Page

25  The Association of Adherence to Osteoporosis Therapies with Fracture, All-Cause Medical Costs, and All-Cause Hospitalizations: A Retrospective Claims Analysis of Female Health Plan Enrollees with Osteoporosis

40  Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products

51  Estimated Cost Savings Associated with the Transfer of Office-Administered Specialty Pharmaceuticals to a Specialty Pharmacy Provider in a Medical Injectable Drug Program

60  Protecting Patients from Adverse Drug Events: Propoxyphene, PIMs and Drugs to Avoid in Older Adults

72  JMCP Article Index by Subject Category — with Hyperlinks
RESEARCH
25 The Association of Adherence to Osteoporosis Therapies with Fracture, All-Cause Medical Costs, and All-Cause Hospitalizations: A Retrospective Claims Analysis of Female Health Plan Enrollees with Osteoporosis
Rachel Halpern, PhD, MPH; Laura Becker, MS; Sheikh Usman Iqbal, MD, MPH, MBA; Lewis E. Kazis, ScD; David Macarlos, MBA; and Enkhjargal Badamgarav, MD, MPH

SUBJECT REVIEW
40 Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products
Burgunda V. Sweet, PharmD, FASHP; Ann K. Schwemm, PharmD, MPH; and Dawn M. Parsons, RPh, MBA

CONTEMPORARY SUBJECT
51 Estimated Cost Savings Associated with the Transfer of Office-Administered Specialty Pharmaceuticals to a Specialty Pharmacy Provider in a Medical Injectable Drug Program
Christopher G. Baldini, PharmD, and Eric J. Culley, PharmD, MBA

DEPARTMENTS
16 Cover Impressions
Ernst Haecckel
Sheila Macho, Cover Editor

60 Editorial
Protecting Patients from Adverse Drug Events: Propoxyphene, PIMs, and Drugs to Avoid in Older Adults
Frederic R. Curtiss, PhD, RPh, CEBS, and Kathleen A. Fairman, MA

70 Letter
A Managed Care Organization’s Initiative to Improve Patient Safety in the Use of Concentrated Insulin
Nick Manno, PharmD, BSpPharm, and Arthur Naliboff, BSpPharm, MS

72 JMCP Article Index by Subject Category — with Hyperlinks

92 Thanks to JMCP Peer Reviewers, 2010
JMCP publishes peer-reviewed original research manuscripts, subject reviews, and other content intended to advance the use of the scientific method, including the interpretation of research findings in managed care pharmacy. JMCP is dedicated to improving the quality of care delivered to patients served by managed care pharmacy by providing its readers with the results of scientific investigation and evaluation of clinical, health, service, and economic outcomes of pharmacy services and pharmaceutical interventions, including formulary management. JMCP strives to engage and serve professionals in pharmacy, medicine, nursing, and related fields to optimize the value of pharmaceutical products and pharmacy services delivered to patients. JMCP employs extensive bias-management procedures intended to ensure the integrity and reliability of published work.

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REFERENCE

Ernst Haeckel (1834–1919) has been chosen as the cover artist for JMCP’s annual issue featuring an artist with a pharmaceutical, medical, or scientific background. A multifaceted individual, he was a biologist, zoologist, naturalist, philosopher, professor, physician, and artist. Haeckel discovered, described, and named thousands of new species and coined many terms in biology, including “phylum,” “anthropogeny,” “phylogeny,” “ecology,” and the kingdom Protista. He also wrote numerous books and scientific papers.

Haeckel was born in Potsdam, Germany (then part of Prussia), and grew up in Merseburg, Germany. From a very early age, drawing and painting were among his favorite hobbies. Haeckel wanted to pursue a career in botany or biology, but his parents encouraged him to study medicine. In 1852, he embarked on his medical studies, spending a semester at the University of Berlin before transferring to the University of Würzburg, where one of his teachers was Rudolf Virchow, “the father of modern pathology.” After 2 years, Haeckel returned to the University of Berlin, studying with the renowned physiologist and comparative anatomist, Johannes Peter Müller, who was instrumental in fostering the young student’s interest in marine biology. In 1857, he graduated with an MD degree, as well as a doctorate in biology.

Haeckel practiced medicine for a brief period of time, but in 1859, he decided to stop working with patients and traveled to southern Italy to study marine organisms from the Mediterranean Sea. While in Italy, he toyed with the idea of becoming a landscape painter, but in the end, he chose science. Olaf Breidbach’s book, Visions of Nature: The Art and Science of Ernst Haeckel contains a letter that Haeckel wrote in 1860 to a friend about his Italian journey: “Nature’s inexhaustible richness produces ever-new, beautiful, and fascinating forms that provide material to speculate and ponder over, to draw and describe. Indeed, this is just the right sort of work for me because, in addition to the scientific element, it involves artistic matters to a large degree. I have once again completely reconciled myself to my dear science, which shall, throughout my entire life, take the highest priority.”

Later that year, Haeckel returned to Germany and studied under anatominist Karl Gegenbaur at the University of Jena, earning a doctorate in biology. He was instrumental in fostering the young student’s interest in marine biology. In 1859, he decided to stop working with patients and traveled to southern Italy to study marine organisms from the Mediterranean Sea. While in Italy, he toyed with the idea of becoming a landscape painter, but in the end, he chose science. Olaf Breidbach’s book, Visions of Nature: The Art and Science of Ernst Haeckel contains a letter that Haeckel wrote in 1860 to a friend about his Italian journey: “Nature’s inexhaustible richness produces ever-new, beautiful, and fascinating forms that provide material to speculate and ponder over, to draw and describe. Indeed, this is just the right sort of work for me because, in addition to the scientific element, it involves artistic matters to a large degree. I have once again completely reconciled myself to my dear science, which shall, throughout my entire life, take the highest priority.”

Later that year, Haeckel returned to Germany and studied under anatominist Karl Gegenbaur at the University of Jena, earning a doctorate in biology. He became a lecturer in comparative anatomy at the university in 1861, and within a year, he was appointed associate professor of zoology. Haeckel was promoted to full professor and director of the University of Jena’s Zoological Institute in 1865. He retired in 1899.

In the summer of 1862, Haeckel married Anna Sethe, who died just 18 months later. He married again in 1867 to Agnes Huschke, with whom he had 3 children. His second marriage was not entirely happy, perhaps because he never fully recovered from the loss of his beloved first wife.

After reading Charles Darwin’s On the Origin of Species, Haeckel became an enthusiastic advocate of the theory of evolution. However, according to Breidbach, “Haeckel represented more than just a wholehearted acceptance of Darwin’s theory of evolution. With his publications—consistently aimed at a broad public—he played a decisive role in shaping how people saw nature.” Haeckel’s popular Kunstformen der Natur (Art Forms of Nature), was published from 1899 to 1904 as a series of 10 booklets and as a complete volume in 1904. The lavishly illustrated book contains 100 ornate paintings of a wide variety of organisms, plants, and animals, plus accompanying text.

Plate number 99 in Kunstformen der Natur is titled Trochilidae (hummingbirds). Haeckel has given the tiny, fluttering creatures a theatrical flair in this well-organized composition. The 12 preserved male hummingbirds that he used as subjects for the painting were sent to him from Central and South America. Trochilidae includes depictions of the Ruby-throated Hummingbird, the Red-tailed Comet Hummingbird, the Buff-tailed Sicklebill Hummingbird, the Dot-eared Coquette Hummingbird, and the Booted Racket-tail Hummingbird. Found only in the Americas, hummingbirds are among the world’s smallest birds. Their name derives from the characteristic hum made by their rapid wing beats, which can beat 12–90 times per second (depending on the species). Hummingbirds can rotate each of their wings in a circle, and this enables them to fly forward, backward, up, down, sideways, and hover in midair.

Haeckel’s paintings were extremely influential in the art world at the turn of the twentieth century, particularly in the Art Nouveau movement. Architects and designers have also been influenced by his work. One notable example is the glass chandelier found in the Oceanographic Museum in Monaco that was based on Haeckel’s Discomedusae (jellyfish) illustration. His marvelous art continues to inspire artists and designers to this day.

Sheila Macho
Cover Editor

COVER CREDIT
Ernst Haeckel, Trochilidae, watercolor on paper. Jena, Germany. Copyright © 1904. Image courtesy of Wikimedia Commons.

SOURCE
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The Association of Adherence to Osteoporosis Therapies with Fracture, All-Cause Medical Costs, and All-Cause Hospitalizations: A Retrospective Claims Analysis of Female Health Plan Enrollees with Osteoporosis

Rachel Halpern, PhD, MPH; Laura Becker, MS; Sheikh Usman Iqbal, MD, MPH, MBA; Lewis E. Kazis, ScD; David Macarios, MBA; and Enkhjargal Badamgarav, MD, MPH

ABSTRACT

BACKGROUND: Osteoporosis affects approximately 10 million people in the United States and is associated with increased fracture risk and fracture-related costs. Poor adherence to osteoporosis medications is associated with higher general burden of illness compared with optimal adherence.

OBJECTIVE: To examine the associations of adherence to osteoporosis therapies with (a) occurrence of closed fracture, (b) all-cause medical costs, and (c) all-cause hospitalizations.

METHODS: This retrospective analysis of administrative claims data examined women with osteoporosis initiating therapy with alendronate, risedronate, ibandronate, or raloxifene from July 1, 2002, to March 10, 2006. Data were from a large, geographically diverse U.S. health plan that covered about 12.6 million females during the identification period. Commercially insured and Medicare Advantage plan enrollees were observed for 1 year before (baseline period) and 540 days after therapy initiation (follow-up period). Outcomes included closed fractures, all-cause medical costs, and all-cause hospitalizations; all outcomes were measured starting 180 days after therapy initiation through follow-up. All subjects had at least 2 pharmacy claims for any of the targeted osteoporosis medications. Adherence was measured with a medication possession ratio (MPR) and accounted for all osteoporosis treatment. High adherence was MPR of at least 0.80; low adherence was MPR less than 0.50. Covariates included baseline fracture, "early" fracture (in the first 180 days of follow-up), baseline corticosteroid or thyroid hormone use, health status indicators, and demographic characteristics. Outcome fractures were modeled with Cox survival regression with time-dependent cumulative MPR. All-cause medical costs and all-cause hospitalizations were modeled, respectively, with generalized linear model regression (gamma distribution, log link) and negative binomial regression.

RESULTS: The sample comprised 21,655 patients—16,295 (75.2%) commercial and 5,360 (24.8%) Medicare Advantage. During the entire follow-up period, 5,406 (33.2%) and 2,253 (42.0%) of commercial and Medicare Advantage patients, respectively, had low adherence. Adherence tended to decrease over the follow-up period. The Cox regression showed that commercial plan patients with low versus high adherence had 37% higher risk of fracture (hazard ratio = 1.37, 95% CI = 1.12-1.68). Adherence was not significantly associated with fracture in the Medicare Advantage cohort. Commercial and Medicare Advantage patients with low versus high adherence had 12% (exponentiated coefficient = 1.12, 95% CI = 1.02-1.24) and 18% (exponentiated coefficient = 1.18, 95% CI = 1.04-1.35) higher all-cause medical costs during months 7 through 18 of follow-up. Commercial and Medicare Advantage patients with low versus high adherence had 59% (incidence rate ratio [IRR] = 1.59, 95% CI = 1.38-1.83) and 34% (IRR = 1.34, 95% CI = 1.13-1.58) more all-cause hospitalizations during months 7 through 18 of follow-up, respectively.

CONCLUSIONS: Low adherence to osteoporosis pharmacotherapy was associated with higher risk of fracture for commercially insured but not Medicare Advantage patients and with higher all-cause medical costs and more all-cause hospitalizations in both groups. These results are consistent with the literature and highlight the importance of promoting better adherence among patients with osteoporosis.

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What is already known about this subject

• Osteoporosis is a public health problem. About 10 million individuals in the United States (80% women) have osteoporosis; another 34 million have low bone density.
• Patients with osteoporosis often have poor adherence to prescribed therapies. Previous analyses show that 50% or less of osteoporotic women are adherent (medication possession ratio [MPR] of at least 0.80) to therapy.
• Poor adherence is associated with undesirable clinical and economic outcomes. Prior research shows that nonadherence to alendronate and risedronate is associated with a higher risk of fracture and higher burden of illness measured with a variety of outcomes.

What this study adds

• Compared with previous research, the present study provides a more contemporary population from a large, geographically diverse health plan, allowing the inclusion of newer and less-examined therapies (ibandronate, raloxifene) and health care costs (not charges).
• Compared with high adherence (MPR of at least 0.80), low adherence (MPR less than 0.50) was associated with 37% higher likelihood of fracture in commercial patients after controlling for demographic, clinical, and fracture risk factors. High adherence was not associated with fracture risk in Medicare Advantage patients.
• For commercially insured and Medicare Advantage patients, respectively, regression-adjusted low adherence versus high adherence was associated with 12% and 18% higher all-cause medical costs and 59% and 34% more all-cause hospitalizations.
Osteoporosis is characterized by loss of bone mass and a structural deterioration of bone tissue. Reduced bone density associated with osteoporosis is a major risk factor for fracture, most notably of the hip, spine, and wrist. Epidemiological data show that an estimated 10 million people in the United States (8 million women) are diagnosed with osteoporosis. Another 34 million individuals have osteopenia (low bone density) that does not meet the criteria for osteoporosis. One-half of women and 25% of men aged 50 years or older will suffer from an osteoporosis-related fracture in their lifetimes.

Fractures resulting from bone disease are common and impose a substantial societal burden. Burge et al. (2007) estimated direct medical costs of osteoporosis in the United States at 13.7-20.3 billion in 2005 dollars. They also modeled U.S. fracture rates and costs until 2025, resulting in estimates of more than 3 million fractures and expenditures of $25.3 billion per year by 2025.

Therapies currently approved in the United States for the treatment of osteoporosis include bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), the selective estrogen receptor modulator raloxifene, calcitonin, and the parathyroid hormone teriparatide. Bisphosphonates are approved for the prevention and treatment of postmenopausal osteoporosis. Raloxifene is approved for use in postmenopausal women to treat or prevent osteoporosis and to reduce the risk of invasive breast cancer among those with osteoporosis. Estrogen/hormone therapy is approved for the prevention of osteoporosis. Teriparatide is an injectable form of human parathyroid hormone indicated for postmenopausal women and men at high risk for osteoporotic fracture. Denosumab, a receptor activator of nuclear factor kappa-B ligand (RANKL), was approved by the U.S. Food and Drug Administration in 2010 for treatment of postmenopausal women with osteopenia who have a high risk of fracture; it is injected subcutaneously every 6 months.

“Real-world” adherence to osteoporosis medications tends to be suboptimal. Analyses by Siris et al. (2006), Huybrechts et al. (2006), Recker et al. (2005), and Sunyecz et al. (2008) showed that less than 50% of osteoporotic women treated with daily and weekly bisphosphonates (with bisphosphonates or hormone replacement therapy in the study by Huybrechts et al.) were adherent to their medication regimens; adherence in all studies was defined as a medication possession ratio (MPR) of at least 80%.

Nonadherence with osteoporosis therapy has been associated with increased fracture risk. Huybrechts et al. found that nonadherence (MPR less than 80%) was significantly associated with a 16.7% higher risk of fracture. McCombs et al. (2004) modeled adherence rather than nonadherence and showed that adherence was associated with 61.8% lower odds of a hip fracture and 39.9% lower odds of vertebral fracture within a year of initiation of osteoporosis therapy. Siris et al. estimated the 24-month risk of fracture along the full spectrum of MPR values from 0.0 to 1.0 and found, importantly, that the regression-adjusted risk of fracture among women who were less than 50% adherent was substantially the same as the risk of fracture associated with no therapy.

Fractures can result in wide-ranging health care resource utilization and costs beyond the direct costs attributable to acute fracture treatment and follow-up. Osteoporotic fractures may also be associated with depression, functional impairment, cognitive impairment, pain, disability, and decline in lung function. Patients whose fractures are treated in inpatient facilities may require subsequent hospitalization for post-operative complications, such as chest infection, cardiac failure, deep vein thrombosis, or pneumonia. Moreover, there are costs associated with osteoporosis that are not specific to fracture, such as physician visits and bone density scans.

Huybrechts et al. found that nonadherence to osteoporosis therapy was associated with a 37.2% higher rate of all-cause hospitalizations per patient-month and higher mean total health care charges ($600 vs. $340 per patient per month, $<0.001). Sunyecz et al. showed that total medical costs were 3.5% lower for patients who were adherent on bisphosphonates compared with their nonadherent counterparts.

Adherent patients (defined as those with 360 days of continuous therapy in the first year after therapy initiation) in the study by McCombs et al. had lower expenditures for physician services during the first year of therapy (U.S. $56 lower than nonadherent patients), hospital outpatient services ($38 lower), laboratory tests ($9 lower), and hospitalizations ($155); adherent patients also had 25.6% lower odds of hospital admissions compared with nonadherent patients.

Although multiple studies have examined the relationship between osteoporosis therapy adherence and fracture, relatively few have examined the broader relationships with costs and hospitalizations (a substantial cost driver). The purpose of this study was to examine clinical, economic, and health resource utilization consequences of osteoporosis in a sample that was updated and diverse.

This study provides several new contributions to the literature. First, the study period is contemporary and includes the more recently approved ibandronate, a monthly bisphosphonate; patient identification periods for the studies described above ranged from 1997 to 2003, and therapies did not include ibandronate. Moreover, raloxifene, a therapy not commonly studied, is included as 1 of the targeted osteoporosis therapies. Second, the costs in this study were computed from health plan and patient paid amounts, rather than from charges; charges may not accurately reflect the dollars expended for medical services. Third, this study separately analyzed outcomes in 2...
discrete populations: women enrolled in the commercial health plan, and women enrolled in the Medicare Advantage health plan. This approach was adopted principally because these populations are distinct with respect to health care delivery, reimbursement, and payers. Although it was beyond the scope of this study to examine the associations between the outcomes and characteristics of the health care delivery systems, we believe that separate analysis of the commercial and Medicare Advantage populations provides more information—information that would be useful in generating questions for further research—than would analyzing the populations together and controlling for health plan type in multivariate analysis.

