, the increase in insulin dose in the pramlintide treatment groups increased 7.9% to 10.9% compared with an increase of 15% with placebo (statistical tests not done). Severe hypoglycemia that required glucagon or intravenous glucose occurred in 8 patients and was comparable in all treatment groups, pramlintide and placebo alike. An increased incidence of nausea was reported among the pramlintide 75-mcg and 150-mcg treatment groups, the majority of which

### TABLE 3 Efficacy and Safety of Pramlintide for the Treatment of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Authors and Study Design</th>
<th>Dose (No. Patients)</th>
<th>Study Parameters</th>
<th>Efficacy Results</th>
<th>Tolerability Results</th>
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<tr>
<td>Ratner et al. (2002)36</td>
<td>Pramlintide: 30 mcg TID (n = 122) 75 mcg TID (n = 136) 150 mcg TID (n = 144) Placebo TID (n = 136) Total: 52 weeks</td>
<td>Primary: • Change in A1C • Change in body weight Secondary: • Change in total daily insulin</td>
<td>At week 52:</td>
<td>Most common with pramlintide 150 mcg vs. placebo: • Nausea (22.9% vs. 16.9%) • Hypoglycemia (64.6% vs. 70.6%) • Headache (16% vs. 13.2%) Highest drop-out rate was with pramlintide 150 mcg due to nausea.</td>
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<td>Hollander et al. (2003)37</td>
<td>Pramlintide: 60 mcg TID* (n = 158) 90 mcg BID (n = 171) 120 mcg BID (n = 166) Placebo TID (n = 161) Total: 52 weeks</td>
<td>Primary: • Change in A1C at week 26 Secondary: • Change in A1C at 52 weeks • Percentage of patients achieving A1C &lt; 7% • Change in body weight</td>
<td>At week 26:</td>
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<td>Riddle et al. (2007)38</td>
<td>Pramlintide: (60-120 mcg) with each major meal (BID or TID) (n = 105) Placebo (n = 107) All patients remained on insulin glargine. Total: 16 weeks</td>
<td>Primarily: • A1C • Composite for diabetes control (A1C &lt; 7%, body weight neutral, no hypoglycemia)</td>
<td>At week 16:</td>
<td>Most common with pramlintide vs. placebo: • Nausea (31% vs. 10%) • Mild/mod hypoglycemia (44% vs. 47%)</td>
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*A1C = glycosylated hemoglobin; BID = twice daily; BW = body weight; DB = double blind; FPG = fasting plasma glucose; HOMA = homeostasis model assessment; MC = multicenter; OL = open label; PC = placebo controlled; PPG = post-prandial plasma glucose; R = randomized; TB = triple blind; TID = 3 times daily.

Among all groups, placebo and treatment alike, the increase in insulin dose in the pramlintide treatment groups increased 7.9% to 10.9% compared with an increase of 15% with placebo (statistical tests not done). Severe hypoglycemia that required glucagon or intravenous glucose occurred in 8 patients and was comparable in all treatment groups, pramlintide and placebo alike. An increased incidence of nausea was reported among the pramlintide 75-mcg and 150-mcg treatment groups, the majority of which
was reported within the first 4 to 8 weeks of initiating therapy. While pramlintide 75 mcg 3 times daily was not an adequate dose to maintain a significant decrease in A1C compared with placebo, the study supported the dose of 150 mcg 3 times daily.

Hollander et al. randomized 656 patients to receive placebo or pramlintide (60 mcg 3 times daily or 90 mcg or 120 mcg twice daily).37 Results for the pramlintide 60 mcg 3-times daily group were not reported. Pramlintide therapy resulted in a decrease in A1C throughout the 52 weeks of the trial, with the most significant drop occurring at week 13. Only the 120-mcg twice-daily regimen proved to be significantly better than placebo at week 52. Like the trial by Ratner et al., both treatment groups experienced significant weight loss compared with placebo, which was only maintained throughout the trial for the pramlintide 120 mcg group (-1.4 kg vs. +0.7 kg placebo, \( P<0.050 \)). There was no overall difference in severe hypoglycemia between treatment groups and placebo. There was a difference, though, when hypoglycemia was analyzed at separate time periods. The pramlintide 120 mcg twice-daily group had a higher incidence of hypoglycemia than placebo or pramlintide 90 mcg twice daily within the first 4 weeks of the study (0.9 event rate per patient year vs. 0.3 and 0.1, respectively). After this point, all groups were similar. Nausea was more common with pramlintide than with placebo, most notably within the first 4 weeks of therapy. Beyond the first 4 weeks until the completion of the trial at 52 weeks, the incidence of nausea was similar between all groups.

The efficacy of pramlintide was also assessed in 212 patients suboptimally controlled with basal insulin (insulin glargine) with or without concomitant oral agents.38 Patients were randomized to receive pramlintide (60 mcg to 120 mcg) or placebo either 2 or 3 times daily, depending on their typical meal pattern (doses were given only with major meals). The primary end points were decrease in A1C relative to baseline and a composite of overall diabetes control (including A1C <7% or reduction by at least 0.5%, body weight neutral, hypoglycemic events). Patients receiving pramlintide had a significant reduction in A1C compared with placebo (-0.70 vs. -0.36, \( P<0.050 \)), and more patients achieved their A1C goal while remaining weight neutral. Pramlintide offered the additional advantage of weight loss (-1.6 kg vs. +0.7 kg, \( P<0.001 \)). This study suggests that pramlintide may be an option to mealtime insulin in patients who are not adequately controlled on basal insulin, with the primary advantage being its ability to result in weight loss rather than the weight gain typically seen with insulin therapy.

**Safety of Pramlintide**

The most common adverse effects with pramlintide therapy are gastrointestinal in nature. Nausea has been reported in 48% of patients compared with 17% of those receiving placebo. Anorexia is also higher with pramlintide therapy than with placebo (17% vs. 2%). The incidence of vomiting, arthralgias, and fatigue was similar to that seen with placebo.35 Although pramlintide does not cause hypoglycemia by itself, it potentiates the effects of insulin. It is recommended that meal-time insulin be decreased by 50% when pramlintide therapy is initiated, and then the mealtime insulin dose be titrated as necessary. The product labeling includes a black-box warning for the potential increased risk for severe insulin-induced hypoglycemia within 3 hours of dosing. Hypoglycemia is more pronounced in patients with type 1 diabetes.35

Pramlintide has not been studied in patients receiving concurrent therapy with other agents that slow gastrointestinal motility or absorption. Extreme caution should be used in these patients in the event that pramlintide could alter absorption or gastrointestinal motility. Although pramlintide does not alter nutrient absorption, it does have the potential to alter absorption of oral medications that may be taken at the time of pramlintide administration. Oral medications, such as pain medications, should be administered 1 hour before or 2 hours after pramlintide.35

Overall, pramlintide was well tolerated in clinical trials. There have been, however, some potentially significant safety concerns with proper dosing. When the product was first available, it was only supplied in multidose vials with a labeled concentration of 0.6 mg per mL. Pramlintide is dosed in micrograms, not milligrams. To further the confusion, patient instructions indicated the volume to withdraw in units using an insulin syringe. Given that pramlintide is dosed at the same time as meal-time insulin, this could potentially have become a serious safety concern.39

Recently, the manufacturer took several steps to address these concerns. While the multidose vial is still available on the market, the product labeling on the vial now states a concentration of 600 mcg per mL. In addition, the product is now also available in 2 concentrations of a pen device to make dosing simpler and safer for patients.30

Pramlintide is not FDA-labeled for use in pediatric patients, but an open-label study in patients aged 12 to 18 years with type 1 diabetes has been published.41 Further research on the safety and efficacy of pramlintide in pediatric patients is needed. Pramlintide is rated pregnancy category C and should only be used in pregnant women if the benefits outweigh the risks. It is not currently known if pramlintide is excreted in breast milk.35

**Dosage and Administration of Pramlintide**

Pramlintide is available as 5 mL multidose vials (600 mcg per mL solution) and disposable, multidose, pre-filled pens in 2 sizes. The 1.5 mL pen accommodates doses of 15 mcg to 60 mcg, and the 2.7 mL pen is for doses of 60 mcg to 120 mcg. Unopened vials and pre-filled pens should be stored in the refrigerator and should not be frozen. Opened vials and pens can be stored at room temperature or under refrigeration and should be discarded after 30 days, even if not empty.35

It is important to note that the pramlintide dosing for treating type 1 diabetes (15 mcg to 30 mcg 3 times daily) is lower than
that for type 2 diabetes. The dose of pramlintide for patients with type 2 diabetes should be initiated at 60 mcg with each major meal that contains at least 250 calories or at least 30 grams of carbohydrate. If patients are able to tolerate the 60 mcg dose after 1 week, the dose may be titrated up to 120 mcg 3 times daily.

Pramlintide appears to be most efficacious when administered immediately prior to meals. The dose of rapid- and short-acting insulins should be decreased by 50% when initiating pramlintide therapy to reduce the potential for hypoglycemia. It is also important to note that pramlintide cannot be mixed with insulin and, therefore, must be given as a separate injection. Pramlintide dosing does not need to be adjusted for the elderly or for patients with renal or hepatic impairment; there are no studies in dialysis patients.

**Summary for Pramlintide**

Pramlintide is another new agent recently approved for the treatment of diabetes. Like exenatide, it offers a novel mechanism of action and can result in modest weight loss. While studies conducted to date have shown it to be effective as adjunctive therapy, lowering A1C by approximately 0.6%, it must be used in patients who are receiving concomitant insulin therapy. Because it is also a subcutaneous injection, there may be compliance problems because it means 3 additional subcutaneous injections daily on top of the existing insulin regimen. Despite these limitations, pramlintide may provide an appropriate option for further glycemic control in highly compliant patients who have failed to achieve adequate glycemic control with an individualized insulin regimen since these patients are difficult to manage.

**Sitagliptin**

Sitagliptin (Januvia, Merck & Co., Inc.) is a dipeptidyl peptidase-4 (DPP-4) inhibitor. While it does not act by mimicking the actions of natural neuroendocrine hormones, it is yet another new class of agents for the treatment of type 2 diabetes. Sitagliptin was approved by the FDA in October 2006 and is labeled for the treatment of type 2 diabetes as monotherapy or adjunctive therapy in combination with metformin, sulfonylureas, or a thiazolidinedione. Since the existing regimen no longer provides adequate blood glucose control.

GLP-1 and glucose-dependent insulinoportropic polypeptide (GIP) are incretin hormones that stimulate insulin secretion in the beta cell, may increase cell glucose sensitivity, aid in insulin synthesis, and improve beta-cell function. GLP-1 and GIP are degraded by DPP-4. Sitagliptin enhances the effect of these incretin hormones by decreasing their metabolism.

Pharmacokinetic studies have shown that there was a 2- to 3-fold increase in active GLP-1 and GIP levels following an oral glucose tolerance test 2 hours after a dose of sitagliptin. Theoretically, by increasing the concentration of active GLP-1 and GIP, DPP-4’s effects on insulin stimulation, cell glucose sensitivity, and beta-cell function should be enhanced.