Objectives
The objectives of this study were to examine the associations of adherence to osteoporosis medications with (a) occurrence of closed fracture, (b) all-cause medical costs, and (c) all-cause hospitalizations. All-cause medical costs and hospitalizations were measured to reflect the more pervasive consequences both of fracture and osteoporosis more generally.

Methods

Study Design and Data Source
This was a retrospective analysis of administrative claims data that examined adherence, fracture, total all-cause medical costs including plan and patient share, and all-cause inpatient stays for women diagnosed with osteoporosis and initiated on osteoporosis therapy. The data included medical claims, pharmacy claims, and eligibility information from a large, national U.S. health plan that offers both commercial and Medicare Advantage insurance. The individuals covered by this health plan, about 14 million per year, are geographically diverse across the United States, with greatest representation in the South and Midwest U.S. census regions. The plan provides full insurance coverage for professional (e.g., physician), facility (e.g., hospital), and outpatient prescription medication services. Medical (professional, facility) claims include International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, ICD-9-CM procedure codes, Current Procedural Terminology, Version 4 (CPT-4) procedure codes, Healthcare Common Procedure Coding System (HCPCS) procedure codes, site of service codes, health plan and patient costs, and coordination of benefits adjustment. Outpatient pharmacy claims provide National Drug Code (NDC) numbers for dispensed medications, quantity dispensed, drug strength, days supply, health plan and patient costs, and coordination of benefits adjustment. All study data were de-identified and accessed with protocols compliant with the Health Insurance Portability and Accountability Act; expedited review by the Privacy Board associated with the New England Institutional Review Board was conducted, and this research project was approved on April 25, 2008.

Patient Identification
The study sample included women who were aged 45 years or older, diagnosed with osteoporosis, and initiated on alendronate, ibandronate, raloxifene, or risedronate. All patients had at least 1 medical claim with a primary or secondary diagnosis of osteoporosis (ICD-9-CM 733.0x) during the identification period of July 1, 2002, through March 10, 2006, and at least 2 pharmacy claims for any of the following osteoporosis therapies following the first observed claim with an osteoporosis diagnosis: alendronate (5 milligram [mg], 10 mg, 35 mg, 70 mg), ibandronate, raloxifene, or risedronate (5 mg, 35 mg). Medications were identified with NDC numbers. Examination of all pharmacy claims for the bisphosphonates showed that 96.2% of risedronate claims were for weekly risedronate, 97.2% of claims for alendronate were for weekly alendronate, and 99.2% of claims for ibandronate were for monthly ibandronate. The service date of the first pharmacy claim for a designated osteoporosis medication was defined as the index date and the medication was the index therapy. The criterion of at least 2 osteoporosis therapy claims was imposed to focus on women who were treated for a minimum time while allowing for variation in adherence.

In addition, patients were continuously enrolled, with medical and pharmacy benefits, in the commercial or Medicare Advantage plan for 12 months before the index date (baseline period) and 540 days after the index date (follow-up period) and had no pharmacy claims for alendronate, ibandronate, raloxifene, risedronate, or teriparatide during their baseline periods. The 540-day follow-up period was selected to allow the osteoporosis medications to achieve their therapeutic effects over the first 180 days and then to observe the study sample for 1 year (i.e., 12 consecutive 30-day intervals) after those first 180 days. The entire study period was from July 1, 2001, the earliest start date of the baseline period, through August 31, 2007, the latest end date of the follow-up period.

Patients with any pharmacy claims for alendronate with 40 mg strength (indicated for Paget’s disease of the bone), risedronate with 30 mg strength (indicated for Paget’s disease of the bone), or calcitriol (indicated for hypocalcemia) anytime during the baseline or follow-up periods were excluded in order to focus on patients treated specifically for osteoporosis. Patients with other conditions treated with the study medications were also excluded. Those conditions were Paget’s disease of the bone and other osteitis deformans and osteopathies, osteogenesis imperfecta, hypercalcemia, malignant cancer, human immunodeficiency virus (HIV), and preventive treatment for breast cancer (Appendix).

Variables
The study outcomes were closed fracture, all-cause medical costs, and all-cause hospitalizations. Closed fractures were identified with primary or secondary diagnosis codes,
ICD-9-CM procedure codes, or CPT codes on at least 1 medical claim (Appendix); the codes were based largely on previous work by Huybrechts et al. (2006) and Weycker et al. (2008). The occurrence of an outcome fracture was defined as at least 1 medical claim with a fracture code, a service date 180 days or more after the index date, and no medical claims with fracture codes in the same fracture site for at least the previous 6 months in order to capture new fractures. The 180-day post-index date criterion was imposed to provide time for the osteoporosis therapies to achieve their therapeutic effects. The check for previous fractures at the same site was used to avoid misclassifying ongoing care for a previous fracture as a new fracture.

All-cause medical costs were the sum of health plan and patient paid amounts for all medical claims from 180 days following the index date through the end of the follow-up period. Costs were adjusted to 2006 dollars using the medical care component of the Consumer Price Index and were adjusted for coordination of benefits based on estimated payments from other payers. The third outcome was the number of all-cause inpatient hospitalizations from 180 days after the index date through the end of the follow-up period. Hospitalizations were measured with a combination of revenue codes and American Hospital Association place-of-service codes.

Adherence was measured with an MPR based on pharmacy claims for any of the designated osteoporosis medications (i.e., both index and nonindex therapies); the objective was to measure the overall impact of osteoporosis therapy, although adherence to the index therapy was also examined. MPR was calculated by dividing the cumulative days supply of osteoporosis medication(s) by the number of days of follow-up. For MPR measured through the entire follow-up period, the denominator was 540 days. Cumulative days supply represents the number of days during the follow-up period when the patients were in possession of their medications; days during which patients possessed more than 1 osteoporosis therapy were counted only once. We assumed that osteoporosis medications were provided to patients during inpatient hospitalizations and adjusted the MPR numerator to account for prescription fills that were interrupted by inpatient stays. Continuous MPR was converted to a categorical variable: “high” adherence was MPR of at least 0.80, “moderate” adherence was MPR of at least 0.50 and less than 0.80, and “low” adherence was MPR less than 0.50.

Binary indicators of fracture risk included early fracture and baseline fracture. Early fracture was defined as at least 1 medical claim with a fracture code and service date during the first 180 days of follow-up including the index date. Baseline fracture was defined as at least 1 medical claim with a fracture code and service date during the baseline period. Drug-related fracture risk during the baseline period identified patients either with oral steroid use, defined as at least 2 pharmacy claims and at least 30 cumulative days supply of corticosteroids, or with thyroid hormone use, defined as at least 1 fill of a thyroid hormone during the baseline period (Appendix).

Health status variables, measured during baseline, included an administrative claims-based Charlson Comorbidity Index score, number of medications defined as unique chemical compounds (e.g., simvastatin would be counted as 1 medication whether the NDC number was for Zocor or for generic simvastatin), not including targeted osteoporosis medications, used during baseline as a measure of polypharmacy; and binary indicators for nontraumatic joint disorders; spondylosis, intervertebral disc disorders, and other back problems; other connective tissue disease; other bone disease and musculoskeletal deformities; disorders of lipid metabolism; eye disorders; respiratory infection; and diseases of female genital organs. All binary health status indicators were computed from the diagnosis-based Clinical Classification Software managed by the Agency for Healthcare Research and Quality. The conditions were selected based on clinical relevance to the outcomes and prevalence within the study population and were distinct from the conditions represented in the CCI. Demographic variables were age and U.S. census region.

Statistical Analysis

Descriptive summary statistics were obtained for all study measures. Commercial and Medicare Advantage patients were analyzed separately. The focus of the analysis was the difference in outcomes between patients with low and high adherence. Patients with moderate adherence and indicators for moderate adherence were included in all analyses. Differences in mean values were tested with t-tests for independent samples, accounting for unequal variance as appropriate. Differences in categorical variables were evaluated with Pearson chi-square tests.

Outcome fractures were analyzed with Cox survival regression with time-dependent cumulative adherence. The dependent variable was time to the first observed outcome fracture. Patients’ adherence levels (low, moderate, high) were calculated from the index date in cumulative 30-day intervals, and the appropriate cumulative adherence was applied to each observed outcome fracture. For example, if a patient had MPR = 1.0 in the first 30 days of follow-up and MPR = 0.70 during days 31-60 of follow-up, the cumulative MPR for the first 60 days of follow-up would be 0.85. If this patient’s MPR during days 61-90 of the follow-up period were 0.70 again, the cumulative MPR for the first 90 days of follow-up would be 0.80. This process of computing and updating cumulative MPR continued for each patient throughout the length of follow-up. When a fracture occurred, the cumulative MPR for the period preceding the fracture was applied; for instance, if a fracture occurred on day 220 of a patient’s follow-up period, the cumulative MPR through day 210 would be the time-dependent covariate.

Two specifications of this model were estimated. The first specification (bivariate model) had only 2 covariates,
time-dependent low adherence and time-dependent moderate adherence, in order to estimate the adjusted bivariate relationship between cumulative time-dependent adherence and fracture. The second specification (full model) also controlled for demographic characteristics, health status characteristics, and fracture risk factors (Table 1). Coefficients were computed as hazard ratios (HRs).

All-cause medical costs from 180 days after the index date through the end of follow-up (i.e., from the seventh through eighteenth 30-day intervals of follow-up) were modeled with a generalized linear model (GLM) with gamma distribution and log link. This period was selected to be consistent with the period during which outcome fractures were measured and to model all-cause medical costs after the time needed for the osteoporosis medications to achieve their therapeutic effects. The gamma distribution was selected based on the results of the Park test. Coefficients were exponentiated to provide a ratio of costs for each covariate. Covariates are shown in Table 1.

All-cause inpatient hospitalizations from 180 days after the index date through the end of the follow-up period (same rationale as all-cause medical costs and outcome fractures) were modeled with negative binomial regression; negative binomial was selected as the estimator based on dispersion of the data ($P < 0.001$ in the likelihood ratio test of $\alpha = 0$). Coefficients were computed as incidence rate ratios (IRRs). Covariates are listed in Table 1.

All analyses were conducted with SAS version 9 (SAS Institute, Inc., Cary, NC) and Stata version 10 (StataCorp LC, College Station, TX). The a priori $\alpha$ value of 0.05 was used for all analyses.

### Results

The study sample included 21,655 patients, 16,295 ($75.2\%$) from the commercial plan and 5,360 ($24.8\%$) from the Medicare Advantage plan. Figure 1 shows subject selection and attrition. Mean (standard deviation [SD]) ages for commercial and Medicare Advantage plan patients, respectively, were 59.3 (8.6) and 75.7 (6.5) years. Summary statistics for demographic, health status, and fracture risk factor measures are provided in Table 2. In both the commercial and Medicare Advantage groups, patients with high adherence were significantly more likely than those with low adherence to have a CCI score equal to zero (commercial: $73.7\%$ vs. $66.6\%$, respectively; Medicare Advantage: $55.6\%$ vs. $49.1\%$, respectively; both $P < 0.001$).

Approximately $88\%$ of patients in both the commercial and Medicare Advantage groups used only 1 of the 4 selected therapies throughout follow-up (data on individual therapies not shown in tables). Alendronate was the most prevalent therapy, used by $45.3\%$ of commercial patients and $50.1\%$ of Medicare Advantage patients. Risedronate was the next most frequently observed therapy ($31.9\%$ of commercial patients, $25.5\%$ of Medicare Advantage patients). Ibendronate was used by $3.2\%$ and $2.4\%$ of commercial and Medicare Advantage patients, respectively. Raloxifene was the osteoporosis therapy for

### Table 1: Summary of Covariates Used in Multivariate Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rationale</th>
<th>Cox Regression Analysis of Outcomes Fractures</th>
<th>Generalized Linear Model of All-Cause Medical Cost</th>
<th>Negative Binomial Regression of All-Cause Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low adherence (MPR less than 0.50) and moderate adherence (MPR at least 0.50 and less than 0.80)</td>
<td>Measure the principal relationships of interest, reference adherence level is high adherence (MPR at least 0.80)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Baseline medication count</td>
<td>Reflects burden of illness and contact with medical system</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Early hospitalization</td>
<td>Represents risk factor associated with subsequent all-cause hospitalization</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Baseline fracture, early fracture, baseline corticosteroid or thyroid hormone use</td>
<td>Represent factors that could be associated with fractures and fracture-related medical services and, consequently, the outcomes</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Baseline CCI score</td>
<td>Reflects general health status</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Baseline disorders of lipid metabolism, eye disorders, respiratory infection, and diseases of female genital organs</td>
<td>Represent prevalent comorbid conditions in study sample and potential predictors of costs and hospitalization</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Baseline nontraumatic joint disorders, spondylitis, intervertebral disc disorders, and other back problems; other connective tissue disease; and other bone disease and musculoskeletal deformities</td>
<td>Represent prevalent bone-related risk factors that could affect the outcomes</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Age, geographic region</td>
<td>Demographic characteristics</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

CCI = Charlson Comorbidity Index; MPR = medication possession ratio.
In addition to diagnoses identified using ICD-9-CM codes (Appendix), at least 70% of patients with low adherence on alendronate, ibandronate, raloxifene, or risedronate therapies over their follow-up periods; 33.2% (n = 5,406) and 42.0% (n = 2,253) of commercial and Medicare Advantage patients, respectively, had low adherence (MPR less than 0.50). Adherence, on average, declined over the follow-up period, as shown in Figure 2. For the first 180 days and subsequent 360 days (days 181-540) of follow-up in the commercially insured group, mean (SD) MPRs were 0.76 (0.25) and 0.59 (0.36), respectively. The corresponding MPRs in the Medicare Advantage group were 0.68 (0.28) during the first 180 days of follow-up and 0.53 (0.37) during the next 360 days (data not shown in tables).

Adherence in the commercial group appeared to be fairly consistent across individual osteoporosis therapies: 32.0% of commercial patients had low adherence on alendronate; 30.0% on ibandronate; 31.8% on raloxifene; 31.4% on risedronate; and 43.3% on multiple osteoporosis therapies. Adherence to individual therapies varied somewhat among Medicare Advantage patients: 42.7%, 28.5%, 37.9%, 44.0%, and 41.1% had low adherence on alendronate, ibandronate, raloxifene, risedronate, and multiple therapies, respectively (data not shown in tables).

Table 3 provides the summary values of the outcome measures overall and for each adherence subgroup based on MPR during the entire follow-up period. The rates of outcome fractures (e.g., fractures that occurred at least 180 days after the index date) were 3.2% (n = 520) in the commercial group (3.0% vs. 3.6% for patients with high vs. low adherence, respectively, P = 0.044) and 5.9% (n = 318) in the Medicare Advantage group (5.8% vs. 6.2% for patients with high vs. low adherence, respectively, P = 0.601).

The majority of patients (93.1% of commercial, 84.1% of Medicare Advantage) had no (zero) outcome hospitalizations (all-cause hospitalizations from 180 days after their index dates through the end of their follow-up periods). Commercial plan patients with high adherence were more likely to have no (zero) outcome hospitalizations compared with patients with low adherence (94.5% vs. 91.3%, respectively, P < 0.001); 86.4% of Medicare Advantage patients with high adherence versus 82.3% of those with low adherence had no outcome hospitalizations (P = 0.004). Mean (SD) all-cause medical costs after the first 180 days of follow-up were $4,824 ($13,875) and $5,329 ($11,769) in the commercial and Medicare Advantage groups, respectively. Mean all-cause medical costs after the first 180 days of follow-up were lower among patients with high adherence in both groups relative to patients with low adherence. Mean (SD) all-cause medical costs for commercial plan patients with high and low adherence, respectively, were $4,295 ($13,179) and $5,596 ($15,291, P < 0.001). Mean (SD) all-cause medical costs were $4,590 ($10,797) for Medicare Advantage patients with high adherence versus $5,801 ($12,378) for those with low adherence (P < 0.001).

Results from the Cox survival regression with time-dependent adherence showed that commercial patients with low adherence, P = 0.004).
### Table 2: Demographic Characteristics, Health Status, and Fracture Risk Factors: Summary Statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Commercial Plan Patients</th>
<th>Medicare Advantage Plan Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All n = 16,295</td>
<td>High Adherence n = 6,955</td>
</tr>
<tr>
<td></td>
<td>Mean [SD]</td>
<td>Mean [SD]</td>
</tr>
<tr>
<td>Age (years)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>59.3 [8.6]</td>
<td>60.1 [8.8]</td>
</tr>
<tr>
<td>Baseline medication count&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.5 [5.6]</td>
<td>5.9 [5.1]</td>
</tr>
<tr>
<td>Baseline CCI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11,491 (70.5)</td>
<td>5,126 (73.7)</td>
</tr>
<tr>
<td>1</td>
<td>3,340 (20.5)</td>
<td>1,278 (18.4)</td>
</tr>
<tr>
<td>2</td>
<td>956 (5.9)</td>
<td>363 (5.2)</td>
</tr>
<tr>
<td>3</td>
<td>314 (1.9)</td>
<td>120 (1.7)</td>
</tr>
<tr>
<td>4</td>
<td>134 (0.8)</td>
<td>49 (0.7)</td>
</tr>
<tr>
<td>5 or more</td>
<td>60 (0.4)</td>
<td>19 (0.3)</td>
</tr>
<tr>
<td>Baseline health status conditions&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontraumatic joint disorders</td>
<td>5,729 (35.2)</td>
<td>2,272 (32.7)</td>
</tr>
<tr>
<td>Spondylosis, intervertebral disc disorders, other back problems</td>
<td>4,556 (28.0)</td>
<td>1,696 (24.4)</td>
</tr>
<tr>
<td>Other connective tissue disease</td>
<td>5,391 (33.1)</td>
<td>2,202 (31.7)</td>
</tr>
<tr>
<td>Other bone disease and musculoskeletal deformities</td>
<td>5,982 (36.7)</td>
<td>2,607 (37.5)</td>
</tr>
<tr>
<td>Disorders of lipid metabolism</td>
<td>7,098 (43.6)</td>
<td>2,943 (42.3)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>5,545 (34.0)</td>
<td>2,558 (36.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5,509 (33.8)</td>
<td>2,257 (32.5)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>4,425 (27.2)</td>
<td>1,788 (25.7)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>4,909 (30.1)</td>
<td>1,858 (26.7)</td>
</tr>
<tr>
<td>Diseases of female genital organs</td>
<td>10,962 (67.3)</td>
<td>4,825 (69.4)</td>
</tr>
<tr>
<td>Fracture risk factors&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline fracture</td>
<td>1,151 (7.1)</td>
<td>475 (6.8)</td>
</tr>
<tr>
<td>Early fracture</td>
<td>647 (4.0)</td>
<td>271 (3.9)</td>
</tr>
<tr>
<td>Baseline corticosteroid or thyroid hormone use&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2,917 (17.9)</td>
<td>1,233 (17.7)</td>
</tr>
<tr>
<td>U.S. census region&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>2,169 (13.3)</td>
<td>1,000 (14.4)</td>
</tr>
<tr>
<td>Midwest</td>
<td>4,650 (28.5)</td>
<td>2,190 (31.5)</td>
</tr>
<tr>
<td>South</td>
<td>7,353 (45.1)</td>
<td>2,741 (39.4)</td>
</tr>
<tr>
<td>West</td>
<td>2,123 (13.0)</td>
<td>1,024 (14.7)</td>
</tr>
</tbody>
</table>

|                   | Low Adherence n = 3,934 | Low Adherence n = 5,406 |
|                   | Mean [SD]               | Mean [SD]               |
| Age (years)<sup>b</sup>               | 58.9 [8.5]              | 58.4 [8.2]               |
| Baseline medication count<sup>c</sup> | 6.5 [5.5]               | 7.2 [6.0]               |
| Baseline CCI score                    |                      | <0.001                  |
| 0                                     | 2,783 (51.9)           | 1,003 (55.6)            |
| 1                                     | 1,451 (27.1)           | 455 (25.2)              |
| 2                                     | 659 (12.3)             | 185 (10.3)              |
| 3                                     | 287 (5.4)              | 97 (5.4)                |
| 4                                     | 104 (1.9)              | 37 (2.1)                |
| 5 or more                             | 76 (1.4)               | 27 (1.5)                |
| Baseline health status conditions<sup>d</sup> |                      |                                |
| Nontraumatic joint disorders          | 2,582 (48.2)           | 817 (45.3)              |
| Spondylosis, intervertebral disc disorders, other back problems | 1,646 (30.7) | 502 (27.8) |
| Other connective tissue disease       | 1,880 (35.1)           | 599 (33.2)              |
| Other bone disease and musculoskeletal deformities | 1,384 (25.8) | 483 (26.8) |
| Disorders of lipid metabolism         | 3,172 (59.2)           | 1,065 (59.0)            |
| Eye disorders                         | 3,262 (60.9)           | 1,146 (63.5)            |
| Hypertension                          | 3,528 (65.8)           | 1,187 (65.8)            |
| Heart disease                         | 2,150 (40.1)           | 678 (37.6)              |
| Respiratory infections                | 1,281 (23.9)           | 381 (21.1)              |
| Diseases of female genital organs     | 1,986 (37.1)           | 765 (37.4)              |
| Fracture risk factors<sup>f</sup>     |                          |                                |
| Baseline fracture                     | 685 (12.8)             | 228 (12.6)              |
| Early fracture                        | 365 (6.8)              | 112 (6.2)               |
| Baseline corticosteroid or thyroid hormone use<sup>g</sup> | 883 (16.5) | 296 (16.4) |
| U.S. census region<sup>e</sup>        |                          |                                |
| Northeast                             | 166 (12.4)             | 193 (10.7)              |
| Midwest                               | 2,893 (34.0)           | 1,036 (37.4)            |
| South                                 | 1,802 (33.0)           | 573 (31.8)              |
| West                                  | 6 (0.0)                | 2 (0.1)                 |

<sup>a</sup>Patient groups are categorized by adherence measured from index date through the end of follow-up period. Low adherence is MPR less than 0.50; moderate adherence is MPR at least 0.50 and less than 0.80; high adherence is MPR at least 0.80. Column percentages may not sum to 100% due to rounding. P values compare the high-versus low-adherence groups using t-tests for independent samples for continuous variables and Pearson chi-square tests for categorical variables.

<sup>b</sup>Age and census region were as of index year.

<sup>c</sup>CCI score was Quan et al. (2005)<sup>22</sup> claims-based adaptation of Charlson score measured during 1-year baseline (pre-index) period.

<sup>d</sup>Baseline health status conditions show numbers and proportions of patients with designated conditions based on diagnosis-based Clinical Classification Software managed by the Agency for Healthcare Research and Quality<sup>23</sup> and measured during 1-year baseline (pre-index) period.

<sup>e</sup>Fracture risk factors show numbers and proportions of patients with fracture-related diagnoses or procedures in Appendix. Baseline is 1-year pre-index; early is first 180 days of follow-up period, including index date.

<sup>f</sup>Baseline corticosteroid or thyroid hormone use shows numbers and proportions of patients with corticosteroid or thyroid hormone use measured with agents shown in Appendix during 1-year baseline (pre-index).

<sup>g</sup>Baseline corticosteroid or thyroid hormone use shows numbers and proportions of patients with corticosteroid or thyroid hormone use measured with agents shown in Appendix during 1-year baseline (pre-index).

CCI = Charlson Comorbidity Index; MPR = medication possession ratio; SD = standard deviation.
adherence were more likely than were patients with high adherence to have an outcome fracture (Table 4). The bivariate models of fracture and time-dependent cumulative adherence indicate that commercial patients with low adherence were 42% more likely than were those with high adherence to have a fracture (HR = 1.42, 95% confidence interval [CI] = 1.17-1.74, \( P < 0.001 \)). When the covariates were controlled, low adherence among commercial patients was associated with a 37% higher fracture risk (HR = 1.37, 95% CI = 1.12-1.68, \( P = 0.002 \)). The HRs for low adherence in the Medicare Advantage group and for moderate adherence in both groups were not significant in any model. In addition, early fracture, baseline fracture, baseline CCI score, and baseline spondylosis, intervertebral disc disorders, and other back problems were significantly and positively associated with increased likelihood of fracture in both groups. Age 65 years or older was positively associated with the risk of fracture compared with age younger than 55 years in the commercial group; the HR for age 75 years or older compared with age younger than 75 years was not significant in the Medicare Advantage group.

In the GLMs, low osteoporosis therapy adherence throughout follow-up was associated with significantly higher all-cause medical costs after the first 180 days of follow-up relative to high adherence (Table 5). Low adherence compared with high adherence was associated with 12% higher medical costs (exponentiated coefficient = 1.12, 95% CI = 1.02-1.24, \( P = 0.022 \)) in the commercial group and with 18% higher medical costs (exponentiated coefficient = 1.18, 95% CI = 1.04-1.35, \( P = 0.012 \)) in the Medicare Advantage group. Moderate adherence compared with high adherence was also significantly and positively associated with higher all-cause medical costs after the first 180 days of follow-up in the Medicare Advantage group (exponentiated coefficient = 1.21, 95% CI = 1.04-1.40, \( P = 0.015 \)), but was not significant in the commercial group. Baseline number of medications, baseline CCI score, baseline spondylosis, intervertebral disc disorders and other back problems, and age (65 years or older compared with younger than 55 for commercial patients and 75 years or older compared with younger than 75 years for Medicare Advantage patients) were significantly and positively associated with all-cause medical costs after the first 180 days of follow-up for both groups.

In negative binomial regression models, low adherence compared with high adherence was associated with more all-cause hospitalizations after the first 180 days of
The Association of Adherence to Osteoporosis Therapies with Fracture, All-Cause Medical Costs, and All-Cause Hospitalizations: A Retrospective Claims Analysis of Female Health Plan Enrollees with Osteoporosis

### Table 3: Outcomes and Adherence: Summary Statistics

<table>
<thead>
<tr>
<th></th>
<th>Commercial Plan Patients</th>
<th>Medicare Advantage Plan Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
<td>High adherence n = 6,955</td>
<td>High adherence n = 1,804</td>
</tr>
<tr>
<td></td>
<td>Moderate adherence n = 3,934</td>
<td>Moderate adherence n = 1,303</td>
</tr>
<tr>
<td></td>
<td>Low adherence n = 5,406</td>
<td>Low adherence n = 2,253</td>
</tr>
<tr>
<td><strong>P-value (High/Low)</strong></td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with at least 1 outcome fracture(a)</td>
<td>520 (3.2)</td>
<td>318 (5.9)</td>
</tr>
<tr>
<td>0</td>
<td>13,169 (93.1)</td>
<td>4,505 (84.1)</td>
</tr>
<tr>
<td>1</td>
<td>932 (5.7)</td>
<td>1,558 (86.4)</td>
</tr>
<tr>
<td>2</td>
<td>137 (0.8)</td>
<td>149 (11.4)</td>
</tr>
<tr>
<td>3 or more</td>
<td>57 (0.3)</td>
<td>305 (13.5)</td>
</tr>
<tr>
<td>Mean [SD]</td>
<td>4.824 [13,875]</td>
<td>5.329 [11,769]</td>
</tr>
<tr>
<td>All-cause hospitalizations after first 180 days of follow-up(c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause medical costs after first 180 days of follow-up(d)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a\)Patients are grouped by categories of adherence measured from index date through the end of follow-up period. Low adherence is MPR less than 0.50; moderate adherence is MPR at least 0.50 and less than 0.80; high adherence is MPR at least 0.80. Column percentages may not sum to 100% due to rounding. P values compare the high versus low-adherence groups using t-tests for independent samples for continuous variables and Pearson chi-square tests for categorical variables.

\(b\)Outcome fractures were measured with diagnosis or procedure codes in the Appendix from 180 days after index date through end of follow-up period.

\(c\)All-cause hospitalizations show numbers and proportions of patients with designated number of all-cause hospitalizations from 180 days after index date through the end of the follow-up period. Hospitalizations were measured using a combination of revenue codes and place-of-service codes.

\(d\)All-cause medical costs are reported as 2006 U.S. dollars. Costs were measured from 180 days after index date through the end of the follow-up period.

Follow-up (Table 6). Commercial patients with low adherence had 59% more hospitalizations (IRR = 1.59, 95% CI = 1.38-1.83, P < 0.001), and Medicare Advantage patients with low adherence had 34% more hospitalizations (IRR = 1.34, 95% CI = 1.13-1.58, P = 0.001) compared with patients with high adherence. Commercial patients with moderate adherence had 29% more hospitalizations (IRR = 1.29, 95% CI = 1.10-1.52, P = 0.002) relative to those with high adherence, but the IRR for moderate adherence was not significant in the Medicare Advantage group (P = 0.589). Other positive and significant predictors for both groups were hospitalizations within the first 180 days of follow-up, baseline corticosteroid or thyroid hormone use, baseline CCI score, baseline respiratory infections, baseline spondylosis, intervertebral disc disorders or other back problems, and older age.

### Discussion

This retrospective analysis of women initiated on osteoporosis therapies was conducted with administrative claims data from one of the largest health plans in the United States and evaluated the association of adherence with several clinical and economic outcomes. Differences in outcomes between patients with low and high adherence were examined. The results establish that low adherence to osteoporosis therapy, defined for this study as MPR less than 0.50, was consistently associated with significantly more all-cause hospitalizations and higher all-cause medical costs compared with high adherence (MPR of at least 0.80). Low adherence was also associated with a significantly higher fracture risk, 37% higher compared with high adherence, in the commercial group. These results are largely consistent with the literature and published reviews on adherence and risk of fracture in osteoporosis.\(^7\)\(^-\)\(^9\)\(^,\)\(^13\)\(^-\)\(^29\) A recent systematic review evaluated the impact of adherence to osteoporosis medications, principally bisphosphonates, on fracture rates in 17 published studies and reported a fracture risk reduction of 17% to 39% in patients who achieved an MPR of at least 0.80.\(^30\)

The HR for low adherence was not significant in the outcome fracture model for the Medicare Advantage group. The adherence model results are consistent with the descriptive results for the Medicare Advantage group (Table 3) that show no significant differences in the rates of closed fracture across adherence categories. A recent study of Medicare beneficiaries enrolled in a Pennsylvania pharmacy coverage assistance program found that high adherence to oral bisphosphonates, defined as proportion of days covered of at least 0.80, was associated with 23% and 26% reductions in hip and vertebral fractures, respectively.\(^31\) There is not, however, a large body of research focusing specifically on osteoporosis medication adherence and fracture among elderly subjects, and no research, to the best of our knowledge, that focuses on patients who forgo traditional fee-for-service Medicare and enroll in...
Medicare Advantage plans.

Low adherence to osteoporosis therapy was associated with significantly more all-cause hospitalizations and higher all-cause medical costs after the first 180 days of follow-up in both the commercial and Medicare Advantage groups, consistent with prior research. These relationships may be attributable to clinical consequences associated with fracture, such as depression and pain; additional care related to fracture-related hospitalizations, such as rehospitalization for pneumonia; and to broader patterns of care for osteoporosis. They also may be indications of the impact of unobserved health behaviors (e.g., adherence to all prescribed medications, general health-seeking and maintenance behaviors). Further research is needed to better elucidate these relationships.

Consistent with published reviews, a substantial portion of the patient sample—33% to 42%—was nonadherent with osteoporosis therapy. Our data also show that adherence tended to decrease over time. Proportions of patients with low adherence appeared to be descriptively similar across weekly and monthly bisphosphonates, particularly in the larger commercial group. This result may be inconsistent with the favorable adherence profile of monthly bisphosphonates over weekly bisphosphonates reported in a previous retrospective study.

Poor medication adherence is a common problem in the treatment of many chronic conditions and is attributable to many factors at the patient, physician, and health care sys-
Although many empirical studies have evaluated osteoporosis therapy adherence from the patient perspective, data from the physician perspective are sparse. Future studies should examine the timing of patient-physician interactions and their relationship with adherence, therapy modifications, and outcomes.

Limitations

There are inherent limitations associated with research conducted with administrative claims data. First, unobserved and unmeasured factors may have influenced the likelihood of adherence, the likelihood of closed fracture, or both. Examples of important unobserved factors include clinical measures not observed in claims, such as bone mineral density measures, and patient health behaviors. In addition, the hospitalization and cost outcomes investigated in this study were not specific to fracture. While providing valuable information, these analyses do not account as thoroughly as they might for other factors that influence these outcomes, so the effects of adherence to osteoporosis medications are likely conflated with other effects.

Second, we excluded individuals with only 1 pharmacy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Commercial Group (n = 16,295)</th>
<th>Medicare Advantage Group (n = 5,360)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exponentiated Coefficient</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Low adherence</td>
<td>1.121</td>
<td>1.016–1.237</td>
</tr>
<tr>
<td>Moderate adherence</td>
<td>1.066</td>
<td>0.958–1.185</td>
</tr>
<tr>
<td>Baseline number of medications</td>
<td>1.060</td>
<td>1.050–1.070</td>
</tr>
<tr>
<td>Early fracture</td>
<td>1.197</td>
<td>0.946–1.514</td>
</tr>
<tr>
<td>Baseline fracture</td>
<td>1.070</td>
<td>0.891–1.283</td>
</tr>
<tr>
<td>Baseline corticosteroid or thyroid hormone use</td>
<td>0.947</td>
<td>0.845–1.061</td>
</tr>
<tr>
<td>Baseline CCI score</td>
<td>1.222</td>
<td>1.154–1.293</td>
</tr>
<tr>
<td>Baseline health status conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseases of lipid metabolism</td>
<td>0.945</td>
<td>0.867–1.029</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1.041</td>
<td>0.951–1.139</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>1.031</td>
<td>0.937–1.134</td>
</tr>
<tr>
<td>Diseases of female genital organs</td>
<td>0.925</td>
<td>0.842–1.015</td>
</tr>
<tr>
<td>Nontraumatic joint disorders</td>
<td>1.202</td>
<td>1.092–1.322</td>
</tr>
<tr>
<td>Spondylosis, intervertebral disc disorders, other back problems</td>
<td>1.108</td>
<td>1.003–1.225</td>
</tr>
<tr>
<td>Other connective tissue disease</td>
<td>1.195</td>
<td>1.083–1.318</td>
</tr>
<tr>
<td>Other bone disease, musculoskeletal deformities</td>
<td>1.013</td>
<td>0.928–1.107</td>
</tr>
<tr>
<td>Age 45 to 54 years</td>
<td>Reference category</td>
<td>NA</td>
</tr>
<tr>
<td>Age 55 to 64 years</td>
<td>1.025</td>
<td>0.930–1.130</td>
</tr>
<tr>
<td>Age 65 to 74 years</td>
<td>1.316</td>
<td>1.138–1.522</td>
</tr>
<tr>
<td>Age younger than 75 years</td>
<td>Reference category</td>
<td>NA</td>
</tr>
<tr>
<td>Age 75 years or older</td>
<td>1.404</td>
<td>1.173–1.680</td>
</tr>
<tr>
<td>U.S. census region: South</td>
<td>0.828</td>
<td>0.726–0.944</td>
</tr>
<tr>
<td>U.S. census region: West</td>
<td>0.894</td>
<td>0.760–1.052</td>
</tr>
<tr>
<td>U.S. census region: Midwest</td>
<td>0.829</td>
<td>0.721–0.952</td>
</tr>
<tr>
<td>U.S. census regions: Midwest or West</td>
<td>NA</td>
<td>0.876</td>
</tr>
</tbody>
</table>

*All-cause medical costs were measured after the first 180 days of the follow-up period through the end of the follow-up period and are reported in 2006 dollars. Deviance for commercial group = 26,616.3; deviance for Medicare Advantage group = 9,270.2.

Adherence was measured from the index date through the end of the follow-up period. Low adherence is MPR less than 0.50; moderate adherence is MPR at least 0.50 and less than 0.80; high adherence is MPR at least 0.80 and less than 0.90; moderate adherence is MPR at least 0.50 and less than 0.80; high adherence is MPR at least 0.80 and less than 0.90; high adherence was the reference category.

Baseline number of medications was count of unique compounds during 1-year baseline (pre-index) period.

Fractures were measured with fracture-related diagnoses or procedures in the Appendix. Early fracture was measured during the first 180 days of the follow-up period, including the index date; baseline fracture was measured during the 1-year baseline (pre-index) period.

Baseline corticosteroid or thyroid hormone use was measured with agents shown in Appendix during 1-year baseline (pre-index) period.