Another DDP-4 inhibitor, vildagliptin, was recently approved for use in Europe but has had delays in coming to the U.S. market due to concerns with skin, kidney, and liver toxicity.

**Efficacy of Sitagliptin**

There are 4 key trials evaluating the safety and efficacy of sitagliptin (Table 4). Raz et al. assessed the efficacy of sitagliptin as monotherapy in 521 patients with type 2 diabetes in a double-blind, placebo-controlled trial. All patients had similar baseline characteristics, with an average A1C of 8.1% and a mean fasting plasma glucose (FPG) of 182.2 mg per dL. Patients were randomized to receive placebo or sitagliptin 100 mg or 200 mg orally once daily for 18 weeks. Patients were either not receiving any medication for their diabetes or they were taking oral regimens that could be discontinued for the duration of the trial. Those using insulin for glycemic control were excluded. A1C significantly decreased in both the sitagliptin 100 mg and 200 mg groups relative to placebo at week 18 (-0.60% and -0.48%, respectively; P<0.001). The ability of sitagliptin to lower A1C does not appear to be dose dependent since the 200 mg dose did not affect any end points to a greater extent than the 100 mg dose. In this trial, there were 2 characteristics that appeared to predict A1C response: patients earlier in their disease (≤3 year history) and those who had a higher baseline A1C (≥9%). These subgroups each had an approximate 1% decrease in A1C at week 18. Sitagliptin also decreased the proinsulin:insulin ratio, indicating improved beta-cell function. There was no significant change in body weight. Side effects were comparable to those seen in patients receiving placebo, with the exception of a few uncommon reactions: nasopharyngitis, back pain, osteoarthritis, and extremity pain.

Aschner et al. conducted a double-blind, placebo-controlled, randomized study of 741 patients with an average baseline A1C of 8%, who received monotherapy with placebo or sitagliptin (100 mg or 200 mg) for 24 weeks. Only 49% of patients had been taking an oral hypoglycemic agent prior to entering the study, which was discontinued upon enrollment. Sitagliptin 100 mg and 200 mg decreased A1C significantly better than placebo (-0.61% and -0.76% vs. +0.18%, respectively; P<0.001). More patients achieved A1C <7% with sitagliptin 100 mg and 200 mg than placebo (41% and 45% vs. 17%, respectively; P<0.001). Both doses of sitagliptin also significantly improved FPG, proinsulin: insulin ratio, 2-hour post-prandial glucose, and homeostasis model assessment (HOMA) beta-cell function compared with placebo. No significant differences in adverse effects between sitagliptin 100 mg and placebo were reported.

Sitagliptin was evaluated as adjunctive therapy to pioglitazone in a double-blind, placebo-controlled trial evaluating 353 patients with type 2 diabetes (mean baseline A1C of 8.1%). All patients also received pioglitazone 30 mg or 45 mg daily. They were randomized to receive placebo or sitagliptin 100 mg once daily for 24 weeks. A significant decrease in A1C was seen with sitagliptin 100 mg daily compared with placebo (-0.85% vs. -0.15%,
Twice as many patients in the sitagliptin group achieved an A1C <7% (45.4% vs. 23%, \(P<0.001\)) at week 24 when compared with placebo. The proinsulin:insulin ratio also decreased in the treatment group versus the placebo group. The most common side effects with sitagliptin affected the gastrointestinal system.

Goldstein et al. conducted a 24-week, double-blind, randomized trial in 1,091 patients with type 2 diabetes comparing placebo, sitagliptin monotherapy, metformin monotherapy, and sitagliptin/metformin combination therapy.\(^3\) Patients were either on previous metformin therapy or were not currently receiving any oral hypoglycemic agent at the time of enrollment. Patients were randomized to 1 of 6 treatment groups: sitagliptin 100 mg daily, metformin 500 mg twice daily, metformin 1,000 mg twice daily, sitagliptin 50 mg/metformin 500 mg twice daily, sitagliptin 50 mg/metformin 1,000 mg twice daily, or placebo. The sitagliptin/metformin combination therapy was administered as a single tablet given twice daily. A1C decreased significantly in all treatment groups when compared with placebo (-0.66% to -1.9% vs. placebo +0.17%). All treatment arms demonstrated improvement compared with placebo with regard to FPG and proinsulin:insulin ratio. HOMA beta-cell function was only improved in the metformin 1,000 mg twice-daily, sitagliptin 50 mg/metformin 500 mg twice-daily, and sitagliptin 50 mg/metformin 1,000 mg twice-daily groups. Both active combination groups (sitagliptin 50 mg/metformin 500 mg

### Table 4: Efficacy and Safety of Sitagliptin for the Treatment of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Authors and Study Design</th>
<th>Dose (No. Patients)</th>
<th>Study Parameters</th>
<th>Efficacy Results</th>
<th>Tolerability Results</th>
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</thead>
<tbody>
<tr>
<td>Raz et al. (2006)(^4)</td>
<td>Sitagliptin: 100 mg once daily (n=205) 200 mg once daily (n=206) Placebo daily (n=110) Total: 18 weeks</td>
<td>Primary: • A1C Secondary: • Change in FPG • Change in proinsulin:insulin • Change in HOMA-(\beta) function • Change in 2 hr. PPG</td>
<td>At week 18:</td>
<td>Most common with sitagliptin 100 mg vs. placebo: • Diarrhea (3.9% vs. 3.6%) • Abdominal pain (2% vs. 2.7%) • Nausea (1% vs. 0%)</td>
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<td>(^{a}P&lt;0.001; {b}P&lt;0.010)</td>
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<td>Aschner et al. (2006)(^5)</td>
<td>Sitagliptin: 100 mg once daily (n=238) 200 mg once daily (n=250) Placebo daily (n=253) Total: 24 weeks</td>
<td>Primary: • Change in A1C Secondary: • Change in FPG • Change in proinsulin:insulin • Change in HOMA-(\beta) function • Change in 2 hr. PPG</td>
<td>At week 24:</td>
<td>Most common with sitagliptin 100 mg vs. placebo: • Overall GI events (16.4% vs. 11.5%) • Diarrhea (4.6% vs. 2.4%) • Nausea (2.1% vs. 1.2%) • Vomiting (1.3% vs. 1.2%)</td>
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</tbody>
</table>

- A1C = glycosylated hemoglobin; DB = double blind; FPG = fasting plasma glucose; GI = gastrointestinal; HOMA = homeostasis model assessment; PC = placebo controlled; PPG = post-prandial plasma glucose; R = randomized.

\(P<0.001\). Twice as many patients in the sitagliptin group achieved an A1C <7% (45.4% vs. 23%, \(P<0.001\)) at week 24 when compared with placebo. The proinsulin:insulin ratio also decreased in the treatment group versus the placebo group. The most common side effects with sitagliptin affected the gastrointestinal system.

Goldstein et al. conducted a 24-week, double-blind, randomized trial in 1,091 patients with type 2 diabetes comparing placebo, sitagliptin monotherapy, metformin monotherapy, and sitagliptin/metformin combination therapy.\(^3\) Patients were either on previous metformin therapy or were not currently receiving any oral hypoglycemic agent at the time of enrollment. Patients were randomized to 1 of 6 treatment groups: sitagliptin 100 mg daily, metformin 500 mg twice daily, metformin 1,000 mg twice daily, sitagliptin 50 mg/metformin 500 mg twice daily, sitagliptin 50 mg/metformin 1,000 mg twice daily, or placebo. The sitagliptin/metformin combination therapy was administered as a single tablet given twice daily. A1C decreased significantly in all treatment groups when compared with placebo (-0.66% to -1.9% vs. placebo +0.17%). All treatment arms demonstrated improvement compared with placebo with regard to FPG and proinsulin:insulin ratio. HOMA beta-cell function was only improved in the metformin 1,000 mg twice-daily, sitagliptin 50 mg/metformin 500 mg twice-daily, and sitagliptin 50 mg/metformin 1,000 mg twice-daily groups. Both active combination groups (sitagliptin 50 mg/metformin 500 mg
Table 4 (continued): Efficacy and Safety of Sitagliptin for the Treatment of Type 2 Diabetes

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<tr>
<th>Authors and Study Design</th>
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<th>Tolerability Results</th>
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</thead>
<tbody>
<tr>
<td><strong>Rosenstock et al. (2006)</strong>&lt;sup&gt;50&lt;/sup&gt; R, DB, PC</td>
<td>Sitagliptin 100 mg once daily (n = 175) Placebo (n = 178)</td>
<td>All patients also received pioglitazone 30 mg or 45 mg daily Total: 24 weeks</td>
<td>At week 24:</td>
<td>Most common with sitagliptin vs. placebo:</td>
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<td>• Abdominal pain (3.4% vs. 0%) • Nausea (1.1% vs. 0%) • Diarrhea (1.7% vs. 1.1%)</td>
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<td><strong>Proinsulin: insulin</strong></td>
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<td>Sitagliptin 100 mg/ pioglitazone</td>
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<td><strong>Goldstein et al. (2007)</strong>&lt;sup&gt;51&lt;/sup&gt; R, DB, PC</td>
<td>Sitagliptin 100 mg daily (n = 175) Metformin 500 mg twice daily (n = 178) Metformin 1,000 mg twice daily (n = 177) Sitagliptin 50 mg/metformin 500 mg twice daily (n = 183) Sitagliptin 50 mg/metformin 1,000 mg twice daily (n = 178) Placebo (n = 165)</td>
<td>Note that the sitagliptin/metformin combination was a single product dosed twice daily. Total: 24 weeks</td>
<td>At week 24:</td>
<td>Adverse events (diarrhea, nausea, abdominal pain) were most common with high-dose metformin therapy, either alone or in combination with sitagliptin.</td>
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<td><strong>Proinsulin: insulin</strong></td>
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<sup>A1C = glycosylated hemoglobin; DB = double blind; FPG = fasting plasma glucose; HOMA = homeostasis model assessment; PC = placebo controlled; R = randomized; TZD = thiazoliolinedione</sup>
twice daily, sitagliptin 50 mg/metformin 1,000 mg twice daily) decreased A1C significantly (-1.57% and -2.07%, respectively; \(P<0.001\)) when compared with sitagliptin 100 mg daily (-0.83%), metformin 500 mg twice daily (-0.99%), and metformin 1,000 mg twice daily (-1.3%). They also decreased FPG significantly (-52.9 mg per dL and -69.7 mg per dL, respectively; \(P<0.001\)) when compared with sitagliptin 100 mg daily (-23.3 mg per dL), metformin 500 mg twice daily (-33.1 mg per dL), and metformin 1,000 mg twice daily (-35.1 mg per dL). Hypoglycemia was uncommon in all treatment arms. This study showed that combination therapy with sitagliptin and metformin is more efficacious than monotherapy with either agent alone.