CCI score was Quan et al. (2005)22 claims-based adaptation of Charlson score measured during 1-year baseline (pre-index) period. Baseline health status conditions were measured with diagnosis-based Clinical Classification Software managed by the Agency for Healthcare Research and Quality.23

Age and U.S. census region were as of index year. Reference U.S. census region was Northeast; Midwest and West regions were combined for Medicare Advantage. CCI = Charlson Comorbidity Index; MPR = medication possession ratio; NA = not applicable.
The Association of Adherence to Osteoporosis Therapies with Fracture, All-Cause Medical Costs, and All-Cause Hospitalizations: A Retrospective Claims Analysis of Female Health Plan Enrollees with Osteoporosis

TABLE 6

Negative Binomial Regression Analysis of All-Cause Hospitalizations During Months 7 Through 18 of Follow-Up*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Commercial Group (n = 16,295)</th>
<th></th>
<th></th>
<th></th>
<th>Medicare Advantage Group (n = 5,360)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospitalization Incidence Rate</td>
<td>95% Confidence Interval</td>
<td>P-value</td>
<td>Hospitalization Incidence Rate</td>
<td>95% Confidence Interval</td>
<td>P-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low adherence</td>
<td>1.586</td>
<td>1.375–1.829</td>
<td>&lt;0.001</td>
<td>1.338</td>
<td>1.133–1.581</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate adherence</td>
<td>1.291</td>
<td>1.099–1.516</td>
<td>0.002</td>
<td>1.203</td>
<td>0.994–1.456</td>
<td>0.058</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early hospitalization</td>
<td>2.392</td>
<td>1.945–2.942</td>
<td>&lt;0.001</td>
<td>2.065</td>
<td>1.674–2.548</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early fracture</td>
<td>1.176</td>
<td>0.913–1.514</td>
<td>0.210</td>
<td>0.976</td>
<td>0.747–1.275</td>
<td>0.857</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline fracture</td>
<td>1.315</td>
<td>1.070–1.616</td>
<td>0.009</td>
<td>1.108</td>
<td>0.897–1.370</td>
<td>0.341</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline corticosteroid or thyroid hormone use</td>
<td>1.227</td>
<td>1.063–1.416</td>
<td>0.005</td>
<td>1.271</td>
<td>1.067–1.515</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CCI score</td>
<td>1.395</td>
<td>1.319–1.474</td>
<td>&lt;0.001</td>
<td>1.287</td>
<td>1.218–1.360</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline health status conditions</td>
<td>0.903</td>
<td>0.797–1.022</td>
<td>0.105</td>
<td>0.897</td>
<td>0.776–1.036</td>
<td>0.139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseases of lipid metabolism</td>
<td>1.088</td>
<td>0.958–1.235</td>
<td>0.195</td>
<td>0.839</td>
<td>0.726–0.970</td>
<td>0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1.227</td>
<td>1.079–1.394</td>
<td>0.002</td>
<td>1.317</td>
<td>1.125–1.541</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Respiratory infections</td>
<td>0.860</td>
<td>0.755–0.979</td>
<td>0.023</td>
<td>0.899</td>
<td>0.774–1.045</td>
<td>0.167</td>
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</tr>
<tr>
<td>Diseases of female genital organs</td>
<td>1.339</td>
<td>1.171–1.531</td>
<td>&lt;0.001</td>
<td>1.066</td>
<td>0.912–1.245</td>
<td>0.421</td>
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</tr>
<tr>
<td>Nontraumatic joint disorders</td>
<td>1.308</td>
<td>1.145–1.493</td>
<td>&lt;0.001</td>
<td>1.473</td>
<td>1.262–1.719</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Spondylosis, intervertebral disc disorders, other back problems</td>
<td>1.307</td>
<td>1.142–1.494</td>
<td>&lt;0.001</td>
<td>0.972</td>
<td>0.831–1.135</td>
<td>0.717</td>
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<tr>
<td>Other connective tissue disease</td>
<td>0.911</td>
<td>0.801–1.037</td>
<td>0.158</td>
<td>0.824</td>
<td>0.698–0.974</td>
<td>0.023</td>
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<td></td>
</tr>
<tr>
<td>Other bone disease, musculoskeletal deformities</td>
<td>2.418</td>
<td>1.953–2.933</td>
<td>&lt;0.001</td>
<td>1.486</td>
<td>1.279–1.727</td>
<td>&lt;0.001</td>
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<td></td>
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<tr>
<td>U.S. census region: South</td>
<td>1.046</td>
<td>0.865–1.264</td>
<td>0.045</td>
<td>1.145</td>
<td>0.897–1.463</td>
<td>0.277</td>
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<tr>
<td>U.S. census region: West</td>
<td>0.823</td>
<td>0.643–1.053</td>
<td>0.122</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. census region: Midwest</td>
<td>1.139</td>
<td>0.934–1.388</td>
<td>0.199</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. census regions: Midwest or West</td>
<td>NA</td>
<td>1.235</td>
<td>0.978–1.560</td>
<td>0.076</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*Hospitalizations were measured using a combination of revenue codes and place-of-service codes. Outcome hospitalizations were measured from 180 days after index date through the end of the follow-up period.

- Adherence was measured from the index date through the end of the follow-up period. Low adherence is MPR less than 0.50; moderate adherence is MPR at least 0.50 and less than 0.80; high adherence is MPR at least 0.80. High adherence was the reference category.

- Early hospitalization was measured during the first 180 days of follow-up including the index date.

- Early fractures were measured with fracture-related diagnoses or procedures in the Appendix. Early fracture was measured during the first 180 days of the follow-up period, including the index date; baseline fracture was measured during the 1-year baseline (pre-index) period.

- Baseline corticosteroid or thyroid hormone use was measured with agents shown in Appendix during 1-year baseline (pre-index) period.

- CCI score was Quan et al. (2005) claims-based adaptation of Charlson score measured during 1-year baseline (pre-index) period. Baseline health status conditions were measured with diagnosis-based Clinical Classification Software managed by the Agency for Healthcare Research and Quality.

- Age and U.S. census region were as of index year. Reference U.S. census region was Northeast; Midwest and West regions were combined for Medicare Advantage. CCI = Charlson Comorbidity Index; MPR = medication possession ratio; NA = not applicable.

claim (i.e., their index date claim) for an osteoporosis therapy. We excluded 2,372 commercial patients and 1,037 Medicare Advantage patients from the study sample for this reason. Although women who stopped osteoporosis therapy after their initial fills were part of a “real-world” population, we limited the study sample to women with a minimum threshold of osteoporosis therapy exposure (at least 2 pharmacy claims) because of the focus on fracture, while retaining variation in adherence and sufficient population size. Generalizability of these study results is, therefore, somewhat limited.

Third, we included patients who used multiple osteoporosis therapies in the study sample. Typically, patients switch medications because of some problems with their initial therapies (e.g., side effects or complicated dosing regimen), and they may therefore differ from patients who continue to use the initially prescribed medication in ways related to adherence. Future research should examine whether switching between osteoporosis medications has an impact on the risk of fracture because of the effect of switching on adherence, as well as whether switching is associated with the risk of fracture independent of adherence.

Fourth, a pharmacy claim for a filled prescription does not
indicate that the medication was consumed as prescribed. Fifth, MPR is measured over a designated period; for example, a patient observed over 1 year could have an MPR of 0.50 if she were (a) fully adherent over the first 6 months of observation and fully nonadherent over the second 6 months, (b) fully nonadherent over the first 6 months and fully adherent over the second 6 months, or (c) adherent and then nonadherent in alternating months. The analyses that examined the relationships between adherence and medical costs and inpatient hospitalizations do not allow us to make distinctions or draw inferences about variations in the effects of different patterns of adherence. The fracture regressions accounted for changing adherence through the use of time-dependent cumulative adherence, although the impact of different patterns of adherence cannot be interpreted from the HRs.

Sixth, not all osteoporosis therapies were included in this analysis: hormone replacement therapy was not included as an index therapy because its use was decreasing during the study period.

Conclusions

To our knowledge, this is the first study that has examined the impact of osteoporosis therapies on fractures, medical costs, and hospitalizations across both commercial and Medicare populations. The results were largely consistent with the literature and corroborate results highlighting the importance of achieving and maintaining treatment adherence to receive the therapeutic and economic benefits of osteoporosis therapy. Future research should explore the relationship between adherence and osteoporosis-related outcomes, fracture sequelae and related costs, and osteoporosis-related costs over longer lengths of follow-up.

DISCLOSURES

This study was funded by Amgen, and 3 of the authors (Iqbal, Macarios, and Badamgarav) are employed by Amgen. The sponsor Amgen took an active role in writing and revision of this manuscript and therefore had influence over the decision to publish this manuscript. Portions of the data in this study were presented in 2 posters at the 31st Annual Meeting of the American Society for Bone and Mineral Research in Denver, Colorado, on September 12-13, 2009, but the data presented in this final revised manuscript have not been presented previously.

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The authors thank Katrine Wallace, MA, for her assistance with the background section of this manuscript; Stephanie Nelson, BA, Senior Lead Analyst, Health Economics and Outcomes Research, i3 Innovus, for her work in data programming; and Leigh Borton, BA, Research Analyst, Health Economics and Outcomes Research, i3 Innovus, for her contribution to data set construction and analysis.

REFERENCES

5. 3.

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The Association of Adherence to Osteoporosis Therapies with Fracture, All-Cause Medical Costs, and All-Cause Hospitalizations: A Retrospective Claims Analysis of Female Health Plan Enrollees with Osteoporosis


# APPENDIX

## Codes for Exclusion Criteria and Identification of Closed Fracture, Corticosteroids, and Thyroid Hormones

<table>
<thead>
<tr>
<th>Condition or Procedure</th>
<th>Type of Code</th>
<th>Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paget's disease of the bone, other osteitis deformans and osteopathies</td>
<td>ICD-9-CM diagnosis</td>
<td>731.xx</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>ICD-9-CM diagnosis</td>
<td>756.51</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>ICD-9-CM diagnosis</td>
<td>275.42</td>
</tr>
<tr>
<td>Malignant cancer</td>
<td>ICD-9-CM diagnosis</td>
<td>140.xx – 208.xx</td>
</tr>
<tr>
<td>HIV</td>
<td>ICD-9-CM diagnosis</td>
<td>042.xx</td>
</tr>
<tr>
<td>Preventive therapy, breast cancer</td>
<td>ICD-9-CM diagnosis plus pharmacy</td>
<td>V10.3, V16.3, V84.01 plus at least 1 pharmacy claim for raloxifene</td>
</tr>
</tbody>
</table>

| **Identification of closed fracture** | | |
| Hip, vertebral, humerus, wrist, radius-ulna, femur, patella, tibia-fibula, ankle, pelvis, clavicle | ICD-9-CM diagnosis | 733.1, 733.10-733.16, 733.19, 805.0x, 805.2, 805.4, 805.6, 805.8, 808.0, 808.2, 808.4x, 808.8, 810.0x, 812.0x, 812.2x, 812.4x, 813.0x, 813.2x, 813.4x, 813.8x, 820.0x, 820.2x, 820.8, 821.0x, 821.2x, 822.0, 823.0x, 823.2x, 823.8x, 824.0, 824.2, 824.4, 824.6, 824.8 |
| Bone repair, plastic, fixation, implanted device, reduction, fusion procedures; application of splints or other support devices | ICD-9-CM procedure | 03.53, 78.1x, 78.40-78.69, 79.00-79.39, 81.0x, 93.51-93.54, 81.62-81.65 |

## Corticosteroids and thyroid hormones

bethamethasone, corticotropin, cortisone, cosyntropin, dexamethasone, fludrocortisone acetate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, levothyroxine, liothyronine, liotrix, protirelin, thyroid

Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products

Burgunda V. Sweet, PharmD, FASHP; Ann K. Schwemm, PharmD, MPH; and Dawn M. Parsons, RPh, MBA

In the United States, drugs and medical devices are regulated by different divisions of the U.S. Food and Drug Administration (FDA). While defined similarly, drugs and medical devices differ in their modes of action. Both are products that are labeled, promoted, or used in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. A device, however, does not achieve its intended purpose through a chemical action within or on the body or by being metabolized by the body. Although both drugs and medical devices must comply with federal regulations regarding labeling, advertising, production, and postmarketing surveillance, there are differences in the FDA premarket review and approval processes. FDA clearance and prescription status of a device do not necessarily mean that safety and efficacy have been shown for the product or that clinical trials have been conducted. We conducted a literature review to (a) examine the historical legislation and approval processes for drugs, medical devices, and combination products and (b) discuss implications of the differences in FDA review processes for clinicians and payers.

Methods
A MEDLINE search (1950 to September 2010) for English-language articles was conducted using the following search terms: drug approval, device approval, combination products, and US Food and Drug Administration (Figure 1). The reference citations from identified articles were reviewed for additional resources, and the FDA website was searched for specific subject areas within the Federal Register, Code of Federal Regulations (CFR), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and general FDA regulatory documents.

Results

Key Laws and Regulations
Over the past century, there have been significant changes and advances in the regulation of drugs by the FDA. These changes evolved in response to catastrophic events in history, because of the advancement of science, and in response to consumer expectations (Figure 2). Prior to the twentieth century, there were essentially no regulations protecting the public from drugs. Manufacturers were able to make curative claims and advertise useless remedies with little fear of repercussions.

The first step towards organizing federal regulation of drugs did not occur until 1902 when Harvey Wiley, a chemist in the Department of Agriculture, began to assess drug ingredients through the Drug Laboratory Program. This process eventually led to the Federal Food and Drugs Act, a law enacted in 1906 that prohibited interstate commerce of misbranded or adulterated foods and drugs and required that drugs meet standards of strength and purity set by the United States Pharmacopeia (USP). The 1906 act, however, did not require that any information be submitted to the FDA prior to marketing to establish safety or efficacy, leaving the government responsible to prove with a preponderance of evidence that a drug’s labeling was false before it could be removed from the market. Six years later, in 1912, the Sherley Amendment was passed prohibiting manufacturers from labeling medications with false therapeutic claims intended to defraud the consumer. Prior to this amendment, false claims for effectiveness did not fall under the scope of the FDA. Although the 1912 amendment was a step in the right direction, it remained difficult for the FDA to prove intent to defraud the consumer.

Although the 1906 Food and Drugs Act was a big step in consumer advocacy, various events occurred over the next 30 years that clearly indicated additional legislation was necessary. In 1933, the FDA produced an exhibit known as the “Chamber of Horrors,” which chronicled the drug- and cosmetic-related adverse events for products brought to market legally under the then-current legislation. In 1937, an antimicrobial product known as “Elixir of Sulfanilamide” came to market in a liquid formulation. Diethylene glycol was used as the base solution, a product that had never been examined for safety in the laboratory or in humans. Ultimately, its use led to more than 100 deaths, many of whom were children. Because there was no standing legislation requiring manufacturers to establish safety before bringing a drug to market, the FDA was able to charge the manufacturer only with misbranding, as it called the drug an elixir when it contained no alcohol.

In 1938, after a 5-year debate, the FDA recommended revisions to the 1906 legislation, and Congress passed the Federal Food, Drug and Cosmetic Act (FDCA). For the first time in history, manufacturers had to submit an application to receive approval from the FDA prior to marketing a new drug. The FDCA required that new drugs be proven safe prior to marketing, but there was no requirement to prove efficacy. The FDCA also expanded the authority of the FDA to control therapeutic devices, although this regulation was limited to ensuring that devices were not adulterated or misbranded. Although the FDCA offered great improvements, particularly in the regulation of drugs, there continued to be flaws.

Drugs were not required to demonstrate proof of efficacy
Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products

Prior to marketing until 1962 when the Kefauver-Harris Drug Amendment was passed.\textsuperscript{7,10} This amendment was a response to the thalidomide tragedy in Europe, where horrible birth defects were seen in babies born to mothers who received this sleeping pill. The extent of the tragedy was reduced in the United States because of the fortunate delay by 1 reviewer in the FDA who was concerned with the safety of the drug.\textsuperscript{11} The 1962 amendment applied to all drugs (prescription and over-the-counter) and required, for the first time, that adequate and well-controlled studies be conducted to prove a drug’s efficacy. It also defined rules for obtaining informed consent from research subjects and required that the FDA approve the marketing application prior to the availability of a new drug.\textsuperscript{3,8}

While the regulation of drugs began in 1906 with the Federal Food and Drug Act, regulation of medical devices did not begin until enactment of the FDCA in 1938 (Figure 2).\textsuperscript{8,12} It was not until the passage of the Medical Device Amendment in 1976 that manufacturers of medical devices were required to register with the FDA and to follow quality control standards prior to marketing.\textsuperscript{7,8,12} This legislation was enacted largely because of increasing reports of injuries associated with medical devices, perhaps the most notable being the thousands of women injured by the Dalkon Shield intrauterine device (IUD), which caused second-trimester septic abortions and maternal deaths.\textsuperscript{13} Postmarketing surveillance and adverse event reporting of permanently implanted devices became required in 1990 through the Safe Medical Device Act, in part because of the 1986 market withdrawal of a mechanical heart valve that had premature strut failure, which affected hundreds of patients.\textsuperscript{13} In contrast, postmarketing monitoring and safety features for drugs had been in place since 1962.\textsuperscript{12}

Over the last 2 decades, multiple amendments have been enacted in an effort to bring safer and more effective drugs and medical devices to market efficiently.\textsuperscript{7} The 1997 Food and Drug Administration Modernization Act brought about the most wide-ranging reforms since 1938, including regulation of advertising for unapproved (off-label) uses for drugs and devices, a step that has resulted in a growing number of warning letters to manufacturers for off-label promotion.\textsuperscript{14} It also provided for accelerated reviews of drugs and medical devices prior to marketing until 1962 when the Kefauver-Harris Drug Amendment was passed.\textsuperscript{7,10} This amendment was a response to the thalidomide tragedy in Europe, where horrible birth defects were seen in babies born to mothers who received this sleeping pill. The extent of the tragedy was reduced in the United States because of the fortunate delay by 1 reviewer in the FDA who was concerned with the safety of the drug.\textsuperscript{11} The 1962 amendment applied to all drugs (prescription and over-the-counter) and required, for the first time, that adequate and well-controlled studies be conducted to prove a drug’s efficacy. It also defined rules for obtaining informed consent from research subjects and required that the FDA approve the marketing application prior to the availability of a new drug.\textsuperscript{3,8}

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devices using less stringent thresholds (e.g., use of surrogate markers to assess efficacy and requiring only 1 well-controlled trial to assess safety and efficacy) to allow new therapies to be brought to market sooner for products used to treat very rare diseases (i.e., orphan drugs) or serious medical conditions for which there are no currently available treatment options (e.g., treatment-resistant malignancies). In addition, fees associated with product applications were imposed on manufacturers of drugs through the Prescription Drug User Fee Act (1992) and for medical devices through the Medical Device User Fee Modernization Act (2002) to provide additional funding to the FDA for the new product review process.12

**FDA Approval Process**

It is generally recognized that all drugs and medical devices carry some level of risk. In fact, each year approximately 1-2 drugs and 6-8 medical devices are removed from the U.S. market because of safety concerns.12 The FDA is charged with reviewing the safety and efficacy of drugs and medical devices and assessing the benefit versus risk of each product.16 However, the FDA approval processes used for drugs and devices can differ widely.
Drug Approval Process. Drugs and biopharmaceuticals are regulated through CDER. The drug development process, which takes an average of 8 to 10 years, begins with preclinical studies that assess safety and biological activity in various animal models. The manufacturer must then submit to the FDA an Investigational New Drug (IND) application to show results of preclinical testing before testing in humans can occur. Studies in humans are typically done in 4 phases, of which must occur prior to FDA approval. Phase I studies are the first studies done in humans and are designed to establish the safety, pharmacology, pharmacokinetics, and safe dose range of the drug. These studies typically involve a small number of subjects, often normal healthy volunteers. Phase II studies include patients with the target disease state. The primary goal of the phase II studies is to identify the optimal dose for the phase III studies to maximize efficacy while minimizing toxicity. These studies produce preliminary data on efficacy and identify the most common short-term adverse effects, but they are not generally powered to evaluate efficacy. Phase III studies are the large, pivotal trials that are often used for the FDA approval of a drug. They usually include a large sample size (hundreds to thousands of patients) and are designed to evaluate efficacy.

Typically, once a drug has made it through phase III testing, a manufacturer submits to the FDA a New Drug Application (NDA), a formal proposal requesting approval to market a new drug in the United States. CDER reviews the preclinical and clinical data for the proposed indication and makes a determination of approval status. In some cases, conditional approval is granted requiring the manufacturer to complete phase IV postmarketing studies to assess efficacy or safety concerns or to address quality of life or cost/benefit issues. From 2003 through September 2008, the average time required for FDA review of a standard NDA was 12.2 months (range 10 to 15 months). As noted earlier, orphan drugs or drugs used to treat conditions for which there are no good treatment alternatives may undergo expedited review and gain approval based on surrogate markers and phase II data. The process for new generic formulations is somewhat shortened, allowing the manufacturer to submit an Abbreviated NDA (ANDA), which requires data supporting bioequivalence of the generic drug to the innovator product but does not require that clinical trials be conducted. This abbreviated process was made possible in 1984 through the Hatch-Waxman Act in an effort to make generic drugs available sooner.

Device Approval Process. The medical device industry, which is very large and diverse, is regulated through CDRH. Although all medical devices marketed in the United States must adhere to controls outlined in the FDCA (i.e., compliance with good manufacturing practices [GMPs], proper labeling, adequate packaging, registration with the FDA), the majority of devices reach the U.S. market through an approval process that is less demanding than that required for drugs and which does not require a true clinical trial testing for safety and efficacy. Since 1990, the FDA device evaluations have become more rigorous, requiring more information about the risks and benefits of new medical devices. However, few new device evaluations use randomized controlled trials (RCTs). There are several reasons for the lack of RCTs, including federal regulations for devices; methodological difficulties for device evaluations (e.g., randomization, appropriate and ethical control groups, measurable outcomes in a reasonable time frame); and the sheer volume of device applications, which forces the FDA to prioritize its review specific to safety over efficacy.

Because of the wide variety of devices that exist (e.g., latex gloves to coronary stents), the Medical Device Amendment of 1976 recognized that not all devices require the same level of regulation. According to this legislation, the FDA classifies all existing and future devices into 1 of 3 categories based on the level of risk posed to the patient, a classification that is well defined in the CFR and that determines the level of FDA review a device receives prior to marketing. Devices on the market prior to 1976 were classified and grandfathered in; they required no retrospective review for marketing to demonstrate safety or efficacy. These pre-1976 devices became known as predicate devices, products that serve as a comparison for premarket review of new devices brought to market. Class I devices have the lowest level of risk and include products such as tongue depressors and band-aids. Class II devices pose more risk and include items such as forceps and surgical lasers. Class III devices are products that support or sustain life or prevent health impairment. They pose the highest risk for injury or illness to the patient and include products such as drug-eluting stents and pacemakers.

All medical devices, regardless of classification, are subject to FDA regulations for adulteration and misbranding, and companies are required to register their information and products with the FDA. The FDA is required by statute to exempt most class I and some class II devices from the formal premarket review processes (510[k]), thereby minimizing FDA premarket scrutiny. Most class II and a few class III devices undergo a traditional 510(k), a process requiring that devices demonstrate substantial equivalence to a predicate device (either a pre-1976 device or a post-1976 device that has received FDA clearance). Substantial equivalence means that the new device performs in a similar manner and is at least as safe and effective as the predicate device, which was never required to prove safety and efficacy and may in fact not be safe or effective. It does not mean that the new and predicate devices...
Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products

Comparison of Drug and Device Approval Processes. While there are differences between the drug and medical device approval processes, there are also some similarities. Manufacturers of drugs or medical devices can market products only for their intended use once approved or cleared by the FDA.12 Both drugs and devices must comply with federal regulations for labeling, advertising, production, and postmarketing surveillance.8,12 Both drugs and medical devices offer a means of providing products to patients for humanitarian use (Orphan Drug or Humanitarian Device Exemption processes, respectively). And, both have a process to allow for the

*Figure 3* Overview of Medical Device Approval Process26-28

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Legislation exists to exempt most Class I devices from the 510(k) process (unless they are intended to prevent impairment of human health or present unreasonable risk of injury).</td>
<td>• Device must show substantial equivalence to a legally marketed (predicate) device.</td>
<td>• Device requires most formal review process for devices known as PMA.</td>
</tr>
<tr>
<td>• Exempt means that premarket notification (510[k]) and FDA clearance are not required prior to marketing.</td>
<td>• Substantial equivalence means that the device performs in a manner similar to already marketed device.</td>
<td>• PMA requires that the product demonstrate safety and efficacy.</td>
</tr>
<tr>
<td>• Companies must still register their name and products with the FDA.</td>
<td>• In general, no clinical trial is required to prove safety or efficacy.</td>
<td>• Device is said to be FDA-approved.</td>
</tr>
<tr>
<td>• Process to allow exempt devices was added by the 1997 FDA Modernization Act, which permitted the FDA to direct resources to more significant public health issues.</td>
<td>• Premarket notification via a 510(k) application is usually required.</td>
<td>• Only 2% of new device applications require this process.</td>
</tr>
<tr>
<td></td>
<td>• If FDA deems device is not substantially equivalent, manufacturer can petition for reclassification or file a de novo process (for those devices for which there is no predicate device and, as such, are automatically classified as class III).</td>
<td>• All novel devices (those with no predicate device) are automatically classified as class III. However, the manufacturer can file a request for designation into class I or II.</td>
</tr>
</tbody>
</table>

CDRH = Center for Devices and Radiological Health; FDA = U.S. Food and Drug Administration; PMA = premarket application.

are identical, differing from generic drugs where bioequivalence must be proven.9 Most studies that support a 510(k) are not true clinical trials demonstrating safety and efficacy.22,23 Medical devices reviewed through the 510(k) process are said to be FDA-cleared, not FDA-approved.12,26 In September 2009, the FDA announced that the Institute of Medicine will study the 510(k) process to ensure it continues to meet the needs of the dramatically changing device industry.30 This decision is particularly important because many of the predicate devices to which substantial equivalence must be shown were on the market prior to 1976 and demonstrating equivalence to a product more than 30 years old may no longer be sufficient.31

The PMA is the most rigorous device application and is required for most class III devices.32 PMA is the device-evaluation process that is most similar to that required for drugs.12,13 Like the NDA process for drugs, PMA requires demonstration of safety and efficacy, which are higher standards than substantial equivalence. Medical devices reviewed through a PMA are said to be FDA-approved. These products must provide sufficient scientific evidence to demonstrate the safety and efficacy of the device for its intended use. It is important to note, though, that only 2% of devices are approved by the PMA process. Between 2003 and 2007, there were 13,199 submissions for class I and II devices via the 510(k) process, compared with only 217 original PMA submissions.31 Similar numbers were reported in 2008, when there were 3,363 510(k) submissions and only 26 original PMA submissions.33 New device applications that are not substantially equivalent to a predicate device automatically fall into class III.34 The manufacturer must either submit a PMA or petition the FDA to reclassify the device into class I or II before the product can be commercially distributed.32
study of the product in humans (Investigational New Drug or Investigational Device Exemption, respectively).

However, there are also some key differences in the requirements for drugs and medical devices. While all drugs are required to demonstrate safety and efficacy in humans, only class III devices have this same requirement. Generic drugs are required to demonstrate bioequivalence to the predicate drug, a higher standard than the substantial equivalence required for 510(k)-cleared devices. And, while all manufacturers of drugs must undergo FDA inspections, manufacturers of medical devices are often not inspected.12,26,34 Despite these differences, and the overall more rigorous review process required for drugs, the FDA review processes for both drugs and medical devices are perhaps the best in the world.3,7

Combination Products. Some products regulated by the FDA do not fit exclusively into the category of drug or device but are instead a combination of 2 or more single-entity products (e.g., drug, biological, and device). A wide variety of combination products exist, but they generally fall into one of a few categories: those that are physically, chemically, or otherwise combined and produced as a single entity (e.g., drug-eluting stents or a patch-containing drug such as Neupro); those that consist of individual products that are packaged together (e.g., surgical trays); and those that have products packaged separately but which must be used together to fulfill the indication for use (e.g., tositumomab and iodine-131 tositumomab [Bexxar; GlaxoSmithKline]).35,36 With increasingly innovative diagnostic and therapeutic products becoming available and technology advancing drug delivery systems, the market of combination products continues to grow with 330 submissions reviewed in 2008 compared with 251 in 2004.37

The FDA formed the Office of Combination Products (OCP) in 2002 in response to requirements defined in the Medical Devices User Fee and Modernization Act.35 The OCP is responsible for classifying each combination product as a drug, device, or biological based on the primary mode of action (PMOA) and then assigning the review of that product to the most appropriate center (CDER, CBER, or CDRH). The PMOA is defined as the single mode of action that provides the most important therapeutic action of the combination product.36 For some products there may not be an obvious PMOA, or the combination product may have 2 distinct mechanisms of action. In these situations, the OCP uses an algorithm to assist in the determination of the PMOA. If no center has experience regulating similar products, the OCP determines the regulatory center that has experience in evaluating the most important safety and efficacy issues that may surround the product.36

Once a product’s PMOA has been determined by the OCP, it can be assigned to the primary regulatory center. If manufacturers disagree with the determination of the PMOA, they can appeal for reconsideration and reclassification by submitting a formal determination for primary jurisdiction known as a Request for Designation.38 A combination product is held to the usual and customary premarket approval and regulatory processes of a single-entity product regulated under that same center.35 Postmarketing safety reporting and GMP requirements have been less clearly defined for combination products than for single-entity products. In 2009, the FDA issued proposed rules to (a) codify the current GMP requirements applicable to combination products and (b) clarify the postmarketing safety reporting requirements that apply to combination products.39,40

Classification of Products—Not as Obvious as You Might Think

Although classification as drug or medical device can be very clear for some products, for others it is not so obvious. Some products that may intuitively be considered a drug may, in fact, actually be classified as a device, and vice versa. It is important to remember that the classification of a product is determined by its mechanism of action, or PMOA for combination products. After the formation of the OCP, a retrospective review of existing combination products was conducted to determine which center should assume primary responsibility for review and regulation. One of the more notable decisions that resulted from this review was the reclassification of heparin flushes from drug to device in October 2006.41 In the announcement of transfer, the FDA stated that heparin flushes exert their PMOA by physically occupying space and applying pressure within the catheter, similar to the mechanism of saline flushes.42 The mechanism of heparin preventing thrombotic occlusions was determined to be a secondary function of the product.41 Both saline and heparin flushes are now classified as class II devices requiring 510(k) clearance for marketing.41-43 This change surprised many health care providers because heparin is considered a high-alert medication.44 Although used to restore rather than maintain catheter patency, alteplase (Cathflo, Activase [LyticExperience; Genentech]) syringes are administered in a manner similar to heparin or saline flush solutions. However, alteplase syringes work to restore the function to venous access devices by chemically initiating local fibrinolysis of a thrombus in an occluded catheter.45 As such, alteplase syringes are regulated as a drug (biological product) under CDER.46 Because all 3 products are used in a similar manner for similar purposes (maintain or restore patency of venous catheters), many health care providers may intuitively consider them to be drugs. They may not be aware that, as class II devices, saline and heparin flush solutions only had to demonstrate substantial equivalence to a device already on the market to obtain FDA clearance.46

The previous example outlined a situation in which a product that may be thought of as a drug (e.g., heparin flush) is regulated as a device. The opposite can also be true. There are currently 2 IUDs on the U.S. market, T 380A intrauterine copper contraceptive (ParaGard [Duramed Pharmaceuticals]) and levonorgestrel-releasing intrauterine system (Mirena [Bayer]). Although both are combination products, they were approved by the FDA as drugs, requiring an NDA for marketing; both
were approved prior to the formation of the OCP in 2002. ParaGard is a copper IUD consisting of a T-frame made of polyethylene and barium sulfate (device component) and a copper wire (drug component). While the exact mechanism of action is not fully understood, it is believed that copper interferes with sperm transport and fertilization and, therefore, prevents egg implantation.46 Mirena is a levonorgestrel-releasing intrauterine system that also consists of a T-shaped polyethylene frame with the levonorgestrel reservoir around a vertical stem. It is thought to act by causing a thickening of the cervical mucosa, inhibiting sperm survival, and altering the endometrial environment.48 In both cases, the device component causes changes in the lining of the uterus and fallopian tubes that affect movement of sperm so that fertilization does not occur. Although their names may be misleading, IUDs are combination products that are classified and regulated by the FDA as drugs.

As noted earlier, the classification of a product as a drug or device is determined by its mechanism of action, with drugs achieving their primary intended purpose through chemical or metabolic action in the body. Topical creams used to treat minor dermatologic conditions are commonly thought to be drugs. However, some topical creams are considered to be barriers and are classified as devices because they impart no chemical or metabolic action and have no active ingredients.3 Tropazone CR (Midlothian Laboratories) is one example of a prescription-only cream used for the management of superficial wounds and first- and second-degree burns.49 This emulsion contains moisturizers that work to keep the area moist and was approved through the 510(k) process, showing technological comparisons to 4 predicate devices. Clinical testing involved only insult patch testing in 50 human subjects, showing it to be a nonprimary irritant or skin sensitizer. No efficacy studies showing benefit to the healing process were reported in the 510(k) application.

Sometimes products with very similar indications for use may be classified and, therefore, regulated differently. Osteoarthritis is a common medical condition that is often managed using intra-articular injections of corticosteroids (e.g., triamcinolone hexacetonide) or tissue stabilizers (e.g., hyaluronan). Both of these products are indicated for the treatment of pain associated with osteoarthritis.50,51 Corticosteroids are regulated as drugs because they impart their action by reducing inflammation. Hyaluronan (Synvisc [Genzyme]), however, is regulated as a class III device because it works as a tissue stabilizer and elastoviscous shock absorber, thereby imparting its action through nonchemical means.52

Formulation of a product may also affect its classification as drug or device. Oral sucralfate (Carafate) acts chemically with hydrochloric acid in a patient’s stomach to form a barrier paste inside the body, thereby creating a protective barrier at ulcer sites.53 The FDA classifies oral sucralfate as a drug because it acts chemically within the body to perform its action. In contrast, sucralfate topical paste (Carapaste [McGrath Pharmaceuticals]) is mixed with hydrochloric acid prior to use, forming a paste that is then applied to oral lesions. The resulting product acts physically as a protective barrier and is classified as a device.54

As illustrated with these few examples and in others shown in Table 1,52,43–48,50–60 the classification of a product as drug or device is not always intuitively obvious to the practicing clinician.

Discussion

The classification of a product as a drug or medical device can have an impact on clinicians and payers. Some of these practical considerations are described below.