In a recently published meta-analysis (2007), Amori et al. performed a pooled analysis of the data from placebo-controlled trials and found a significant reduction in A1C with sitagliptin therapy (-0.74%; 95% CI, -0.85% to -0.62%).\(^{33}\) Overall, the DPP-4 inhibitors were slightly less effective than other hypoglycemic agents. Patients receiving sitagliptin were also more likely to achieve an A1C <7% compared with those receiving placebo. Sitagliptin was weight neutral, a potential advantage to the weight gain seen with the sulfonylureas and thiazolidinediones. Hypoglycemia was rare, but there was an increased risk of some infections (e.g., nasopharyngitis and urinary tract infections). Based on their analysis, the authors considered sitagliptin therapy to produce moderate improvement in glycemic control, without the added benefit of weight loss seen with exenatide.

**Safety of Sitagliptin**

The most commonly reported adverse effects with sitagliptin are gastrointestinal in nature, specifically, abdominal pain (2.3%), nausea (1.4%), and diarrhea (3%).\(^{13}\) Hypoglycemia has also been reported, but the incidence is not significantly higher than that reported with placebo (1.2% vs. 0.9%). Post-marketing experience has reported hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson syndrome. Sitagliptin was designed to be specific for the GLP substrate. However, it is not known yet whether it will have any effect on levels of the other DPP-4 substrates such as proteins involved with immunity or other hormones, which could impact its safety profile.\(^{19}\) At this time, no drug-drug interactions have been reported.\(^{43}\)

Sitagliptin has not been approved for use in pediatric patients. It is rated pregnancy category B, meaning that it is believed to be relatively safe for use in pregnancy based on studies in animals showing no fetal risk without studies available in pregnant women, or studies in animals showing a fetal risk that was not confirmed in studies conducted in pregnant women. Sitagliptin is secreted in the milk of lactating rats, but it is not known if it is secreted into human milk. Therefore, caution should be used in nursing women.\(^{43}\)

**Dosage and Administration of Sitagliptin**

Sitagliptin should be dosed at 100 mg daily with adjustments for renal insufficiency (50 mg for creatinine clearance (CrCl) \(\geq 30\) to <50 mL per minute; 25 mg for CrCl <30 mL per minute). No dosage adjustment is necessary for the elderly. It is administered orally and can be taken with or without food. If taken in combination with a sulfonylurea, the dose of sulfonylurea may need to be reduced to decrease the risk of hypoglycemia.\(^{43}\)

**Summary of Sitagliptin**

Sitagliptin is the first drug in yet another new class of agents available for the treatment of type 2 diabetes. Unlike exenatide and pramlintide, sitagliptin offers the advantage of oral administration and is labeled for either monotherapy or adjunctive therapy with metformin, sulfonylureas, or a thiazolidinedione. It has not been studied in combination with insulin. In clinical trials, it has been shown to reduce A1C by 0.6% to 1%, but it does not appear to have a positive effect on weight loss. Although the published data suggest sitagliptin to be relatively safe, it has only been tested in a limited number of patients in short-term trials. It is difficult to define the place in therapy for sitagliptin at this time because of the limited experience with it in practice, its lack of effect on weight loss, its moderate effect on lowering A1C, and its high cost. Interestingly, despite the mild to moderate improvement seen with glycemic control and lack of long-term safety and efficacy data, 14% of new prescriptions for diabetes medications were for sitagliptin within the first 6 weeks of its approval.\(^{10}\)

**Place in Therapy for These Three New Agents**

Effective management of type 2 diabetes is handled in a step-wise approach (Figure).\(^{1,10,12}\) Diet and exercise are important for all patients. However, diet and exercise alone are often inadequate to provide sufficient, sustainable clinical benefit. The current ADA guidelines recommend initial therapy with metformin at the time of diagnosis.\(^{1,10}\) Patients unable to tolerate metformin or in whom it is contraindicated should initiate therapy with a sulfonylurea.\(^{12}\) Many patients will eventually require an additional agent over time in order to maintain adequate blood glucose control. ADA guidelines recommend adding either a sulfonylurea, a thiazolidinedione, or bedtime insulin to metformin at this point.\(^{10}\) The choice of agent should take into consideration patient preferences, medication cost, and side-effect profile. Many patients are reluctant to initiate parenteral therapy and favor oral treatment options. For this reason, sulfonylureas are often added to metformin because they are affordable and have long-term clinical experience.\(^{12}\) Thiazolidinediones offer the advantage of oral administration, but they are a costly option, and their definitive role remains unclear, because there is concern with potential adverse cardiovascular effects with rosiglitazone.\(^{1,52-54}\) Insulin is the preferred option for patients in whom A1C is still high (≥8.5%) because it remains the most potent glycemic-lowering agent available; however, it is often associated with considerable
Managed Care Perspective on Three New Agents for Type 2 Diabetes

**FIGURE** Treatment Algorithm for Managing Patients With Type 2 Diabetes

**Diet and Exercise Combined With Monotherapy:**
- Metformin or
- Sulfonylurea (for patients in whom metformin is contraindicated or is not tolerated)

**Combination Therapy:**
- Add sulfonylurea to metformin
- If sulfonylurea/metformin combination is not an option or not providing adequate glycemic control (proceed below)

**Oral Agents:**
(for patients refusing injectable medications)
- Thiazolidinedione— if no cardiovascular concerns exist
- Sitagliptin

**Parenteral Agents:**
(for patients who require greater A1C reduction or in whom weight loss is critical to diabetes control)
- Insulin— for patients with high A1C
- Exenatide— if weight loss is desired and the A1C reduction needed is modest

**Pramlintide**— for patients already receiving optimal insulin therapy who need additional glycemic control

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*a Note: Costly compared with other treatment options.*

Adapted from ADA Guidelines and modified by the authors to include the 3 new agents. A1C = glycosylated hemoglobin.

Weight gain. Insulin offers the advantage of being the oldest agent available, with a vast amount of clinical experience, and it is relatively affordable.

The availability of the 3 newest agents—exenatide, pramlintide, and sitagliptin—has expanded the available treatment options. To date, neither the ADA nor the AACE has defined the place in therapy for these new agents in the treatment algorithm given their relative lack of long-term safety and efficacy data. All 3 agents decrease A1C to an equivalent extent (0.5% to 1%), notably less than the reduction seen with the long-standing treatments: insulin, metformin, and sulfonylureas. Each agent offers a unique set of advantages and disadvantages, which must be considered when selecting therapy. Exenatide and pramlintide have a favorable effect on weight loss, which is the most attractive feature of these agents, but they must be administered by subcutaneous injection. In addition, pramlintide must be used in combination with insulin, thereby requiring multiple additional injections daily. Sitagliptin has the advantage of being an oral agent that does not cause hypoglycemia, but it is weight neutral (unlike exenatide and pramlintide). All of these new agents are considerably more costly than most of the older agents (Table 1). Because these costs are not insignificant, they should be considered when selecting an appropriate agent for any given patient.

Several factors must be considered when determining appropriate treatment options for the management of patients with type 2 diabetes. Side-effect profile (risk for hypoglycemia, history of cardiovascular disease, effect on weight), route of administration (oral vs. subcutaneous), ability to pay for the medication, and
patient preferences are all important factors to consider so that the treatment regimen is well tolerated, affordable, and accomplishes the goals for the individual patient. Selection of the most appropriate treatment option should assess risk versus benefit. In patients who cannot tolerate or are unwilling to use agents that have established long-term safety and efficacy (i.e., insulin, metformin, sulfonylureas), a newer agent may be a reasonable treatment option.

As these new, high-cost agents for the management of diabetes have become available, managed care organizations (MCOs) are faced with the potential overuse or misuse of these agents and the associated expense. The ability of drug companies to influence prescribing through direct and indirect marketing strategies can make it difficult for physicians and patients to objectively assess the benefits and risks of the new agents. Exenatide and pramlintide have been considered by some clinicians for their ability to cause weight loss. This same benefit, though, has been viewed as a concern by many managed care providers because of the potential for misuse. Although typically covered in some manner by MCOs and Medicare Part D plans, the use of these new agents is often restricted in some way because of their high cost, limited published data, lack of data about their long-term safety and efficacy, limited clinical experience, and concerns of potential misuse for weight loss. Some plans have implemented step edits requiring a prior history of the use of older hypoglycemic agents in order to allow for coverage of the new agents.56

MCOs can also implement electronic edits to ensure prior or coincident therapy with an antihyperglycemic agent to ensure that exenatide is being used in patients with diabetes and not solely for weight loss. In addition, quantity limits on the prescribing of these agents may be used to limit the dosing to that which has been approved by the FDA and beyond which additional benefit has not been seen (e.g., maximum 100 mg of sitagliptin per day). In some cases, plans may require prior-authorization for the use of these new agents. Ideally, health plans can implement automated control measures that look back in the claims history to gather relevant data. Doing so is transparent to the prescriber and helps to reduce the volume of prior-authorization requests needing processing, a function that is time consuming and costly to the managed care plan. However, even with an automated system, criteria for appropriate use need to be defined for new patients or employers where no claims history exists. The control systems that managed care plans use to restrict the use of these agents will differ depending on the capabilities of their claims processing systems. While restrictions on use can be problematic for health care professionals, they force a thought process to assess appropriateness of use, particularly in light of the limited data that exist to date and the aggressive marketing of these newer agents.

## Conclusions

Exenatide, pramlintide, and sitagliptin are the 3 newest agents available for the management of type 2 diabetes. While each of these new agents yields only modest glycemic effects, they provide new and differing mechanisms for managing patients with diabetes. Each agent offers a unique set of advantages and disadvantages that must be considered on a per-patient basis. The primary advantage of exenatide and pramlintide, compared with sitagliptin, is the positive, although modest, effect on weight loss. However, there is limited experience with all of these agents, and their long-term safety and efficacy remain to be determined. While these 3 new agents should generally not be used early in the treatment of most patients because of their higher cost, limited efficacy, and absence of long-term safety data, they offer treatment options for patients not adequately controlled by or who have contraindications to the use of the standard therapies.

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## DISCLOSURES

This research was not funded, and the authors reported that there are no past, current, or anticipated financial relationships (including service on advisory boards) that might be viewed as a conflict of interest.

The authors disclose that this article includes mention of exenatide LAR that is not yet approved by the FDA.

All authors contributed approximately equally to the concept and design of this study, data collection, data interpretation, and writing and revision of the manuscript.

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Managed Care Perspective on Three New Agents for Type 2 Diabetes


Overactive Bladder Disease: The Urge for Better Therapies

Lisa Thomas, PharmD, and Eric J. Culley, PharmD

In the April 2008 issue of JMCP, D’Souza et al. compared persistence, adherence, and switch rates for immediate-release (IR) and extended-release (ER) formulations of oxybutynin and tolterodine for patients enrolled in a regional managed care health plan. Only 55.5% of patients refilled their first prescription for an overactive bladder (OAB) medication, and 13.2% persisted with the index medication for 1 year. The switch rate was 13.3% for the overall sample and 24.0% of patients with at least 1 refill. Although no difference was observed for persistence rates for any of the 4 OAB drugs, adherence rates were slightly higher for ER versus IR drugs.1 We commend D’Souza and colleagues for their efforts in the development of these findings. However, the results of this analysis are confounded by 2 major factors: (1) several limitations of retrospective data analyses and (2) the challenges associated with the clinical management of OAB. Also, the slight advantage offered by ER drugs raises a potential question regarding the “true” value offered by once-daily dose regimens versus multiple-dose regimens.

In the category of difficulty in clinical management, low persistence and adherence rates associated with OAB therapies may be attributable to the undesirable adverse events associated with anti-cholinergic agents, including dry mouth, constipation, tachycardia, and blurred vision.2 Some postulate that the ER drug formulations could minimize the undesirable events and increase patient compliance by maintaining flat plasma drug concentrations.3-5 However, available data suggest that less frequent dosing intervals do not necessarily translate to increased compliance, indicating that side effects and inconvenience alone cannot explain non-adherence.

Medication adherence and persistence are also dependent on the perceived benefit of therapy experienced by the patient. Humanistic outcomes, such as quality of life, offer a greater understanding of the potential benefits offered by various drug therapies but are just starting to be included in clinical trials. This lack of quality-of-life data is an important deficit in currently available information that needs to be addressed since the statistically significant effects observed for anti-muscarinic drugs in clinical trials (e.g., urinary frequency, volume voided per micturition) may not always translate to a clinically relevant benefit for patients in the real world.

Limitations of Retrospective Claims Analyses

The analysis by D’Souza et al., like other administrative claims analyses of OAB, provides a glimpse of the challenges faced both by researchers and by clinicians in the effort to identify improved strategies to diagnose and manage OAB.3 Various adherence and persistence studies pertaining to OAB and anti-muscarinic agents have been published. In long-term, open-label studies, the percentages of patients who persisted on therapy for approximately 10 to 12 months were 46%, 76%, 81%, and 81% for oxybutynin ER, tolterodine ER, trospium, and solifenacin, respectively.6-8 It should be recognized, however, that the observed persistence rates in controlled trials might not be reflective of real-world clinical settings. Furthermore, there are few published studies on the topic of long-term persistence with drug therapy among OAB patients in the United States within a usual-care setting. For example, a 1995-1996 study of treatment of urge incontinence in U.S. veterans (receiving primarily oxybutynin chloride [39.8%], dicyclomine hydrochloride [16.0%], or imipramine hydrochloride [13.9%]) demonstrated that fewer than 30% of patients continued on therapy for 1 year.9

Although findings of D’Souza et al.’s database analysis and other similar studies highlight differences between real-world and clinical trial results, among the most pressing challenges in research on OAB is the question of whether samples used in most database studies adequately represent the population of patients with the disorder. The prevalence of OAB increases markedly with advancing age in both men and women.10 A population-based U.S. study of women enrolled in a large health maintenance organization suggests a rate of urinary incontinence greater than 50% among women aged 60 to 90 years.11 Unfortunately, data relating to the prevalence and impact of OAB are sparse for this subset of patients. Most OAB studies, including the current analysis published by D’Souza et al., include patients aged 18 years or older, with the mean age of patients ranging from 56 to 61.12-14 Therefore, it is difficult to assess how the truly older population with OAB responds to anti-muscarinic therapy. Anecdotally, there is a belief that antimuscarinic agents are often underutilized in the elderly despite the marked increase in the prevalence of OAB. This alleged underuse may result from concerns about the frequency of more serious anti-cholinergic adverse events, such as cognitive impairment and sleep disturbances, as well as drug-drug interactions with existing pharmacotherapy.12

Additionally, studies conducted with commercial databases, like the one used by D’Souza, may not adequately represent the populations in which research is most urgently needed. For example, although not included in D’Souza et al.’s analysis, Medicaid enrollees represent an important potential target of better treatment interventions for OAB. Both the proportion of women and per-capita health care expenditures are higher for adults with Medicaid coverage than adults with other types of insurance coverage.15 Contributing factors to poor compliance include low level of education, cultural and social support factors, and adverse drug reactions.16,17 These factors may be more prevalent among underserved populations such as Medicaid beneficiaries. Therefore, a higher prevalence of OAB and lower...
persistence rates are more likely to exist in the Medicaid population as compared with commercially insured plans.18

One study that addressed the need for research on OAB in Medicaid populations was reported by Yu et al. in 2005.19 Yu et al. studied persistence (discontinuation of OAB drug therapy and time to discontinuation) and adherence (medication possession ratio [MPR]) in a Medicaid population with chronic OAB or urinary incontinence from January 1999 to April 2002. The average age of OAB patients at the time of index pharmacy claim was 63.2 years (SD = 16.1), slightly higher than the mean age reported in the analysis by D’Souza et al. (55.7, SD = 14.5). Most Medicaid patients in the study by Yu et al. began treatment with tolterodine or oxybutynin. Of the 2,496 eligible patients that were included in the Yu et al. study, 36.9% had no refill after the index pharmacy claim. During the 6-month follow-up period, two thirds (66.9%) of patients did not remain on their treatment regimen for more than 90 days, and 77.7% of patients did not remain on their treatment for longer than 150 days. The median time to discontinuation was 50 days. On average, about one third of the follow-up period was covered by OAB medications, only 4.8% of patients renewed their prescriptions within a 30-day gap allotted for refills, and 50% of patients received pharmacological treatment for less than 60 days cumulatively during the 6-month follow-up period. Only 122 patients (4.9%) exhibited > 80% MPR in the initial 6-month follow-up period. During the additional 6-month follow-up period, the rate of discontinuation increased to 88.6%, the mean MPR dropped to 0.22, and the adherence rate, measured as MPR > 0.80, was a mere 0.7%.19

Despite different populations, 100% Medicaid in Yu et al. versus 58% commercially insured, 19% Medicare, and 23% self-insured employers in D’Souza et al., their findings regarding low persistence and medication adherence are similar. D’Souza found that only 55.5% of patients refilled their index OAB medication (they did not report continuation on any OAB drug for at least 1 refill but did report 80% discontinuation of all OAB medications at 6 months follow-up) compared with 63.1% of patients who had at least 1 refill in the Medicaid population studied by Yu et al. D’Souza et al. found a median 31 days to discontinuation of the index OAB drug therapy versus 50 days in Yu et al.19

However, a comparison of the Yu et al. and D’Souza et al. reports provides a reminder of the need to consider the appropriateness of study methodologies in interpreting study findings. For example, although the gap between prescription fills was used to determine discontinuation rates in both analyses, D’Souza used a medication-uncovered interval of 45 days to define discontinuation versus > 30 days in the study Yu et al. The length of this gap varies between studies; 45 days has been used prior to D’Souza et al.’s analysis.5,20 Evidence to suggest which gap length is most appropriate to assess persistence among OAB patients or why patients may even have a gap in therapy is lacking, suggesting a need to reevaluate this potentially important methodological decision.19

Similarly, evaluation of the methods and outcome measures in the 2 studies by Yu et al. and D’Souza et al. precipitates consideration of the appropriate measure of medication adherence for OAB. Both studies used the common MPR benchmark of ≥ 0.80 to define adherence. Yu et al., in fact, suggest that the nature of clinical differences among various therapeutic classes may warrant the use of different definitions of adherence for drugs used for different diseases or conditions; in other words, use of the same definition of adherence may result in overestimation or underestimation of true compliance among drug classes. Therefore, there is a need for further research to develop disease-specific MPR threshold values to achieve a more accurate estimation of clinically meaningful adherence rates.19

In comparing the results reported by D’Souza et al. and Yu et al., it is also necessary to consider how different methods to select patients may affect study findings. Yu et al. identified patients with a pharmacy claim for at least 1 OAB medication in addition to either (a) 2 or more confirmed diagnoses during the study period or (b) at least 1 diagnosis of OAB made at any time after the index date. Yu et al. did not report the proportion of Medicaid patients who received an OAB drug but did not meet either of the second criteria for inclusion in the study, while D’Souza et al. found that only 53.7% (n = 600) of 1,117 patients who received OAB drug therapy were diagnosed with at least 1 symptom characteristic of OAB based on International Classification of Diseases, Ninth Revision, Clinical Modification codes during the 18-month eligibility period. The additional criteria for selection in the analysis by Yu et al. may yield a higher degree of confidence that the patients had chronic OAB than in the D’Souza analysis.

Another potential issue with D’Souza et al.’s methodology is the definition of persistence used. For any given chronic disease state, a switch in therapy is neither uncommon nor inappropriate. Due to the tolerability profile of anti-muscarinic agents, it is likely that patients switch to another dose of the same drug or are switched to an entirely different drug. Hence, in the analysis by Yu et al., a patient making a switch from one brand of OAB drug to another was considered to be persistent with therapy since the patient was considered to still be receiving active therapy. In contrast, D’Souza et al.’s definition of non-persistence included a switch to a different OAB medication or even to a different dosage form of the same drug. This analysis also failed to look past a first-time switch to determine if patients remained on the second treatment.

Failure to consider the possible role that other medication classes play in producing the observed outcomes represents another limitation of the analysis by D’Souza et al. Of growing concern among geriatricians (and others) is the potential for adverse events of drug treatment for 1 condition that affects other coexisting conditions.21 Polypharmacy and the chronic use of multiple drugs are realities for many elderly patients.22 Depression and anxiety are common comorbidities among OAB
patients. Approximately 17% of patients in D’Souza et al.’s sample were diagnosed with comorbid depression or anxiety, yet they failed to examine concomitant drug utilization that could potentially cause anticholinergic toxicity. This limitation may have significantly confounded the study’s reported rates of adherence and persistence.

Pharmacy benefit design can also influence medication adherence and persistence and is often overlooked in studies using large databases of administrative claims that are compiled from multiple employers, health plans, and payer types; the effects of benefit design were also unstudied in the D’Souza et al. analysis. Employers and health plans offering drug benefits employ a variety of management tools to manage utilization and costs. Many of these tools are centered on the use of a drug formulary, prior authorization, quantity level limits, and mail-order pharmacies. Mail-order pharmacies typically dispense a 90-day supply of medication during a single fill, as well as provide automatic refills for most drugs. These policies can inflate measures of adherence as measured by the days supply of drug received. D’Souza et al. failed to provide an assessment of the drug groups’ comparability with respect to formulary status, tiering, benefit design, and management of edits (e.g., step therapy, prior authorization), which could possibly have confounded persistence, adherence, and switch rates within this analysis. Furthermore, this analysis failed to address the impact of the exclusion of cash-paying customers on a study drug during the time frame of this analysis. Lastly, no information specific to mail-order use in this population was addressed, although any mail-order use could have significantly impacted the results of this analysis.

The Importance of Patient-Reported Outcomes in OAB

The work of D’Souza et al. and similar studies, suggest areas for improvement in future research. OAB disease is a prevalent condition that has a negative impact on an individual’s health-related quality of life (HRQL). Although the efficacy of anti-muscarinic agents has been demonstrated in various clinical trials, information pertaining to the clinical significance of these data are a more recent addition to the literature. Data to support patient satisfaction with the purported benefits of drug therapy is essential in order to determine the true strengths and limitations of this class of medications.

Traditionally, clinicians have greatly relied on objective measures, such as urodynamic studies (series of office tests to observe the function of the lower urinary tract) for evaluating the efficacy of treatment. Objective measures can help facilitate the diagnosis and management of OAB, but because OAB is a symptom-based syndrome, its management is highly contingent upon a patient’s report of symptoms. Patient-reported outcomes, assessed by subjective measures, provide an opportunity to improve one’s understanding of OAB outcomes and may even help to redefine a treatment success. As stated by Fairclough et al., “While we can measure a biological response, we may not be able to determine whether that response makes a noticeable difference to the patient.”