Clinical Considerations

As discussed earlier, all drugs must prove safety and efficacy prior to marketing, although they are not required to prove benefit over existing therapies. A similar requirement exists for most class III devices that undergo the PMA process. However, most devices enter the market through the less rigorous 510(k) process where they, at most, need only to show equivalence to a predicate device, indicating that the device does what it is intended to do and is reasonably safe. Demonstration of efficacy is not required for approval.16 It is important that clinicians are aware of these differences in premarketing scrutiny and take them into consideration when selecting treatment for a patient.57 Incorporation of medical devices into routine clinical practice without adequate safety and efficacy data can mean that products are used that have little benefit over existing alternatives or, worse, that they offer no benefit at all. For example, in the late 1990s the FDA continued to receive 510(k) applications for intermittent positive pressure breathing devices even after the Agency for Health Care Policy and Research determined that they offered no benefit to patients.23,68

The level of premarket scrutiny is relevant not only to the level of clinical evidence available, but also to standards for quality of the product. Medical devices cleared through the 510(k) process are required to submit notification to the FDA of their intent to market a new device at least 90 days prior to marketing. The 510(k) process does not require FDA inspection of the manufacturing plant prior to marketing, although the manufacturer must be prepared for a quality inspection at any time after clearance.26 This process has resulted in adverse patient consequences such as when marketed heparin flush solutions were found to be contaminated with Serratia marcescens, causing infections in more than 40 patients.34,69 The affected heparin flush solution was brought to market legally as a class II device by demonstrating substantial equivalence to a predicate device, but the quality standards of the manufacturing facility were not adequate. Notably, when the FDA shifted all heparin flush solutions from CDER to CDRH in 2006, it recognized the potential for serious patient consequences if a suboptimal product came to market and, as such, required a premarket plant inspection prior to FDA clearance of this product.51
### Examples of Various Product Classifications by the U.S. Food and Drug Administration

<table>
<thead>
<tr>
<th>Category</th>
<th>Product</th>
<th>Indication for Use</th>
<th>Mechanism of Action</th>
<th>FDA Classification</th>
<th>Review Requirements/References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Products with Similar Indications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter patency</td>
<td>Saline flush</td>
<td>Enhance the performance and maintain patency of indwelling catheters</td>
<td>Physically occupies space within the catheter and exerts pressure on the patient’s circulating blood, thereby preventing blood from back-filling into the catheter and clotting.</td>
<td>Device (Class II) [Prescription]</td>
<td>510(k)26</td>
</tr>
</tbody>
</table>
|                           | Heparin flush                    | Enhance the performance and maintain patency of indwelling catheters                   | Device: Physically occupies space within the catheter and exerts pressure on the patient’s circulating blood (PMA) 
Drug: Heparin acts chemically to prevent thrombotic occlusions within the catheter. | Device (Class II) [Prescription] Combination producta | 510(k)25 |
|                           | Aleplase (Activase) (CathFlo)     | Restore function to venous access devices that have become occluded                  | Acts chemically to initiate local fibrinolysis of a thrombus within the catheter, thereby restoring catheter function. | Drug [Prescription] | NDA41,46 |
| Osteoarthritis            | Hyaluronan (e.g., Synvisc)        | Treatment of pain associated with osteoarthritis of the knee                          | Tissue stabilizer and elastoviscous shock absorber that is injected into the affected joint. | Device (Class III) [Prescription] | PMA37,52 |
|                           | Triamcinolone hexacetone (Aristospan) | Treatment of pain associated with osteoarthritis of the knee                          | Corticosteroid that is injected into the affected joint, which reduces inflammation through limiting capillary dilation and permeability of vasculature. | Drug [Prescription] | NDA21 |
| Topical analgesic or antipruritic | Tetrax topical cream            | To relieve itching and burning associated with various dermatoses including atopic dermatitis and contact dermatitis. | Maintains a moist wound and skin environment, which is beneficial to the healing process. | Device (Class I) [Prescription] | 510(k)25 |
|                           | Epicrerr skin barrier emulsion    | To improve dry skin and relieve burning and itching associated with various dermatoses including atopic and contact dermatitis. | Maintains a moist wound and skin environment. | Device (Class I) [Prescription] | 510(k)20 |
|                           | Benadryl topical cream            | To relieve pain and itching associated with insect bites, minor burns, and contact dermatitis. | Blocks the action of histamine and provides topical analgesia. | Device (Class I) [Prescription] | 510(k)10 |
|                         | Ethyl chloride spray              | Topical anesthetic and vapocoolant (skin refrigerant)                                 | Provides numbness by freezing the skin. | Device (Class I) [Prescription] | 510(k)10 |
|                         | Benzocaine                        | Fast-acting topical anesthetic spray                                                  | Local anesthetic that numbs the skin. | Drug [OTC] | OTC monograph57,58 |
| Wrinkles                 | Hyaluronic acid (Restylane)       | Dermal filler                                                                        | Injected into the skin to temporarily restore volume to fill moderate to severe wrinkles. | Device (Class III) [Prescription] | PMA65 |
|                           | Onabotulinum toxin A (Botox)      | For temporary improvement in the appearance of moderate to severe lines associated with aging | Blocks neuromuscular transmission by inhibiting release of acetylcholine, which causes denervation of the muscle. | Drug [Prescription] | NDA52 |
| Electrolyte solutions for dialysis | Normocarb sterile bicarbonate renal dialysis concentrate | Dialysate for use in hemodialysis                                                     | Physically applies pressure inside the filter to help push toxins and excess water in the blood through the dialysis filter. | Device (Class II) [Prescription] | 510(k)82 |
| Scurfate                 | Carapaste topical                 | Barrier used to relieve pain of oral wounds and protect against further irritation. | Product is mixed with hydrochloric acid prior to use and is then applied to oral lesions, physically adheres to and forms a protective layer over the oral mucosa. | Device (Class I) [Prescription] | 510(k)14 |
|                         | Carafate oral tablets             | Barrier used for healing of duodenal ulcers and protection against further irritation. | Reacts with hydrochloric acid in the stomach to form a paste-like substance that adheres to proteins on the surface of ulcers. | Drug [Prescription] | NDA33 |

### Miscellaneous Products

<table>
<thead>
<tr>
<th>Category</th>
<th>Product</th>
<th>Indication for Use</th>
<th>Mechanism of Action</th>
<th>FDA Classification</th>
<th>Review Requirements/References</th>
</tr>
</thead>
</table>
| Intrauterine devices      | Mirena ParaGard                  | Intrauterine contraception                                                          | Device: causes changes in the lining of the uterus and fallopian tubes that affects movement of sperm so that fertilization does not occur. 
Drug: Thickens cervical mucus, inhibits sperm survival and alters endometrium, thereby affecting fertilization. | Drug [Prescription] Combination producta | NDA41,48 |
| Viscoselastic device, ophthalmic | Sodium hyaluronate (Healon Ophthalmic) | A nongaseous fluid injected into the eye to aid performance of surgery. | Physically occupies space in the eye during surgery, maintains anterior chamber depth, preserves tissue integrity, protects tissue from surgical trauma. | Device (Class III) [Prescription] | PMA51 |
| Tissue glue              | Intraocular tissue adhesive      | Closure of topical skin incisions in areas of low skin tension                      | Cytoskeletal-based synthetic tissue adhesive that closes wounds painlessly in seconds. | Device (Class III) [Prescription] | PMA46 |

*aDenotes a product that does not fit exclusively into the category of drug or device but is instead a combination of 2 or more of these single-entity products (e.g., drug, biological, and device). CRRT = continuous renal replacement therapy; FDA = U.S. Food and Drug Administration; IV = intravenous; NDA = New Drug Approval; OTC = over-the-counter; PMA = Premarket Approval; PMOA = primary mode of action; Rx = prescription.*
**Payer Considerations**

Centers for Medicare and Medicaid Services (CMS) projected prescription drug expenditures for 2010 are $260.1 billion, or 10.1% of all national health care expenditures. From a payer’s perspective, dollars are best spent on evidence-based, value-added prescription products given the limited funding resources available to support health care. Although both drugs and devices must be approved or cleared through the FDA, such review does not guarantee coverage by government or third-party payers. For example, when heparin flushes were reclassified as devices, notices were distributed to Medicaid medical directors informing them of future noncoverage of these products under the pharmacy benefit since they were no longer classified as drugs. Heparin flushes are also not covered under Medicare Part D because they are not prescription drugs.

Prescription drug claims payable by third parties (e.g., employers, union groups, Medicaid, and Medicare) are typically processed at point-of-sale through a pharmacy benefit management (PBM) company or claims processor. Rules of coverage are established within the claims processing system to determine drug coverage status, copayments, coinsurance, quantity limits, and any number of plan coverage parameters. Prescription claims processed by a PBM on behalf of a third-party payer will cascade through a set of plan coverage and payment rules. Coverage rules are typically established at the highest possible level of product classification, on an exclusion basis, with continued greater specificity as required to obtain the third-party payer’s coverage intent. For example, the rules may be set to exclude all over-the-counter (OTC) products with the exception of such products as OTC insulin and syringes. Because the highest level of exclusion is typically the prescription/OTC status of a product, all prescription devices will automatically be covered unless excluded by lower-level rules. Unfortunately, the current system is not well equipped to exclude prescription devices or to provide a trigger to the managed care pharmacist prompting the need to review a new product.

There are primarily 2 companies that market product files to pharmacy claims processors: First DataBank (First DataBank, Inc., San Francisco, CA) and Medi-Span (Wolters Kluwer Health, Indianapolis, IN). Until 2008, neither company’s product file contained an indicator denoting the FDA review or approval path taken for a given product. In 2008, First DataBank added an indicator noting if a drug product was approved by an NDA or an ANDA and will be adding biologics license application (BLA) information in late 2010. The Medi-Span product file currently contains NDA, ANDA, and BLA information. Neither company has a notation for products reviewed as medical devices. The absence of an FDA drug approval indicator is the only prompt that the managed care pharmacist has to suggest that the product may be regulated as a medical device, and the pharmacists see these items only if they review each line item added to these databases on a regular basis.

Because an efficient method to determine the review or approval path for a given product is not currently available, prescription devices often gain unintended prescription plan coverage simply because they were coded as prescription products. Depending on the device manufacturer’s marketing efforts, these products can prove to be costly to individual prescription drug plans. For example, several emollient products were approved through the device process: Tropazone CR, Biafine (Ortho Dermatologics), and Zenieva (Gorbec Pharmaceutical Services, Inc). There are no active ingredients in these products, all of which were approved as prescription devices through the 510(k) process, with each claiming substantial equivalence to the others. As stated earlier, there were no clinical trials reported in the 510(k) application for Tropazone CR showing improved wound healing. Yet, all of these products require a prescription, and their costs are not insignificant: average prices range from $54 per 90 grams (Biafine) to $122 per 140 grams (Tropazone) from drugstore.com. These costs are considerably higher than those of many of the OTC alternatives. Unless a health plan specifically coded these products for noncoverage, their claims would be paid.

This example illustrates how understanding the differences between drugs and medical devices and being aware of the current limitations of the drug product files available to process claims can assist payers in making informed prescription drug coverage decisions. Many pharmacy benefit plans have rules that exclude coverage of prescription devices. However, it is difficult for plans to manage this coverage exclusion given the limited functionality of the current information systems to provide the needed information in a user-friendly manner. Further improvements in the information sources available to plans to include the FDA review designation of devices coupled with a thorough understanding by plan managers of the differences in the drug and device review processes (i.e., the typical lack of RCTs demonstrating clinical outcomes for many devices) will help plans provide a sustainable, quality prescription drug benefit.

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DISCLOSURES
The authors report no financial relationships or other potential conflicts of interest related to this review. Sweet designed the study with the assistance of Schwemm. Sweet and Schwemm collected and interpreted the data and wrote the manuscript. Sweet revised the manuscript with the assistance of Schwemm and Parsons.

REFERENCES
Estimated Cost Savings Associated with the Transfer of Office-Administered Specialty Pharmaceuticals to a Specialty Pharmacy Provider in a Medical Injectable Drug Program

Christopher G. Baldini, PharmD, and Eric J. Culley, PharmD, MBA

ABSTRACT

BACKGROUND: A large managed care organization (MCO) in western Pennsylvania initiated a Medical Injectable Drug (MID) program in 2002 that transferred a specific subset of specialty drugs from physician reimbursement under the traditional “buy-and-bill” model in the medical benefit to MCO purchase from a specialty pharmacy provider (SPP) that supplied physician offices with the MIDs. The MID program was initiated with 4 drugs in 2002 (palivizumab and 3 hyaluronate products/derivatives) growing to more than 50 drugs by 2007-2008.

OBJECTIVE: To (a) describe the MID program as a method to manage the cost and delivery of this subset of specialty drugs, and (b) estimate the MID program cost savings in 2007 and 2008 in an MCO with approximately 4.6 million members.

METHODS: Cost savings generated by the MID program were calculated by comparing the total actual expenditure (plan cost plus member cost) on medications included in the MID program for calendar years 2007 and 2008 with the total estimated expenditure that would have been paid to physicians during the same time period for the same medication if reimbursement had been made using HCPCS (J code) billing under the physician “buy-and-bill” reimbursement rates.

RESULTS: For the approximately 50 drugs in the MID program in 2007 and 2008, the drug cost savings in 2007 were estimated to be $15.5 million (18.2%) or $290 per claim ($0.28 per member per month [PMPM]) and about $13 million (12.7%) or $201 per claim ($0.23 PMPM) in 2008. Although 28% of MID claims continued to be billed by physicians using J codes in 2007 and 22% in 2008, all claims for MIDs were limited to the SPP reimbursement rates.

CONCLUSION: This MID program was associated with health plan cost savings of approximately $28.5 million over 2 years, achieved by the transfer of about 50 physician-administered injectable pharmaceuticals from reimbursement to physicians to reimbursement to a single SPP and payment of physician claims for MIDs at the SPP reimbursement rates.

What is already known about this subject

• Specialty pharmaceuticals include injectables as well as some oral drugs that are expensive or warrant close monitoring to ensure appropriate use. National trend data show that spending for specialty drugs increased by 19.5% from 2008 to 2009, compared with an increase of 4.8% for traditional drugs and 6.4% for all prescription medications; spending for specialty drugs is projected to rise by more than 20% annually for 2010 through 2012.

• Injectable specialty pharmaceuticals may be covered and managed by managed care organizations (MCOs) under the medical or pharmacy benefit, or both, often determined by whether the drug is more often administered in the physician’s office, referred to as an office-administered agent (OAA), or more commonly self-administered by the patient and referred to as a self-administered agent (SAA). About 55% of specialty pharmaceuticals are covered under the medical benefit.

• OAAs billed under the medical benefit pose challenges in the areas of cost containment for the payer, financial risk and administrative burden for the physician, and possible barriers in access to quality, affordable health care for the patient.

• By December 2008, 96% of health plans reported present or pending contracts with 1 or more specialty pharmacy providers (SPP) to contain costs and manage the utilization of specialty pharmaceuticals, and nearly one-half of health plans contracted with 1 SPP exclusively.

What this study adds

• This MCO’s solution to the clinical, financial, and operational challenges of managing office-administered specialty pharmaceuticals involved (a) the transfer of certain office-administered, nononcology medical injectable drugs (MIDs) from “buy and bill” physician reimbursement using HCPCS (J codes) to purchase from a single, exclusive SPP at discounted reimbursement rates based on National Drug Code (NDC) numbers, and (b) reduction in physician reimbursement for MIDs to the SPP rates for medical offices that opted to continue to use the buy-and-bill method.

• Significant drug cost savings of approximately $0.25 PMPM over 2 years in 2007 and 2008 were realized from this MID program; however, because physician participation in this program was not mandatory in all geographic areas, 28% of all MID claims in 2007 and 22% in 2008 were paid to physicians under the “buy-and-bill” method.
Prescription drug spending is a relatively small proportion of total national health care expenditures compared with spending on hospital services and physician/clinical services. Spending for hospital services accounted for 31% of total health care spending in 2008, versus 21% for physician-clinical services, and 10% for prescription drugs. The rate of increase in prescription drug spend—one of the fastest growing components of total health care expenditures—has slowed to single-digit annual increases in recent years. Possible drivers of this trend include patent expirations for commonly used brand name drugs, more frequent use of benefit management policies, and the transition of some previously prescription-only brand-name products to over-the-counter status.

In contrast to the deceleration in overall prescription spending growth in recent years, spending for specialty drugs covered under the pharmacy benefit continued to rise sharply. Specialty drug spending per member per year increased by 19.5% from 2008 to 2009, compared with an increase of 4.8% for traditional drugs and 6.4% for prescription medications as a whole. The primary contributors to this trend for specialty medications are greater increases in both unit cost and utilization. Increases in utilization can be attributed in part to increased supply from an extensive biotech pipeline—about 30% to 40% of the medicines in late stage development are specialty drugs—and increased demand associated with new U.S. Food and Drug Administration (FDA)-approved indications for existing specialty products, resulting in an expanded population of patients with a medical need for such drugs.

Spending on specialty drugs is projected to increase by more than 20% per year for 2010 through 2012. The term “specialty drugs” typically refers to medications that have some or all of the following characteristics: (a) specialized delivery, storage, handling, or administration requirements; (b) significantly higher cost than traditional medications; (c) customized treatment protocols and requirements for close clinical monitoring and management; (d) availability through limited distribution channels; (e) derived via biotechnology; (f) often administered via injection or infusion; and (g) use that is limited or for the treatment of uncommon conditions. Since some specialty medications require administration by a health care professional in the office setting (office-administered agents [OAAs]) while others may be self-administered by the patient at home (self-administered agents [SAAs]), specialty pharmaceuticals may be managed under the pharmacy benefit, the medical benefit, or both.

Survey data obtained from a sample of health plans for year-end 2008 show that coverage of specialty pharmaceuticals varies by type of drug, with 58% of health plans reporting coverage of SAAs under the pharmacy benefit only, 13% under the medical benefit only, and 25% under both the medical and pharmacy benefit. Stern and Reissman (2006) described the cost and utilization management strategies for specialty pharmaceuticals as often “stop-gap” approaches developed in response to rising costs, and concluded that the determination of coverage in pharmacy versus medical benefits could be related to categorization of injectable drugs as either SAAs or OAAs.

Traditionally, specialty drugs covered under a medical benefit have been purchased and reimbursed through a buy-and-bill model in which a medical office would purchase a specialty medication, administer it, and subsequently bill an insurer for the drug and drug administration services. The purchase and administration of specialty drugs under the buy-and-bill model may present financial risk and operational challenges for some medical practices, but may also be a significant source of revenue for medical practices that have enough volume of these products to yield a profit. Financially, prescribing physicians may not be aware of whether they will be reimbursed until after a specialty drug is administered, based on traditional post-payment review procedures for medical benefits. The risk posed by uncertain reimbursement could result in drug administration being inappropriately delayed or omitted altogether. The administrative burden and financial consequences of the collection of member payment for denied services pose further risk for the medical practice. For those medical practices that have adapted well to the buy-and-bill model, such a model may generate considerable revenue, and there may be physician resistance to its discontinuation for certain services.

The objectives of this article are to describe a program employed by a managed care organization (MCO) to manage the cost and delivery of a subset of primarily office-administered specialty drugs, and to estimate the cost savings associated with operation of this program during 2007 and 2008. The MCO in this study is a regional Blues plan located in western Pennsylvania. For the years examined in the present study, 2007 and 2008, total MCO membership was 4.6 million and 4.8 million, respectively.

Methods

Description of the Medical Injectable Drug Program

In 2002, the MCO recognized an opportunity to implement a program designed to address some of the challenges surrounding specialty drugs that are paid under the medical benefit through the traditional buy-and-bill model. The Medical Injectable Drug (MID) Program was created to allow the strategic management of certain specialty drugs while maintaining the balance between quality, cost, and access.