Treatment with anti-muscarinic agents in the management of OAB typically requires at least 4 to 8 weeks of continuous therapy before the benefits of therapy are realized. There is also evidence to suggest that OAB patients who continue their medication have greater improvement in relevant symptoms and utilize fewer resources. Few studies have assessed the clinical benefit of persistence with OAB/urinary incontinence (UI) drug therapy, but the logistic regression analysis performed by Yu et al. suggests that the risk of urinary tract infections is 37% (odds ratio [OR] = 1.37, 95% confidence interval [CI] = 1.03-1.84, P = 0.03) higher among those who discontinue OAB therapy. D’Souza et al.’s work would have provided more insight regarding the management of OAB if patient-reported outcomes (PROs) had been included as end points, but this is a limitation of administrative claims data in which clinical information is not captured.

Incorporating patient-reported outcomes into clinical trials has more recently become a common means of assessing treatment efficacy for symptom-based conditions. Studies that include assessments of both subjective and objective outcomes provide results that represent a more global patient experience compared with those captured by evaluating either type of measure alone. In some studies, objective end points demonstrated larger differences between treatment groups compared with subjective measures. For example, a trial of oxybutynin IR in elderly patients demonstrated that patients receiving oxybutynin IR experienced statistically significant reductions in daytime micturitions during a 2-week period compared with those receiving placebo. After 6 weeks of treatment, the percentage of patients who perceived a benefit of treatment appeared to be greater in the treatment group compared with placebo group (79% vs. 55%), but the difference was not statistically significant (P = 0.09). Furthermore, patients were asked to grade their improvement based on a 4-point ranked ordinal scale; ratings failed to demonstrate significant differences between groups at the end of the study.

In a placebo-controlled trial of tolterodine IR and oxybutynin IR, 12 weeks of treatment with tolterodine IR significantly reduced 24-hour micturitions compared with placebo. Patients receiving oxybutynin IR demonstrated statistically significantly reduced 24-hour urge UI episodes compared with placebo. Both active treatments increased volume voided per micturition. Despite the favorable effects of tolterodine IR and oxybutynin IR on bladder diary end points, the percentages of patients perceiving improvement in bladder condition after 12 weeks of treatment were comparable for placebo, tolterodine IR, and oxybutynin IR at rates of 47%, 50%, and 49%, respectively.

Objective measures are important in the assessment and management of patients, but they are probably not valid indicators of the disease burden experienced by patients with OAB.
Despite the importance of including subjective measures in the management of OAB, few studies include subjective measures as a primary end point. Future studies with a greater emphasis on subjective measures using instruments that have undergone validation studies, such as OAB questionnaires, are needed in order to gain a greater understanding of OAB as a chronic disease.35

**Defining an Optimal Dosing Regimen for Medication Compliance**

In a real-world setting, achieving adherence to prescribed medication is challenging. Specific disease characteristics associated with various chronic disease states may have a significant impact on adherence.30 For example, asymptomatic diseases, such as hypertension and hyperlipidemia are commonly associated with poor compliance and adherence.31,32 A prospective study examining adherence to the Joint National Committee on Hypertension (JNC VI) treatment guidelines in the New York metropolitan area demonstrated that only 37% of the 821 patients surveyed reported consistent adherence to their anti-hypertensive regimen.33 In a 1982 study of a cross-sectional sample of 800 adults in Detroit, Michigan, 21% of the 206 hypertensive patients interviewed had stopped drug treatment without being instructed to do so.34 Patient perception of health status was the most common factor found to distinguish dropouts from those adherent to their medication regimens; poorer perceived health was associated with higher rates of adherence to the prescribed treatment regimen. Patients who felt well without medication were more likely to discontinue their medications on their own. Therefore, the clinical efficacy rates demonstrated by numerous “blockbuster” medications in controlled clinical trials frequently do not correlate with outcomes observed in real-world settings. The implication for real-world results is that large reductions in morbidity and/or mortality seen in clinical trials may not always translate into a better prognosis for patients.30

ER formulations of many drugs have been developed, in theory, to offer increased patient compliance versus multiple daily-dosing regimens by reducing tablet burden. Although limited information is available within the literature specific to compliance patterns of ER drug formulations in OAB, data extrapolated from studies specific to osteoporosis and epilepsy suggest that less frequent dosing intervals do not guarantee increased medication compliance and may actually compromise therapeutic efficacy. For example, compliance and persistence studies conducted in patients with osteoporosis have demonstrated a limited benefit of bisphosphonates dosed monthly or even weekly. One-year persistence rates across several analyses ranged from 18.5% to 55.7% for the daily-dosed regimen versus 22.1% to 69.7 % for the weekly-dosed regimen.35 Furthermore, Weiss et al. determined that, on average, persistence with monthly dosed ibandronate (98 days) was significantly lower than with weekly alendronate (116 days) or weekly risedronate (113 days) (P<0.001).35

In disease states such as epilepsy, it is questionable whether flat plasma concentrations offered by ER drug formulations of anti-epileptic drugs (AEDs) improve anti-epileptic efficacy compared with fluctuating plasma concentrations. It is more certain that they minimize concentration-related adverse effects.3,4 From a patient compliance perspective, it is unknown whether once-daily administration of AEDs is “better” than twice-daily administration. Levy et al. demonstrated that switching dosing schedules from multiple doses per day to once daily by the use of ER drug formulations did not generally improve therapeutic coverage.35 Also, from a pharmacokinetic perspective, the impact of a missed dose is greater with large doses and less frequent administrations.37 Therefore, the potential risk of breakthrough seizure is greater during AED once-daily administration versus twice-daily administration. Consequently, the potential for increased compliance should be weighed against the real impact of a missed dose. In general, from a (theoretical) pharmacokinetic perspective, unless the incidence of non-compliance is reduced by greater than two thirds when a medication is normally taken once daily rather than 3 times daily, the increased compliance offered by the reduction in dose administration frequency is likely to be of no advantage and can be counterproductive in minimizing the occurrence of subtherapeutic drug concentrations.38 In essence, as stated by Urquhart et al., focusing only on dosing frequency can lead to false conclusions about therapeutic superiority, with the crucial matter being not the percentage of prescribed doses taken, but rather the continuity of therapeutic action.38

Despite advances in our understanding of the pathophysiology of the lower urinary tract, muscarinic receptor antagonism remains to be the only clinically proven mechanism of relieving the symptoms of OAB. OAB patients who discontinue treatment are unable to obtain the full benefit of therapy. Establishing effective intervention programs to improve patient persistence and adherence would seem to be a worthwhile initiative with respect to improving health outcomes. While patient education is an important factor, improved patient monitoring by both physicians and pharmacists to identify noncompliant populations is equally important. It would be useful to see the results of a study assessing the effect of upfront counseling on a patient’s attitudes, realistic treatment goals, and compliance barriers. Although the therapeutic armamentarium for OAB has expanded, the discontinuation rates of the antimuscarinic agents observed in clinical trials remain a common shortcoming. This suggests that there is still an unmet need for agents with superior clinical effectiveness and tolerability profiles that can provide increased rates of adherence and persistence.5,30,40 Lastly, although research databases contain useful information pertaining to real-world adherence and persistence patterns, several assumptions pertaining to patient-reported outcomes, benefit designs, and other confounding factors must be made when interpreting such results. Until more effort is made to incorporate such information into these
types of analyses, the clinical and practical utility of results obtained from research databases remains questionable.

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DISCLOSURES
The authors report no conflicts of interest related to the subject of this commentary.

REFERENCES
Overactive Bladder Disease: The Urge for Better Therapies


What Pharmacy Benefit Designers Need to Know About Perception and Reality: Never Forget the Elephant in the Pharmacy

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Tell the patient that the pill contains nothing but sugar, and there is no pain relief; tell him (falsely) that it contains a powerful analgesic, and the perceived level of pain falls. [Defendants insist that a] product that confers this benefit cannot be excluded from the market... just because they told the lies necessary to bring the insistence that a product that confers this benefit cannot be excluded from Donizetti’s “L’Elisir d’Amore.”

With these words, the judges of the U.S. Seventh Circuit Court of Appeals dismissed as “blather” and “poppycock” the purported analgesic effect of the “Q-Ray Ionized Bracelet.” Sold at an approximately 650% markup for retail prices of up to $250, the bracelet had been marketed on more than 42,000 occasions from April 2001 through June 2003 in late-night television infomercials that had touted the “ionized” jewelry as a “miraculous cure for chronic pain.” 1, 2 In response to this promotional campaign, which resulted in the sale of Q-Ray bracelets to more than 800,000 customers, the U.S. Federal Trade Commission (FTC) filed a complaint against the bracelet’s manufacturer for what the appeals court described as “thoroughly dishonest” advertising. The manufacturer cited in its defense a study indicating that both “active” (“ionized”) and “inactive” (placebo) bracelets conferred approximately the same pain-relief benefits. Arguing that a placebo effect was, in fact, an effect, thereby supporting Q-Ray’s advertising, the defendant claimed that the requirement of clinical benefit greater than placebo was an “excessively rigorous standard of proof” that would “keep useful products off the market.” 1 The appeals court disagreed, noting that “medicine aims to do better than the placebo effect,” and ordered the bracelet’s manufacturer to pay more than $16 million in damages to “consumers who have been taken in.”

New Evidence of the Elephant in the Pharmacy

Although certainly an unusually entertaining explication of the placebo effect, the Q-Ray Bracelet ruling is just one of several recent reminders that patient perception is sometimes more powerful than reality in determining the outcomes of health care interventions. In the April 2008 issue of the British Medical Journal, Kapchuk and colleagues reported the results of their randomized controlled trial of several “treatments”—all placebos—for irritable bowel syndrome (IBS). 3 Study authors assigned 262 adults to either (1) a “waiting list” (no treatment and no interaction with health care providers other than routine study assessments, n=87), (2) a “sham acupuncture,” which “does not actually pierce the skin but creates the illusion of doing so” (twice-weekly 20-minute sessions, n=88), or (3) an “augmented” condition consisting of the “sham acupuncture” plus a “warm, empathetic, and confident patient-practitioner relationship” (45 minutes at each “acupuncture” session, n=87). Warmth and confidence were introduced into the augmented condition with statements like “I can understand how difficult IBS must be for you,” and “I have had much positive experience treating IBS...,” as well as 20-second periods of “thoughtful silence while feeling the pulse or pondering the treatment plan.” All study participants (including those assigned to the waiting-list arm) received assessments at baseline, 3 weeks, and 6 weeks. At the 3-week follow-up, the proportions of patients reporting “adequate improvement in your IBS symptoms” were 28% in the waiting-list arm, 44% in the sham acupuncture arm, and 62% in the augmented (sham acupuncture plus interaction) arm. Similar trends in global improvement scale, symptom severity score, and quality-of-life measurement were noted. Findings were also similar at 6 weeks for a subgroup of patients randomized to continue with placebo treatment after the 3-week marker. 1

Similar findings were observed by Waber and colleagues when they conducted a randomized trial, published as a letter in JAMA in March 2008, to assess the effects of a medication’s price on perceptions of its efficacy. 4 Study authors paid 82 healthy volunteers $30 to participate in the trial, telling study subjects that they would be testing a new opioid analgesic that was “similar to codeine with faster onset time.” One half of the sample was told that the drug was priced at $2.50 per pill; the other half was told, without explanation, that the drug had been discounted to $0.10 per pill. Pain was induced by electric shocks to the wrist at various intensity levels, pre-calibrated according to each participant’s pain tolerance, and rated by participants using a visual analog scale (range from “no pain at all” to “the worst pain imaginable”). Pain reduction rates, measured by change in mean pain scores, were 85.4% in the regular-price group and 61.0% in the discount-price group (P=0.02). For a subgroup analysis of the most painful shocks (50th percentile and up, again calibrated to each subject), pain relief rates were 80.5% and 56.1% for the regular-price and discount-price groups, respectively (P=0.03).

Waber et al.’s findings suggested that simply believing a drug to be higher in price results in a perception of better efficacy—even if that “drug” is just a placebo pill. Study authors posited that their results help explain the popularity of higher-cost prescription drugs over lower-cost equivalent options, such as generic medications. 4 Additionally, they suggested that more effective “quality cues” in communicating with patients, such as “de-emphasizing” features that would detract from a drug's
perceived quality (e.g., lower price, generic status), might help to improve patient satisfaction with lower-cost options.

To those working routinely with health plan members, Waber et al.’s quantative findings probably confirm anecdotal experience with the sometimes perplexing economic behavior of patients making medication purchasing decisions. For example, Fairman and Curtiss’s editorial in the September 2007 issue of JMCP recounted the story of Ray Lindell, an elderly Arizona man who traveled more than 4 hours by car to purchase brand-name Valium from a Mexican pharmacy, only to be arrested and spend 8 weeks in a Mexican prison on charges of illegally purchasing narcotics—all because his wife believed that the generic anxiolytics promoted by her insurance company’s new mandatory generic substitution policy were less effective than brand-name products. That editorial suggested that the “elephant in the pharmacy”—an important challenge receiving insufficient attention in the managed care industry—was how to encourage patients to make more evidence-based decisions when purchasing prescription drugs.

Translating the “elephant in the pharmacy” challenge into the language of economists, health care policy should encourage patients and members to value what is objectively valuable (i.e., healthy and cost-effective behaviors and treatments, such as full compliance with chronic drug therapy or using a generic medication when appropriate), and devalue what is clinically or economically wasteful (i.e., behaviors and treatments that are harmful or produce unacceptably low value relative to their cost, such as non-compliance with an antihypertensive drug in uncontrolled hypertension). Yet the question of how best to accomplish this goal is far from straightforward because it is, at its heart, a question of how humans judge value. Put simply, to make health care policy that encourages use of objectively valuable options, we must first understand perceived value, that is, what health plan members value and why.

**How Human Beings Determine Value—What Psychologists Know**

Questions about cost and value are becoming particularly important in managed care policy now, as the debate over financing and structuring the health care system becomes increasingly prominent. Proponents of reducing out-of-pocket (OOP) cost for important preventive treatments, including chronic disease medications (e.g., statins, antihypertensives, anti-diabetics), argue that tailoring copayments according to clinical value (i.e., lower copayments for higher-value services) will “increase use of the highly valued services and lower use of less valued ones, guaranteeing more health per dollar spent.”6 Underlying this optimistic view is a fundamental assumption of economic “rationality”; that is, it is assumed that demand for chronic medications will be elastic (responsive to price change) because patients will tend to act in their own economic self-interest. But for patients to engage in economically rational (price-sensitive) behavior, requires that they view lower cost as a positive attribute that connotes better value for the money spent.

Unfortunately, information about how human beings ascribe value to objects and events, although well studied by psychologists for some 6 decades, has gone largely unnoticed in the health care industry’s current debates about treatment adherence and cost sharing. Evidence of patients’ sometimes puzzling behavior when it comes to purchasing medications would come as no surprise to those familiar with psychological studies of cost and value. The seemingly intuitive assumption that lowering prices for health care services will increase the use of those services is largely, although not completely, inconsistent with evidence from psychological experiments conducted over many decades.

**From Simplistic to More Realistic: How Humans Value What They Have Already Paid for—Cognitive Dissonance Theory**

The first effort to explain the relationship between cost and value, associative theory, was the prevailing view in the 1950s7 and is closely analogous to the assumption of economic rationality underlying today’s copayment reduction proposals. Associative theory posited a simple and economically rational inverse relationship between price and consumption: if prices go up, perceived value relative to cost, and therefore consumption, will go down. But beginning in 1957, associative theory was challenged by a competing and ultimately much better supported view. According to that view, known as “cognitive dissonance theory,” humans who are required to pay a high price for something will subsequently (i.e., after the price has been paid) value it highly to avoid a cognitive contradiction between the price that they have already paid and the perception of what they’ve paid for.7 8

The earliest test of cognitive dissonance theory, an elegant and now classic experiment published in 1959, recruited 63 college student volunteers to participate in what they were told would be a series of group discussions on the psychology of sex.8 Unbeknownst to the subjects, they had been randomly assigned into 3 groups (n=21 in each group): (1) no group initiation; (2) a “mild” initiation, consisting of reading titillating but not obscene words aloud; and (3) a “severe” (by 1950s standards) initiation, consisting of reading a list of obscene words aloud. Words were read only in the presence of the investigator; there was no actual group interaction at all (and, in fact, there was actually no group). Following the initiation condition, all 63 volunteers listened to what they were told was the discussion group in live action (in reality, actors were used and the “live discussion” had been pre-scripted and tape-recorded) and then were asked to rate the group.

Study results fully supported cognitive dissonance theory. Subjects who had been randomly assigned to undergo a severe initiation in advance of hearing the group’s “discussion” rated the group more highly than did either the mild initiation or no initiation groups. For example, the quality of the discussion,
which had been pre-scripted to be “as dull and banal as possible… one of the most worthless and uninteresting discussions imaginable,” according to study authors, was rated by study subjects on a scale of 0 to 120. Mean ratings were 97.6 for the severe initiation group, 81.8 for the mild initiation group (P<0.02 for severe vs. mild), and 80.2 for the control group (P<0.001 for severe vs. control).8

The lively debate that ensued after the initial promulgation of cognitive dissonance theory is widely recognized as a hallmark in the field of social psychology9,10 for a reason that should sound familiar to anyone currently engaged in health care benefit design. Specifically, the debate raised the fundamental question of whether human beings passively respond to external stimuli (associative view) or actively engage in cognitive processes about their choices (cognitive dissonance view).9,10 Like Waber et al.’s recent study suggesting that higher-priced drugs are perceived as more valuable just because they cost more,4 the psychological experiments of some 40 to 50 years ago began to suggest that active, not entirely rational, cognitive processes affect human purchasing behavior.

For example, a series of experiments published in 1969 provided additional support for cognitive dissonance theory in an assessment of the “introductory low price offer,” in which an initially low selling price is followed by a return to pricing at normal levels.11 Cognitive dissonance theory predicts that this intuitively appealing strategy will ultimately result in fewer sales because “the higher the price a person initially pays for a product, the more he will come to like it.”11 To test the effect of low introductory pricing, Doob et al. randomized chain discount stores to sell identical new store-brand products using either (1) initially discounted pricing for 1 to 3 weeks depending on the product, followed by a return to the normal price, or (2) normal undiscounted pricing throughout a 20-week study period. Store managers were unaware of the experimental conditions. Products priced at normal price throughout the study exhibited a steadily growing sales trend, described as “brand loyalty” by the study authors. Products priced initially at discount exhibited higher initial sales, followed by either a drop in sales or a reduced upward trend after the price increase. The initially higher sales volume for the discounted products was not enough to offset the steady climb in sales for the normally priced products. Thus, higher initial pricing was associated with significantly higher long-term sales volume.11

Increasing Realism Through Personal Equity-comparison and Signaling Theories: The Role of Expectations in Determining Perceived Value

In discussing their low introductory price study, Doob et al. pointed out that a phenomenon other than cognitive dissonance could have explained their results. If customers seeing the introductory price began to identify the product as a low-cost option, the increase to the normal price might have been viewed as “overpricing,” prompting product discontinuation.11 In raising this possibility, the authors were introducing the notion of the importance of expectations in the value attribution process.

The importance of setting expectations lies at the heart of a theory of cost and value that is more complex than either associative theory or cognitive dissonance theory—personal equity-comparison theory (PECT). According to PECT, humans assess the value of phenomena (e.g., objects, events, actions) in a constantly evolving process of comparison between expectations, cost, and outcomes. PECT is generally consistent with cognitive dissonance theory in that it associates moderately high costs with better expected (and therefore perceived) outcomes than minimal costs.9 However, PECT accounts for complexities in human cognition not addressed by cognitive dissonance theory.

One of the complexities addressed by PECT and relevant to the setting of health care cost-sharing levels is the “ceiling effect.” If the cost paid by an individual is so high that it generates an expectation that cannot possibly be met given the actual value of the outcome, the individual will tend to separate or “contrast” the outcome from the cost, thereby devaluing the expected outcome. Thus, the relationship between cost and perceived value is posited to be curvilinear: phenomena with a moderate cost will be perceived as more appealing than phenomena with a low cost, but if the cost is too high, the perceived value may decline.9

Another factor affecting expectations and, therefore, value is history or reputation; for example, when an experience that would normally result in devaluation occurs (e.g., a distressing interaction with a close friend or a bad meal in a restaurant that usually serves great food), a person with very positive past experiences with a person or group will tend to develop a “compensatory expectation,” the belief that eventually a positive outcome will come about in the future. Finally, the salience of cost is important; to cause a change in perceived value, a cost must be of sufficient magnitude to be noticeable.9,12

PECT was tested and well-supported in a series of 4 experiments published in 1993.12 All 4 experiments were conducted with undergraduate volunteers recruited from introductory psychology classes. In the first 3 experiments, subjects were told that they would be reading an essay written by a college sophomore. Subjects were then either given no task to perform (control condition) or were given the task of writing signatures at varying levels of difficulty (i.e., low or minimal effort [4-6 signatures], moderate effort [12-16 signatures], or high effort [32 signatures]). Following completion of the task condition, subjects were asked to rate their expectation of the essay’s quality in advance of reading it. Key findings of the studies were that:

1. Subjects who were required to expend moderate effort subsequently rated the anticipated quality of the essay more highly than did control subjects who were required to expend no effort.
2. Subjects assigned to the no-effort and low-effort conditions did not significantly differ in their ratings of anticipated essay quality because, the investigators posited, the low-effort level of difficulty was not sufficiently salient to cause a difference in perceived value.

3. Subjects assigned to the high-effort condition (32 signatures) rated the anticipated essay quality lower than did subjects assigned to the moderate effort condition because of the ceiling effect, according to the investigators; if a person expends a large amount of effort, “the person may be unable to discover aspects about a particular event that will compensate for the cost experience.”