The MID program specifically focuses on an MCO-defined set of specialty drugs that possess certain characteristics that make them conducive for inclusion in the program. First, the drug has to be covered under the medical benefit. The drug may also be covered under the pharmacy benefit, and in such cases the MID program would manage only those services that...
are reimbursed through the medical benefit (i.e., through the buy-and-bill model). Second, the drugs are commonly administered in a physician’s office, but do not have to strictly meet the definition of an OAA. The specialty drugs included in the program (Table 1) are specified by the plan and may be either OAAs or SAAs. For SAAs that are included in the program, such as etanercept, growth hormone products, and the interferons for the treatment of multiple sclerosis (MS), the MID program applies only when the drug is administered in the medical office (e.g., first dose administration when monitoring for adverse events or hypersensitivity). Subsequent fills are shipped directly to the patient’s home for self-administration and are reimbursed under the pharmacy benefit, not through the MID program. Lastly, the specialty drug must be available to the exclusive specialty pharmacy provider (SPP) responsible for the distribution of the program drugs.

The MCO initiated a phased roll-out of the MID program in 2002 by initially transitioning 4 specialty drugs (palivizumab [Synagis]; sodium hyaluronate [Hyalgan and Supartz]; and hylan G-F 20 [Synvisc]) from the traditional buy-and-bill model to an average wholesale price (AWP)-based reimbursement formula facilitated by the distribution of the program drugs through an exclusive SPP, Walgreen’s Specialty Pharmacy, LLC. The MID program included more specialty injectable drugs in subsequent years (Table 1).

The SPP’s distribution system allows for timely delivery of medications to medical offices, which can be coordinated with patients’ scheduled appointments, decreasing the amount of injectable medication that must be kept on hand in the medical offices. The SPP’s ancillary care and disease management services include dissemination of disease- and patient-specific educational materials, as well as telephonic interactions (outbound educational and care coordination calls and inbound patient information lines) with plan members and prescribing physicians. The SPP has disease-focused teams that provide counseling and assistance in the coordination of benefits and reimbursement, compliance monitoring, nursing and social work support networks, and clinical management of disease-specific programs (Table 2).

In 2007, claims for drugs in the MID program that were submitted by the SPP were billed using Healthcare Common Procedure Coding System (HCPCS) J codes and were reimbursed based on the median of AWP values for all of the National Drug Code (NDC) numbers in each J code, less an additional negotiated discount that was deeper (greater) than the standard physician network discount (“standard discount”). The standard discount is the percentage off the median AWP that is applied to reimbursement for non-MID program drug products. The additional negotiated MID program discount was calculated for all NDC numbers in each HCPCS J code (Table 3). The negotiated additional discounts were specific to individual drugs in the MID program, and the size of the additional discount varied by drug (i.e., reimbursement for

| TABLE 1: Drugs Added to the Medical Injectable Drug Program by Year* |
|-----------------|-----------------|
| **Brand (Generic) Drug Name** | **2002-2003** |
| Hyalgan (sodium hyaluronate) | Synagis (palivizumab) |
| Supartz (sodium hyaluronate) | Synvisc (hylan G-F 20) |
| **2004** | |
| Actimmune (interferon gamma-1b) | Growth hormone agents |
| Aldurazyme (laronidase) | IVG products |
| Amevive (alfacept) | Lioresal Intrathecal (baclofen) |
| Antagon (ganirelix acetate) | Myobloc (botulinum toxin type b) |
| Avonex (interferon beta-1a) | Pergonal (menotropins) |
| Betaseron (interferon beta-1b) | Protropin (somatrem) |
| Botux (botulinum toxin type a) | Raptiva (calfilumab) |
| Cerezyme (miglitolase) | Refil (interferon beta-1a) |
| Copaxone (glatiramer acetate) | Remicade (infliximab) |
| Embrel (etanercept) | Repronex (infliximab) |
| Fabrazyme (agalsidase beta) | Risperdal Consta (risperidone) |
| Cloting factor products | Thyrogen (thyrotropin alfa) |
| Follistim (follicle stimulating hormone) | Visudyne (verteporfin) |
| Gonal-F (folitropin alfa) | Xolair (omalizumab) |
| **2005** | |
| Bravive (urofollitropin) | Tev-Tropin (somatropin) |
| Cetrotide (cetrorelix acetate) | Theracy (BCG live [intravesical]) |
| Eligard (leuprolide acetate) | TICE BCG (BCG live [intravesical]) |
| Lupron Depot (leuprolide acetate) | Trelstar (triptorelin pamoate) |
| Macugen (pegaptanib) | Vantas (histrelin implant) |
| Orthovisc (high molecular weight hyaluronan) | Viadur (leuprolide acetate implant) |
| Plenaxis (abarelix) | Zoladex (goserelin acetate) |
| Prialt (ziconotide) | |
| **2006** | |
| Lucentis (ranibizumab) | Vivaqlobin (immune globulin subcutaneous [human]) |
| Orenica (abatacept) | |
| **2007** | |
| Myozyme (alguclosidase alfa) | Soliris (eculizumab) |
| **2008** | |
| Cimzia (certolizumab pegol) | Lupon Depot–Ped (leuprolide acetate) |
| Euflexxa (highly purified hyaluronan) | Omnitrop (somatropin [rDNA origin]) |
| H.P. Acthar (repository corticotropin injection) | Supprelin LA (histrelin acetate) |

*The list of drugs covered under the MID program and available from the specialty pharmacy provider increased each year. There were only 4 injectable drugs in the MID program in the first 2 years (2002 and 2003).

bThese drugs may be covered under the MID program for administration of an initial dose in the physician’s office. Subsequent doses are covered under the pharmacy benefit.

BCG = Bacillus Calmette-Guerin; IVG = intravenous immune globulin; LA = long-acting; MID = medical injectable drug; Ped = pediatric; rDNA = recombinant deoxyribonucleic acid.
MIDs was calculated as the median of AWP values minus the standard discount minus an additional discount for each drug. The terms of the MCO-SPP contract dictated that if the SPP dispensed a drug product with an AWP less than the median AWP for the HCPCS J code, the lower AWP cost was submitted.

New claims processing functionality was introduced in the MCO in January 2008 that allowed the SPP to submit claims with a HCPCS code and a specific NDC for the dispensed drug. The NDC-specific claims processing functionality allowed the MCO to reimburse the SPP more precisely by using the actual product AWP as opposed to the median AWP. The MID program reimbursement formula in 2008 therefore became actual AWP for the dispensed drug minus the standard MCO network discount percentage minus the additional negotiated discount. The new NDC-specific reimbursement was implemented to improve the accuracy and consistency of claims payment and did not represent additional cost savings to the MID program. Table 3 shows the specific reimbursement formula that was applied to each provider type in 2007 and 2008.

When the MCO implemented the MID program in 2002, physicians were encouraged but not required to participate; however, physician reimbursement for the drugs in the MID program was limited to the reimbursement rate for the SPP. Physician participation in the MID program was based on physician networks and was mandatory in western Pennsylvania where the MID program was part of the physician network contractual agreement. In other regions, such as central Pennsylvania and the Lehigh Valley, participation was optional; however, payment to physicians who opt out is limited to the SPP-contracted reimbursement rates for all drugs included in the MID program (Table 3). Because claims submitted by physicians outside of western Pennsylvania who opt out of the MID program are submitted using a HCPCS J code rather than an NDC number, reimbursement for these claims is less specific. In such cases, reimbursement is based on the median AWP for all of the NDC numbers for each HCPCS J code.

The SP does not charge additional fees for dispensing, delivery, or administrative costs other than the contracted reimbursement rate for each specific drug in the program. The SP ships the medication(s) directly to the physician’s office, and reimbursement of that medication is made by the MCO directly to the SPP. The member cost share associated with the medication is collected by the SPP. When a physician administers a medication to a patient, there can be 3 separate charges: the charge associated with the physician visit, the charge for administration of the drug, and the charge for the drug itself. Physician medical offices that order MIDs continue to be reimbursed under the traditional reimbursement model for the office visit and medication administration services, when applicable, and any member cost share related to such services is collected by the medical office.

Utilization management criteria are applied prospectively in the MID program, and coverage is confirmed prior to the distribution of the drug by the SPP. Under the traditional buy-and-bill model, the vast majority of utilization management criteria are applied on a retrospective, post-pay basis. This aspect of the MID program removes a level of risk and uncertainty for physician practices for their administrative management of specialty drugs (e.g., inventory management, reimbursement confirmation, and collection of member cost share for services provided). A pharmacist from the SPP obtains any information needed from the physician’s office and, as an authorized agent of the MCO, the SP pharmacist then reviews the request based on the MCO’s utilization management criteria (e.g., omalizumab, Figure 1). The SP pharmacist can approve coverage for cases that meet the clinical criteria established by the MCO, but all cases that do not meet the MCO’s utilization

![TABLE 2](image1.png)

<table>
<thead>
<tr>
<th>Therapy Management Services Provided by the Specialty Pharmacy Provider for MIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>Hemophilia</td>
</tr>
<tr>
<td>Immune disorders</td>
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<tr>
<td>MID = medical injectable drug; RSV = respiratory syncytial virus.</td>
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</tbody>
</table>

![TABLE 3](image2.png)

<table>
<thead>
<tr>
<th>Reimbursement Formula for Medical Injectable Drugs by Provider Type – 2007 and 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider Type</td>
</tr>
<tr>
<td>------------------------------------</td>
</tr>
<tr>
<td>Specialty pharmacy provider</td>
</tr>
<tr>
<td>Physician (buy-and-bill)**</td>
</tr>
<tr>
<td>Any medical provider</td>
</tr>
</tbody>
</table>

*Median AWP refers to the median of AWP values for all NDC numbers in each HCPCS J code. Standard discount refers to the MCO discount applied to medical claims for drugs billed under the medical benefit.

**In 2007, the basis for payment to the specialty pharmacy provider (SPP) was the lower of the discounted median AWP price for the HCPCS J code or the discounted NDC-specific AWP. In 2008, the basis for reimbursement to the SPP was the discounted NDC-specific AWP.

***Additional discount refers to the negotiated reimbursement rate specific to MID program drugs. The discount varies by individual drug and is in addition to the standard MCO network discount.

**Physicians practicing outside of western Pennsylvania were permitted to opt out of the MID program distribution channel in 2007 and 2008, but were reimbursed at the same rate as the specialty pharmacy provider.

AWP = average wholesale price; HCPCS = Healthcare Common Procedure Coding System; MCO = managed care organization; MID = medical injectable drug (Table 1); NDC = national drug code.
management criteria are forwarded to the MCO’s medical directors for individual case evaluation. All policies and criteria are created and maintained by the MCO. The MCO conducts quarterly reviews/audits of the SPP to confirm accuracy and consistency in applying the MCO’s prior authorization and utilization management criteria, compliance with timeliness guidelines, and requirements from all applicable regulatory bodies.

Pre-Implementation Steps for the MID Program
Prior to the implementation of the MID program, the MCO took multiple steps to minimize member, employer group, and physician disruption, and to increase acceptance of the program. Throughout the implementation period in 2001 and 2002, network physicians were educated and feedback was solicited. A dialogue between the MCO and network primary care physicians and specialists was identified as an essential component for the initiation and long-term viability of the MID program. Pre-implementation strategies were focused on achieving understanding and acceptance among those physicians (and affected members) who were to be mandated to participate in the program.

Pre-program implementation activities in 2001 and 2002 included the following:
- Presentations and announcements by the MCO’s sales staff to affected medical groups
- Notification to the physician community at multiple points in the implementation process through mailings and electronic communications
- Utilization of historical claims data to send targeted

**FIGURE 1** Highmark Medical Policy I-53 Omalizumab (Xolair)

General Policy Guidelines
Indications and Limitations of Coverage
Xolair (omalizumab) is indicated for use in patients who meet all the following criteria:
- greater than or equal to 12 years of age;
- moderate-to-severe persistent asthma in those who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids;
- baseline IgE titre greater than or equal to 30 IU/mL;
- baseline FEV 1 less than 80% of predicted; and
- does not require oral steroids for maintenance therapy.

Omalizumab has not been shown to alleviate acute asthma exacerbations and should not be used for the treatment of acute bronchospasm or status asthmaticus.

The recommended dosage of omalizumab is 150 mg to 375 mg subcutaneous every two to four weeks based on body weight and pre-treatment serum total IgE level. Limit injections to not more than 150 mg/site.

The use of omalizumab for any indication not listed on this policy is considered experimental/investigational, and therefore, not covered. A participating, preferred, or network provider can bill the member for the non-covered service.

Coverage for omalizumab is determined according to individual or group customer benefits. Omalizumab is not reimbursable under the prescription drug benefit.

Although the risk of anaphylaxis following administration of omalizumab necessitates the need for observation, this is not separately reimbursable and is considered part of the administration of this drug.

Reconstitution and preparation of this drug is considered part of the administration and is not separately reimbursable.

A participating, preferred, or network provider cannot bill the member for observation, reconstitution, preparation, or other additional administration costs.

NOTE: This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person’s unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Procedure Codes
J2357
Diagnosis Codes
493.00


**FEV** = forced expiratory volume; **IgE** = immunoglobulin E; **IU** = international units; **mL** = milliliter.
physician letters that identified specific health plan members who would be affected by implementation of the MID program

- Internal staff education and training for the pharmacy, member services, provider contracting, and other departments affected by MID coverage and payment
- System changes to the medical claims processing system including expanding capabilities to allow future enhancements to the program, such as creating crosswalk tables for J codes and NDCs, allowing for NDC-specific reimbursement
- Face-to-face meetings with key physicians and decision makers to highlight the benefits of this program

**Calculation of Cost Savings**

The calculation of cost savings was performed by comparing the actual total expenditures (plan cost plus member cost) for the drugs in the MID program in 2007 and 2008 with the estimated payments that would have been made under the buy-and-bill model had the MID program not existed. These expenditure estimates were calculated by multiplying the actual utilization for the individual drug by the negotiated additional discount for the given drug (i.e., the total cost savings from the MID program are attributed to the additional discount that was negotiated for each drug included in the program). Cost savings were calculated and aggregated by month based on date of service for medical claims for drugs included in the program, from January 1, 2007, through December 31, 2008. For drugs that were added to the MID program mid-year, the total amount paid and total savings were calculated from the time of inclusion of each drug in the MID program.

Per member per month (PMPM) savings were calculated from the sum of cost savings for the 12 months for each of the 2 calendar years and divided by the average MCO membership in each year (approximately 4.6 million members in 2007 and 4.8 million in 2008) divided by 12.

**Results**

The total amount spent on drugs that were included in the MID program was approximately $69.4 million in 2007, and the estimated amount that would have been paid for these same claims using the reimbursement rate for physicians under the traditional buy-and-bill model (i.e., median AWP less standard MCO network discount) was $84.9 million (Table 4). The net drug cost savings generated by the additional negotiated discounts for the MID program in 2007 were approximately $15.5 million (18.2%) or an average of $290 per claim or $0.28 PMPM. In 2008, the total amount spent on drugs that were included in the MID program was approximately $89.9 million, and the estimated amount that would have been paid for these claims using the traditional buy-and-bill reimbursement rate was approximately $102.9 million. For 2008, the net drug cost savings generated by the additional negotiated discounts for the MID program drugs were approximately $13.1 million (12.7%) or an average of $201 per claim or $0.23 PMPM. Of the medical claims for drugs included in the MID program, 28% in 2007 and 22% in 2008 (average 25% for the 2 years) were paid to physicians under the traditional buy-and-bill model, and all were all reimbursed at the SPP reimbursement rates (i.e., the medical offices were reimbursed based on the median of AWP values for the drug or drugs in each HCPCS J code minus the standard discount minus the additional discount that was applied to the SPP; Table 3).

**Discussion**

The published literature to date does not contain an example of a specialty drug management program that is directly comparable with the MID program described here. However,
a survey conducted in late 2008 of 69 health plans with a total of 83 million members reported that 72% of Medicaid plans, 71% of Medicare Advantage Prescription Drug (MA-PD) plans, and 67% of commercial health plans engaged in some form of reduced reimbursement for specialty drugs (not limited to the specific drugs included in the MID program) to non-oncology physicians. The survey also reported that 87% of Medicaid plans, 85% of MA-PDs, and 69% of commercial plans had implemented mandatory use of an SPP for SAAs in 2008. Mandatory use of an SPP for OAAs is less common, with requirements for members to obtain some or all OAAs reported by 54% of Medicaid plans, 33% of MA-PDs, and 35% of commercial health plans.

When determining how to manage specialty drugs, MCOs may choose to contract with a single (exclusive) SPP or a small network of 2 or more SPPs, and the use of the SPP may be voluntary or mandatory. Survey data from 2008 showed that 96% of health plans contracted with 1 or more SPPs, an increase from 78% in 2005. Regarding the use of a single, exclusive SPP versus multiple SPPs, 45% of health plans contracted with a single SPP exclusively in 2008, reflecting a decrease from 60% reported in 2005.

Published studies exploring the advantages and disadvantages of exclusive versus small network versus open network arrangements with SPPs are lacking. The potential benefits of using a single, exclusive SPP may include a more consistent level of service and improved clinical collaboration with the health plan, physicians, and members. If the responsibility for essential components of care management and coordination is delegated exclusively to a single SPP, the MCO should be able to expect that the care provided is more consistent from patient to patient. For example, the SPP for this MID program supplies the MCO with a single report that documents intervention detail and frequency including contacts with individual patients and/or physicians, and the nature of the interactions that take place between the SPP and all of the MCO's members with a given disease state who are being treated with a drug in the MID program.

Further, an exclusive arrangement between an MCO and an SPP may allow for a plan to better engage an SPP in plan-specific initiatives that require a modest to high level of customization. Managing even moderately customized initiatives across multiple SPPs may be difficult given operational, contractual, and other variations among organizations. Depending on the level of the individual plan's interest in engaging SPPs in more intensive clinical or other collaborative activities, the decision to contract with an exclusive SPP and, moreover, the organizational characteristics to be desired when choosing an exclusive SPP become rather important.

In the case of the MID program in this MCO, an exclusive arrangement with an SPP allowed the MCO to negotiate deeper reimbursement discounts for the specialty drug products that are included in the program, which generated cost savings for the plan. Specifically, the MID program generated estimated drug cost savings of approximately $28.5 million over 2 years in 2007 and 2008 or about $0.25 PMPM. The impact of these savings is realized not just by the MCO, but by plan members as well. Members who have a coinsurance benefit design realize direct savings because the price discounts for drugs in the MID program are included in the allowable charge, which is used to determine the member financial responsibility. Members in high-deductible health plans are also likely to see a decrease in out-of-pocket cost share as a result of lower reimbursement rates for drugs in the MID program.