In the fourth experiment, instead of rating the anticipated quality of the essay without actually reading it, subjects read an essay of either low or high quality, following a task of 0 signatures, 6 signatures, or 20 signatures. All 6 conditions were randomly assigned. Results for the 20-signature group were compared with pooled results for the 0- and 6-signature groups combined. Confirming the ceiling effect, researchers found that higher effort (20 signatures) was associated with lower ratings of the low-quality essay (i.e., the high cost outweighed the value of a low-quality essay, invoking the ceiling effect). However, confirming the role of cost in setting expectations, the higher (20-signature) cost was also associated with higher ratings of the high-quality essay (i.e., a positive expectation was generated by the higher cost, without a ceiling effect because the essay was good).12

**Signaling Theory in Economics: Further Exploration of How Expectations Are Set**

In the early 1970s, as social psychologists were analyzing the effects of cost on perceived value and “brand loyalty” (repeat sales), theoretical mathematical models in economics began to examine the same phenomenon from a different perspective—that of the producer of goods or services. The signaling hypothesis was first advanced as a theory of labor-market economics by Michael Spence in a 1973 Nobel prize-winning paper. Signaling theory posits that the seller of a product, who holds more information than the prospective purchaser, will leverage that information asymmetry by sending “signals” about the value of the product. However, the signals might or might not accurately represent actual product quality.13-15 For example, Spence argued that workers will acquire additional years of education to send a signal about the quality of their work, prompting a response from a prospective employer (a higher wage) even if the increased education does not actually result in better productivity.

Signaling theory suggests that, in making purchase decisions, individuals may rely on multiple sources of information about product quality, including price, brand name, recommendations of friends, previous experience, warranties, advertisements, and product packaging.14 Thus, like psychological theories of cost and value, signaling theory holds that the role of price in purchasing behavior is complex. Specifically, the recognition that price represents not only the cost to the consumer (i.e., a price increase would tend to reduce purchasing) but also a potential signal of quality (i.e., a price increase would tend to increase purchasing) leads to an understanding that the 2 effects of price are in conflict, making “price responsiveness more inelastic than would otherwise be the case.”14

**Behavioral Economics Identifies Additional Irrational Responses to Price**

In recent years, the field of behavioral economics has come to the fore, rooted in the belief that many of the assumptions of traditional economics are demonstrably incorrect in realistic studies of human economic action (e.g., purchasing goods, making job choices). Daniel Kahneman, winner of a 2002 Nobel Prize for his groundbreaking work in behavioral economics, explained the field in a recent interview: “Standard economics is mostly a mathematical discipline. It makes assumptions, and one [assumption] routinely made is that economic agents are rational. Behavioral economics is simply economics without the rationality assumption. Economists find it very difficult to give up the assumption, but [those who do] … can get to a richer and more realistic model of how people behave.”16

For example, a notable exception to psychological rules about the relationship between cost and value is the zero-cost product. Consumers are innately drawn to “free” products, even at the cost of purchasing higher priced goods to get what is “free,” such as spending tens of thousands of dollars more on a high-end automobile to get a year of “free” oil changes.17 To test the power of “free” goods, behavioral economist Dan Ariely conducted a clever experiment in which he and his associates set a table laden with chocolates—fine Lindt truffles on one side and Hershey’s Kisses on the other—in a public place. In the first phase of Ariely’s experiment, he priced the Lindt truffles at 15 cents and the Kisses at 1 cent. Those who purchased the chocolates acted, as a group, in an economically rational way; 73% chose the truffles and the remaining 27% chose the Kiss. In the second phase of the experiment, Ariely maintained the same 14-cent price differential but this time he offered the truffles for 14 cents and the Kisses at no charge. Acting irrationally in response to the “free” label, only 31% of customers chose the truffles, and 69% chose the free Kiss.17

A similarly powerful and irrational effect, well known to product marketers, is price relativity, a process by which consumers compare prices relative to each other or to a price “anchor” (a ceiling or floor price value established in the mind of the consumer). For example, Ariely points out, restaurant menu designers will place the dish that they most want to sell at the second-highest price on the menu, knowing that customers are unlikely to purchase the highest-priced item but will evaluate the remaining menu items against the highest price.17 Similarly, retailers will present price lists arrayed in order, with the item
that they would most like to sell priced at a mid-range between highest and lowest price. A guide for start-up restaurant owners, written by a menu pricing consultant, openly acknowledges that sound pricing strategy is rooted in an understanding of economic irrationality: “Customers will come in with ‘reference’ prices that they expect to pay for certain items and will not think twice about paying $1.50 for a glass of iced tea that has a cost of about a nickel…” Similarly, retailers use “odd cents” pricing to encourage the illusion that a cost is lower than it actually is. For example, items are priced at $9.95 with the understanding that consumers will tend to round to $9 even though technically, in an economically rational world, it is understood that 9.95 rounds to 10. 18

### Psychological and Behavioral Economic Research

- Moderate cost sharing encourages higher perceived value. 8,9,11,12
- Cost differences do not produce changes in perceived value unless they are large enough to be salient 9,11,12
- Higher-priced drugs are perceived as more effective than discount drugs, even when the “drug” tested is a placebo. 4

### Summary Pharmacoeconomic Research

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### Table: Summary of Research in Psychology, Behavioral Economics, and Pharmacoeconomics: Cost Sharing for Prescription Medications

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<td>Offering “free” products or services is an often used and powerful marketing tool. 17 The effect of using this tool in pharmacy benefit design is unknown.</td>
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**OOP = out-of-pocket.**

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### Pulling the Pieces Together from Psychology and Pharmacoeconomics to Inform Us About Pharmacy Benefit Design

Controlled studies across the disciplines of psychology, economics, and pharmacoeconomics have produced remarkably similar guidance about the effects of prescription drug cost-sharing on medication purchasing behavior (Table). To optimize clinical and economic outcomes requires incorporating this multidisciplinary understanding into the testing and implementation of innovations in pharmacy benefit designs:

1. **Human economic behavior is not entirely rational.** Research conducted over the past 6 decades has produced a growing awareness that human beings do not always make the most objectively healthy or cost-effective choices; in other words, the empirically measured value of a behavior or treatment does not consistently equate to its perceived value. This is not to say that human beings are unintelligent, merely that their personal preferences might not always be what they would be in a world of perfect information and decision making based solely on evidence. Rather than ignore this reality of human nature, benefit designers must live with it, overcome it as much as possible, and capitalize on it when feasible. Pharmacy benefit designers should be aware that, in promoting objectively healthy choices, influencing the perceived value of a medication may be an essential—and relatively inexpensive—way to encourage both cost-effective medication choices and adherence to medication therapy.
2. Prescription drug copayment reduction strategies are not yet supported by research in any of the 3 disciplines (Table).

To date, there is no empirical support for the strategy of reducing medication copayments to increase adherence with chronic medication therapy. The relationship between price and purchasing behavior is clearly complex, belying the simplistic assumption that copayment reductions will *ipso facto* translate to increased compliance with prescription medications. Psychological and behavioral studies suggest that paying a moderate cost up front is associated with subsequently higher perceived value and increased purchasing loyalty, with the exception of situations in which costs have reached a “ceiling effect” (a cost so high that it is not feasible for a product’s value to equal its cost).\(^9,10,11,12\) Perhaps more importantly, these studies suggest that unless a cost difference is salient (noticeable to the consumer), it will not affect purchasing behavior.\(^9,12\)

Results of these psychological and behavioral studies are completely consistent with findings of pharmacoeconomic studies of prescription drug cost sharing to date. In controlled studies of commercially insured populations (i.e., not low income, not publicly insured), only unusually salient or large copayment changes (e.g., a change from a 1-tier to 3-tier design coupled with a $23 non-formulary brand increase in one study, increases of up to $25 in another study) have been associated with decreased chronic medication adherence, and these studies employed unusual or questionable methods.\(^10,21\) Controlled studies of typical amounts of change in prescription drug cost-sharing levels (e.g., change amounts ranging from $5 to $13 per 30-day supply for brand medications) have documented very modest effects on utilization overall and little or no impact on adherence to chronic medications.\(^19\) The reduced rate of growth in net payer prescription drug cost observed in controlled research was primarily attributable to increased shifting of cost from payer to patient and, to a lesser extent, a shifting of utilization from non-formulary to formulary brand and generic medications.\(^19\)

3. The body of economic and psychological research to date suggests that copayment reduction strategies may tend to increase the rate and cost of unnecessary brand medication use.

Waber et al.’s findings suggest that simply knowing of a drug’s higher cost or “brand” status may increase its perceived value or, in the language of signaling theory, send a signal to the consumer that it is a better product (even if it isn’t).\(^4\) Signaling theory would also suggest that advertising, such as marketing of drugs directly to consumers, plays a role in encouraging consumers to believe that brand drugs are of higher quality than generic drugs.\(^15\)

PECT would suggest that, in copayment reduction initiatives, these differences in perceived quality could interact with lower OOP cost to modify drug selection in undesirable ways. Specifically, PECT indicates that if a brand-generic copayment differential is so small that it is not salient to the consumer, there is no reason for the consumer to prefer a generic drug.\(^12\) Additionally, if the generic drug is perceived as lower quality than the brand drug, the “ceiling effect” (the limit to the amount that the consumer is willing to pay for it) is more easily invoked for the generic than for the brand.\(^12\) Thus, the combination of perceived higher quality and lower OOP cost for brand drugs has the potential to shift use away from generic drugs, even when brands and generics are objectively clinically equivalent.

These psychological and economic research findings have 3 implications for pharmacy benefit design today. First, studies of copayment reductions should include assessments of change in generic dispensing ratio and claims volume (e.g., tier-1 claims per member per month). Second, while we await research results, payers should be very cautious in reducing brand-generic copayment differentials. Third, strategies that successfully encourage a positive perception of generic medications should be seriously considered as an approach that has the potential to be more cost-effective (i.e., to deliver equal or greater benefits at lower cost) than copayment reduction strategies.

4. Studies are needed to test the effect of “free” medication in encouraging specific desired behaviors (e.g., switch to a generic medication). The power of “free” is the sole potential exception to the present lack of evidence to support prescription drug copayment reduction. Psychological and behavioral studies suggest that providing a service free of charge has a strong incentive effect on human behavior.\(^17\) Notably, however, the only study to report this type of intervention in health care found that providing glucose test strips free of charge to patients with diabetes “shifted costs from patient to health plan, without improving adherence” in blood glucose monitoring.\(^22\) Unfortunately, the present literature comes up short in providing the quantitative information that benefit designers need about the effects of providing free medication on clinical and economic outcomes. A recent highly publicized study by Chernew et al. of reduction in the amount of prescription drug cost sharing included an undisclosed number of patients whose medication was provided free of charge, but its design was weak and not transparent, the results for the “free” subgroup were not reported separately, the cost of the copayment intervention was not reported at all, and the observed effects of reduced cost sharing on medication possession ratio (adherence) across all copayment levels were statistically significant but not clinically significant at 7 to 14 days per year.\(^23,24\)

5. Benefit designers must test not just objective benefit design conditions but also the effects of messaging—how those conditions are described to plan members. In a world in which patient expectations and perceptions are often the most important factors in determining the success of an intervention, it is critical that studies of insured benefit changes (e.g., copayments, tiers, formularies) include tests of different messaging strategies or “quality cues,” to use Waber et al.’s term,\(^4\) to accompany the change. For example, members in a group with a copayment increase might be randomly assigned to 1 of 4 messaging subgroups: (1) education about the therapeutic equivalency and reduced OOP cost for
generic medications, (2) therapeutic equivalency education only, (3) OOP cost education only, and (4) no education.

6. Messaging suggesting a “bargain” may be particularly effective. Given recent research demonstrating that patients may value higher-cost medications based solely on knowledge of their price, communication that effectively describes generic medications as a bargain—the receipt of a higher-price medication at a lower cost—has the potential to promote therapeutic switches, thereby lowering both payer outlays and consumer OOP cost. Similarly, communications that effectively describe improved health as a bargain relative to the OOP cost for prescription drugs have the potential to improve adherence by overcoming the ceiling effect. The importance of salience, as documented in psychological studies, suggests that attractive coupons or other creative communications approaches might work better than less noticeable differences in OOP cost at the point of sale.

7. Strong research designs are critical. Across all disciplines, studies with strong research designs (e.g., the very strong randomized designs of psychological and behavioral research and quasi-experimental designs in pharmacoeconomic research) have produced markedly similar findings about the relationship between cost paid and perceived value. Specifically, controlled studies in these disciplines all suggest that purchases of prescription medications are predicted to be (psychological and behavioral studies) and are (well-controlled pharmacoeconomic studies) relatively price inelastic (not price sensitive), unless copayment changes are extreme, or there is a real issue with affordability (as in low-income or publicly insured populations).19 In contrast, pharmacoeconomic studies with weak cross-sectional designs have found price elasticity in the purchasing of prescription drugs. The discrepancy between well controlled and weakly controlled work is probably attributable to the effect of confounding factors on weakly designed studies. That is, plans with higher prescription drug copayments often are characterized by other features that tend to reduce costs (e.g., differences in organizational culture, history of cost-conscious behavior, step-therapy requirements, or formulary differences). When these plans are compared with lower copayment plans in non-randomized designs, what appears to be an effect of cost sharing actually may be an effect of other unmeasured factors. Thus, it is critical that future research in prescription drug cost sharing and benefits design messaging should employ study designs that include randomization or pseudo-randomization with comparable study groups.

Paying for the Elephant in the Pharmacy—Not Just Peanuts

Recent popular press coverage indicates that several pharmacy benefits managers (PBMs) are engaged in either considering or developing interventions to educate consumers about the benefits of generic medications.23 One PBM recently reported that, after witnessing the failure of a generic switch promotion program based solely on economic incentives, it began using behavioral economic principles to encourage therapeutic switching from brand Lipitor to generic simvastatin. Although this analysis has not yet been published, the PBM announced that its change in messaging has resulted in a “doubling or tripling” of the switch rate, which was 8% prior to the behavioral intervention.23 Peer-reviewed assessments of programs of this type, using strong research designs, are urgently needed.

Yet, no matter how complete our understanding of how human beings determine what to value, we are left with the fundamental nagging question of who should pay for the incremental cost that results when efforts to encourage economically rational decision making fail. “How do we deal with the fact that expensive medicine (the 50-cent aspirin) may make people feel better than cheaper medicine (the penny aspirin)”? asks Dan Ariely. “Do we indulge people’s irrationality, thereby raising the costs of health care? Or do we insist that people get the cheapest generic drugs (and medical procedures) on the market,” despite our understanding that mere knowledge of higher product cost might make the patient feel better?37 Identification of irrational behaviors and determination of how to discourage them are the stuff of empirical investigation; determination of who should pay for irrationality is the stuff of philosophical debate. Yet, whether one’s approach to health care is to encourage financial responsibility for personal choice (as in some market-based health care system proposals) or to attempt to guarantee equivalent outcomes irrespective of personal choice (as in some universal coverage proposals), the need for better information about choice is the same.

For a health care system that, in 2006, spent nearly 2% of its gross domestic product on prescription medications dispensed in community pharmacies,26 “the elephant in the pharmacy” may represent the most important key to success or failure in the endeavor to make prescription drug therapy both high quality and affordable. We need to know the customer, and perhaps behavioral economics (i.e., without the rationality assumption), is part of our requisite education. With an armada of effective low-cost generic drugs (“gold”) for most chronic diseases, perhaps our challenge in managed care is to make the value of this gold—the drugs within therapeutic classes that have similar clinical outcomes at lower cost—more real (salient) for health plan members. Understanding how to meet that challenge will likely require the investment of a little more “gold”—in high-quality, quantitative, and transparent research on the costs and benefits of benefit design interventions.

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DISCLOSURES

The associate editor reports no conflict of interest on this subject.

REFERENCES


Letters to the Editor

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Informing Patients About Drug Effects
Using Positive Suggestion

To the Editor:

Informed consent, as codified by statutory law in many nations, refers to the permission given by a person before surgery or other kinds of medical treatments. The patient, or a parent/guardian, must understand the potential risks and benefits of the treatment and legally agree to accept those risks, in writing. Furthermore, the risks and possible side effects must be explained in easy-to-understand language.

Informed consent is essential to the clinician’s ability to diagnose and treat patients, as well as the patient’s right to accept or reject clinical evaluation, treatment, or both. Informed consent should be an exchange of ideas that strengthens the fiduciary patient-physician relationship. Clinicians must recognize that informed medical choice is an educational process and has the potential to affect the patient-physician alliance to their mutual benefit. It is particularly important for a large number of interventions whose merits remain uncertain or whose benefits and risks may be viewed differently by different patients. One patient might find a side effect intolerable while another is willing to risk it, even if the benefits of the treatment are uncertain.

Clinicians and patients should discuss the treatment, weighing its risks and benefits together, and then the patient can make an informed decision. When clinicians and patients take medical informed consent seriously, the patient-physician relationship becomes a true partnership with shared decision-making authority and responsibility for outcomes. It is fundamental to the patient-physician relationship that each partner understands and accepts the degree of autonomy the patient desires in the decision-making process.

Informed consent in drug therapy was not common many years ago. When initiating treatment, it has been shown that only one quarter of the physicians would discuss potential side effects with patients. There were several possible reasons, but, in particular, many physicians were concerned that the power of suggestion might lead some patients, especially suggestible ones, to experience an increase in side effects if they are fully informed about them. Yet, a few studies, conducted to determine whether providing patients with information about potential side effects increases the reported incidence of those side effects, found no relationship between informed consent and side-effect incidence rates.

Morris et al. pioneered a study more than 25 years ago on informing patients about drug side effects. Two hundred forty-nine newly diagnosed hypertensive patients prescribed thiazide medication were recruited for their study. Two thirds were given a leaflet or patient package insert that described the drug and its possible side effects, and one third were given no written information. At a revisit about 1 month later, patients were asked whether they had experienced any of 17 different “health problems.” Patients who received the package insert reported experiencing about the same number of side effects as the patients who had received no written material.

Howland et al. (1990) investigated whether patient education caused drug side effects. Ninety-eight adults treated with erythromycin for a variety of illnesses were randomized to 2 groups: the informed group received patient education about drug side effects, and the uninformed group was given no such information. Overall, 10% of the uninformed and 8% of the informed group felt that the erythromycin bothered them in some way. There were no significant differences in the occurrence of various individual side effects.

Lamb et al. (1994) designed a study to determine the outcome of providing patients with information about potential side effects of 2 new medications. Two hundred three clinic patients receiving new prescriptions for angiotensin-converting enzyme inhibitors, trimethoprim/sulfamethoxazole, or nonsteroidal anti-inflammatory drugs were recruited and randomly assigned to 1 of 4 teams. Each team consisted of faculty, residents, and nurses. Two teams served as the intervention group and 2 teams served as control groups. Intervention patients (n=104) received verbal instructions and a handout describing the name, purpose, dose, and 3 most common side effects of the drug. Control patients (n=99) received usual discharge instructions. Patients were interviewed 14 to 21 days later, using a standardized questionnaire. The results showed that there was no difference in incidence of targeted side effects for specific medications between the study groups (38% vs. 37% for intervention patients vs. control patients, respectively; P=0.87).

Things have changed with the passage of time. Today, because of the threat of malpractice liability, many physicians are practicing defensive medicine and “overtreating” their patients. Defensive medicine is one of the largest contributors to wasteful spending, and it can manifest in many forms: unnecessary CT scans, MRIs, cardiac testing, and hospital admissions. Nearly all (93%) physicians practicing in high-risk specialties (emergency medicine, general surgery, neurosurgery, obstetrics/gynecology, orthopedic surgery, and radiology) reported, in a mail survey, that they practice at least 1 form of defensive medicine, measured by the survey as prescribing unnecessary drugs, tests, or invasive procedures; making unnecessary specialty referrals; or avoiding certain high-risk procedures or patients. In such a social, political, and economic environment, medical professionals have to be careful to fully inform patients. They are prone to informing patients about all matters regardless of importance, attempting to maintain the safest legal position possible. The subtext of providing a patient with full information from any medical professional inevitably leads to this question: Are we providing patients with information that is clinically helpful or harmful?

Dyck et al. (2005) conducted a descriptive study of pharmacists’ discussions of medication side effects with patients. Ten community pharmacists were videotaped while providing their customary patient counseling to 2 standardized patients.
receiving new prescriptions within staged scenarios. All of the pharmacists discussed side effects and management strategies. They found that pharmacists focused most on safety aspects of using medications and spent far less time discussing potential therapeutic benefits.

The problem is that, if a pharmacist provides more information about the risks of a drug than the benefits of that drug, he might ‘overinform’ the patient into risks instead of benefits. Thus, a suggestion that was intended to be helpful to the patient might actually be harmful.

Suggestion transcends both verbal and nonverbal communications. Usually, a suggestion reaches the conscious mind, is examined critically, then is either accepted or rejected. But during a highly emotional or stressful time, the suggestion may bypass the conscious mind and go directly to the subconscious, where it is accepted uncritically and literally, especially by suggestible persons.

There is a saying that if you think something is going to happen, it will. The power of suggestion can be very strong. I was reminded of this many years ago when I went to donate blood with my friend, M. Ying, in Beijing. It was the first time Ying gave blood. She was a healthy young woman. Before we went, I told her it was “a piece of cake.” At the Congwen donations center, one phlebotomist inserted the needle and initiated the blood flow on her, and another did the same to me. Ying didn’t look pale or diaphoretic. We chatted together, and Ying seemed just fine after a month, she revisited and reported great improvements in emotion and sleep.

My goal here is not to discuss the benefit or risk of fully informing patients. Rather, I would like to raise concerns regarding the potentially negative consequences of suggestion when informing patients and encourage all clinicians to remember that the power of positive suggestion can be used to attain beneficial outcomes.

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DISCLOSURES
The author discloses no potential bias or conflict of interest relating to this letter.

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