The savings reported here include only those associated with a decrease in the unit cost of the medications included in the MID program. Changes in utilization patterns may also impact the actual savings a plan can expect to realize from such a program. It is possible that the MID program contributed to an increase in utilization by facilitating physician access to MID drugs including reduction in provider financial risk through prospective utilization management and eliminating inventory costs for medical offices. Thus, although price savings were achieved in the MID program, it is possible that some of these price savings were offset by increased utilization. However, any increased utilization of the MIDs would appear to be appropriate because utilization management was an integral part of the MID program.

The implementation of NDC-specific billing and reimbursement to the SPP in 2008 may in part explain the decrease in the calculated cost savings from 2007 to 2008. While NDC-specific billing is more accurate, it may also cause the plan to incur additional costs because reimbursement is based on the actual AWP for a product as opposed to the median of AWPs for the drugs in each J code. Any NDC with an AWP above the median value for a specific J code would result in a higher payment amount from the health plan to the SPP after conversion to NDC-specific reimbursement. In 2007 prior to NDC-specific billing, the SPP was contractually obligated to submit the lower of the discounted median AWP price for the HCPCS J code or the NDC-specific reimbursement amount. The exact amount that this lower-of-provision may have saved in 2007 was not calculated.

**MID Program Obstacles**

The MID program and its implementation encountered several obstacles. One of the main barriers to the development of the MID program was resistance by physicians, fueled in part by the perception that this distribution system would reduce access, create an obstacle to obtaining medications, or reduce physician revenue. Most of the initial resistance toward this program came from orthopedists, which would be expected since 3 of the first 4 medications included in the MID program were orthopedic drugs (hyaluronate). Although a systematic assessment of physician opinions of or satisfaction with the MID program was not
conducted, we observed anecdotally that physician opinions were mixed. Smaller physician offices tended to favor the MID program because they felt that it removed a level of administrative burden from the office and freed up cash flow for the practice. Perception of the program was more negative among some larger medical practices, because they viewed the transition to the MID program as lost revenue. This negative perception appears validated by the fact that 28% of claims for MID drugs were submitted using HCPCS codes via the "buy-and-bill" method in 2007 and 22% in 2008. These statistics suggest that there remains a significant physician provider base that is able to profit under the traditional buy-and-bill model despite the decreased reimbursement for the MID program drugs.

In an attempt to minimize physician resistance, MCOs considering implementation of such a program should also give consideration to (a) the types of medications that are added to the program and (b) the medical specialties that would be affected by such additions. For example, this MID program did not include chemotherapy drugs, and expansion of this program to oncology could be expected to be met with greater resistance because oncologists traditionally have generated a large share of their office revenue from the purchase and administration of certain chemotherapeutic agents. A recent analysis showed that reduction in reimbursement rates for specific chemotherapeutic agents had no negative effect on access to medications but was associated with a shift in the medications that were used, away from the agents for which reimbursement had been reduced and toward similar agents with higher reimbursement margins.

In an attempt to minimize resistance from physicians and other stakeholders, the MCO in the present study developed and distributed comprehensive educational materials that emphasized the positive attributes of the MID program including simplification of the distribution process. The communications campaign included frequent updates to all network physicians highlighting the details and advantages of the new MID program, pre-implementation notices to employer groups, and targeted communication to affected members. Furthermore, despite some resistance to the MID program, the MCO believes that simply decreasing reimbursement of the drugs in this program across all physician groups without providing another means to obtain these medications would have been much more disruptive and likely would not have been sustainable. This outcome would likely have been due to the community outcry as many physician offices would not have been able to buy and bill at the new, lower SPP rate, and therefore would have lost money on many of the drugs in the program.

**Limitations**

Aside from the limitations associated with the implementation of programs such as MID that affect provider reimbursement, particularly physician resistance, there are limitations to the present analysis. Foremost, we performed a cost savings analysis that estimated what would have been paid in 2007 under the reimbursement formula that existed prior to the MID program (i.e., we did not compare spending under the MID program compared with actual spending prior to the MID program). Second, we did not assess financial effects of the MID program on members. However, because most medical benefits require member coinsurance (e.g., 20% of the allowed charge), most MCO members would have had lower cost-share amounts, in proportion to the lower reimbursement rates for the MIDs. Third, we did not examine the financial effects on members from the transfer to the pharmacy benefit of certain MIDs after the first fill. Effective and efficient management of specialty pharmacy programs that involve drugs that are commonly administered in medical offices requires MCO consideration of the design and administration of pharmacy and medical benefits. For example, our MID program was designed with the recognition that more than one-quarter of our members have pharmacy benefits that are carved out (30.1% in 2007 and 29.5% in 2008), and many high-volume drugs in the MID program such as etanercept and the injectable drugs for MS (i.e., beta-interferons and glatiramer acetate) are covered only in pharmacy benefits after the first fill. Health plans vary considerably in these characteristics.

Fourth, as noted previously, this cost savings analysis is primarily a price savings analysis because we did not attempt to examine how the MID program might have increased utilization. Fifth, the present analysis did not investigate the source of MID program savings by individual drug. Sixth, we did not assess other outcomes associated with the MID program such as member satisfaction; however, the MID program was expected to be primarily transparent to health plan members. Seventh, we did not investigate the source of the smaller cost savings per claim as a percentage of MID spending in 2008 under NDC-specific reimbursement compared with 2007.

Finally, we did not assess the administrative costs associated with implementation of the MID program, such as (a) physical mailings that included targeted letters to the providers and articles in provider and member newsletters and face-to-face meetings with key stakeholders; and (b) establishment of internal workgroups to address system coding and enhancements, internal communications, and training. Other ongoing costs and resource requirements include compiling the necessary claims reports, performing an ongoing business analysis, and performing routine oversight audits to ensure that the SPP is consistently and appropriately applying the MCO’s utilization management criteria and meeting any contractually defined thresholds for measures such as timeliness and accuracy. These administrative costs, while potentially substantial, were ultimately nominal for the MCO relative to the savings that the MID program has generated. However, these administrative costs and organizational commitments may present a significant barrier for smaller health plans. Other health plans will need to assess potential savings based on their own
medical-specialty drug volume and their existing infrastructure to determine if the startup and administrative costs will yield total savings. We estimate an initial time commitment of approximately 9 months to 1 year to establish a similar MID program.

Conclusions

Specialty pharmaceuticals provide hope for patients with chronic, complex, or rare disease states that do not respond to traditional drug therapies as well as challenges for providers and payers who must address issues of limited distribution, administrative burden, high cost, and appropriate clinical management. The MID program was developed as a method to manage specialty pharmaceuticals that are commonly administered in physician offices and reimbursted under the medical benefit. The MID program was initiated in this MCO in 2002 and grew to more than 50 medications by 2007, generating an estimated $15.5 million in injectable drug cost savings in 2007 and about $13 million in 2008. Anecdotal reports from smaller physician offices suggested that the MID program helped to reduce financial risk and transfer the administrative burden associated with MIDs from physicians to the MCO and SPP. Nevertheless, about 25% of the MID claims in 2007 and 2008 were submitted by physicians under buy-and-bill reimbursement rather than using the SPP.

REFERENCES


Protecting Patients from Adverse Drug Events: Propoxyphene, PIMs, and Drugs to Avoid in Older Adults

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

The base of evidence for the relative harm versus benefit for commonly used prescription drugs expanded in 2010, including developments late in 2010 that reinforced the value of pharmacovigilance and the need for critical appraisal of warnings of threat to patient safety. In October 2010, the U.S. Food and Drug Administration (FDA) announced additions to the labels of all bisphosphonates warning of the increased risk of atypical fracture of the femur, an outcome that although rare (representing less than 1% of all fractures of the hip and femur) had been “predominantly reported in patients taking bisphosphonates.”1 These drugs already carried a label warning regarding osteonecrosis of the jaw, and the additional warning precipitated widespread discussion among patients and health care professionals regarding the safety of bisphosphonates and the observation that these widely used drugs were associated with adverse events that they were intended to prevent.2 In September 2010, a 4-year controversy over the relative benefit versus harm of rosiglitazone culminated in withdrawal of the drug from the European market and exceptionally restricted use in the United States including the requirement that patients “acknowledge they understand the [cardiovascular] risks” associated with use of rosiglitazone.3 The clinical irony for rosiglitazone is that it was used by millions of people with type 2 diabetes to prevent the very adverse cardiovascular events that were found to be associated with its use.4,5 It is not yet clear how much of the cardiovascular adverse event profile pioglitazone shares with rosiglitazone,6 and pioglitazone has a black-box warning regarding the possibility to “cause or exacerbate congestive heart failure.”7

New Evidence About Relative Harm of Opioids, NSAIDs and COX-2 Drugs in Older Adults

In December 2010, Solomon et al. reported the finding that opioids pose a higher risk of harm than nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors among elderly patients with arthritis.8 This observational analysis of pharmacy and medical claims data for 12,840 low-income Medicare beneficiaries enrolled in pharmaceutical assistance programs in 2 states (New Jersey and Pennsylvania) over the 7-year period from January 1, 1999, through December 31, 2005, used extensive propensity score matching in an attempt to remove the effects of confounders, and the analysis was limited to new users of prescribed analgesics in an effort to increase comparability among groups. The scope of outcome measures was also impressive, with assessment of 15 well-documented and transparently reported individual safety events (e.g., myocardial infarction, stroke, upper gastrointestinal bleed, falls, and 4 fracture types), grouped into 6 composite outcome measures. An important limitation of the study was that data on over-the-counter (OTC) use of nonselective NSAIDs were not available; thus, it is possible that the incident users of prescribed medications had previously used OTC NSAIDs or that opioid users were taking OTC NSAIDs concomitantly.

Compared with nonselective NSAIDs, composite cardiovascular events (including fatal and nonfatal myocardial infarction and 4 other individual outcomes) were more common with COX-2 inhibitors (hazard ratio [HR] = 1.28, 95% confidence interval [CI] = 1.01-1.62) and opioids (HR = 1.77, 95% CI = 1.39-2.24) in this sample of older adults (mean age 80.0 years; approximately 85% female). Risk of the second composite outcome, gastrointestinal bleeding, was lower for COX-2 inhibitors compared with nonselective NSAIDs (HR = 0.60, 95% CI = 0.35-1.00) but similar for nonselective NSAIDs and opioids. The composite outcome of fracture risk (hip, pelvis, wrist, and humerus) was higher for opioids compared with nonselective NSAIDs (HR = 4.47, 95% CI = 3.12-6.41) but similar between nonselective NSAIDs and COX-2 inhibitors; and the composite outcome for all-cause mortality was higher for opioids compared with nonselective NSAIDs (HR = 1.87, 95% CI = 1.39-2.33) but similar for COX-2 drugs and nonselective NSAIDs. There was no significant difference among the 3 classes of drugs for death related to an adverse event, but the absolute counts were small (68 events in the sample overall, incidence rates of 12 to 13 events per 1,000 person years). Adverse events that required hospitalization were the most common safety event, and opioids but not COX-2 inhibitors were associated with increased risk of harm compared with nonselective NSAIDs (HR = 1.68, 95% CI = 1.37-2.07); the absolute rates per 1,000 person years were 100 for COX-2 inhibitors, 105 for NSAIDs, and 155 for opioids.

The class of opioids in the study reported by Solomon et al. included propoxyphene, but the adverse events were not reported for specific drugs.8 However, in a coincident report, these researchers found differences in safety among specific opioid products.9 Like the report on safety of analgesics overall, the opioid-specific study used propensity score matching in an attempt to reduce the effects of confounders in a cohort.
analysis of pharmacy and medical claims. The opioid-specific study examined dates of service from January 1, 1996, through December 31, 2005, for 31,375 Medicare beneficiaries in 2 states (New Jersey and Pennsylvania) who qualified for pharmaceutical assistance programs and were new users of opioid therapy for nonmalignant pain (i.e., cases with a cancer diagnosis or use of hospice care were excluded).

Over the 10-year study period, propoxyphene and tramadol were associated with a lower risk of fracture compared with hydrocodone (rate ratio [RR] = 0.54, 95% CI = 0.44-0.66; and RR = 0.21, 95% CI = 0.16-0.28, respectively). Among the 5 types of opioid therapy (hydrocodone, oxycodone, codeine, propoxyphene, and tramadol), the risk of cardiovascular events was significantly higher for codeine during the first 180 days after initiation of therapy (RR = 1.62, 95% CI = 1.27-2.06) but not during the first 30 days, and there was no significant difference in the risk of gastrointestinal events in either time period. Compared with hydrocodone, oxycodone and codeine were associated with increased risk of all-cause mortality during the first 30 days of therapy (RR = 2.43, 95% CI = 1.47-4.00; and RR = 2.05, 95% CI = 1.22-3.45, respectively). Becker and O’Connor posited separately in a commentary that the lower potency of tramadol and propoxyphene may explain the lower risk of fracture compared with the more potent opioids hydrocodone and oxycodone.

Public Health Implications of Evidence About Analgesic Safety in Older Adults

The report by Solomon et al. of greater harm in older adults associated with opioids compared with NSAIDs and COX-2 drugs followed action by the FDA intended to better manage the safety of opioid use. In July 2010, a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee advised the FDA that its proposed risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioid drugs did not go far enough because the misuse of both immediate-release and extended-release opioids “has a huge impact on public health,” indicating a need for REMS for both opioid categories and “a concerted public health campaign” involving “prescribers, pharmacies, patients, and industry.”

Nearly 9 years after the Department of Health and Human Services (DHHS) called for a “national action plan” to ensure the appropriate use of therapeutic agents among older adults, the nagging question is, are we making progress? The 2 studies by Solomon et al. raise an important issue with potential implications both for public health and for provider education campaigns—whether clinicians are running from the fear of gastrointestinal toxicity and nephrotoxicity associated with nonselective NSAIDs and cardiovascular toxicity of COX-2 drugs toward potentially more dangerous opioids, resulting in avoidable harm to older adults.

In commenting on the work of Solomon et al., Graf suggests that clinicians need to pay attention to these findings indicating that nonselective NSAIDs may be safer than either opioids or COX-2 drugs in the care of older adults with the common condition of arthritis because analgesic use is becoming an increasingly important public health issue. Graf argues that several factors—public perceptions about inadequate pain control, insufficient provider attention to diagnosing and treating the underlying causes of pain, institutional pain assessment protocols, and even legislation specifying patient “rights” to opioids—have contributed to increased use of opioids, especially among females aged 65 years or older with chronic noncancerous pain. Supporting Graf’s assertion of the need for provider attention to the problem, Solomon et al. concluded that opioid use for nonmalignant pain in older adults is a clinical concern, based in part on the calculation of the number needed to harm during the first 365 days of therapy; only 27 patients would need to be treated with an opioid or 66 patients with a COX-2 inhibitor instead of a nonselective NSAID to result in 1 excess all-cause death.

With a Stroke of the Pen in November 2010, Are Older Adults Safer?

The FDA announced on November 19, 2010, that it had obtained agreement from the manufacturer of brand propoxyphene products (Darvon and Darvocet) to withdraw these drugs from the U.S. market and that it was working with the generic manufacturers to voluntarily withdraw all propoxyphene-containing products. The FDA cited new safety data submitted by the manufacturer that confirmed previous data indicating an increased risk of potentially fatal cardiac arrhythmia associated with propoxyphene, advising health care professionals to stop prescribing propoxyphene and patients to contact their prescribers to obtain alternative therapy. Data from SDI/Verispan (SDI Health, Plymouth Meeting, PA) showed that there were 17.5 million prescriptions dispensed for propoxyphene brand and generic products in 2009, making it the 38th most prescribed generic drug in the United States in 2009.

The decision by the FDA in November 2010 to withdraw propoxyphene from the U.S. market was neither sudden nor unexpected. Propoxyphene was banned from the United Kingdom (U.K.) in 2005 and from the European Union in 2009. An FDA advisory committee voted 14-to-12 in January 2009 to recommend U.S. market withdrawal of propoxyphene, and the FDA asked the manufacturer for additional safety data; a black-box warning was added to the propoxyphene label in September 2009 regarding increased risk of death from overdose. Interestingly, the observational research reported by Solomon et al. in December 2010 did not provide convincing support for the FDA’s decision the previous month to remove propoxyphene from the U.S. market. Specifically, in
addition to their finding of higher rates of cardiovascular risk for codeine compared with hydrocodone during the first 180 days of opioid therapy, Solomon et al. found similar risk of cardiovascular events for propoxyphene compared with 3 other opioids (hydrocodone, oxycodone, and tramadol) during both the first 30 days and 180 days of therapy. The FDA’s decision was based in part on new data reported by the manufacturer of Darvon-Darvocet in July-August 2010 indicating that cardiac arrhythmias occurred at normal doses of propoxyphene, contradicting a previous assumption that cardiac arrhythmias occurred only at higher than recommended doses. Uncertainty about safety evidence for different opioids, such as that suggested by a comparison of the Solomon et al. findings with the manufacturer’s study of propoxyphene, raises a broader question: how much do we know about which drugs are truly harmful for older patients?

**Utilization of Potentially Inappropriate Medications (PIMs) in Older Adults: Are We Targeting the Right Drugs?**

With implementation of the Medicare Part D drug benefit imminent on January 1, 2006, the National Committee for Quality Assurance (NCQA) announced in mid-2005 that it would adopt a list of “drugs to be avoided in the elderly” (DAE) as a quality measure for health plans in 2006. The Healthcare Effectiveness and Data Information Set (HEDIS) DAE list in 2006 represented a subset of a drug list derived from the work of a 2003 expert panel (Table 1). The 2003 panel classified 48 drugs/classes into 3 categories: Always Avoid, Rarely Appropriate, and Some Indications. Drugs in the Always Avoid and Rarely Appropriate categories composed the 2006 HEDIS measure.

**TABLE 1**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Target Population</th>
<th>Number of Drugs and Changes to Previous Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beers, 1991</td>
<td>Older adults in nursing homes</td>
<td>Expert consensus panel of 13 members developed 30 criteria, identifying 19 individual drugs or classes to avoid.</td>
</tr>
<tr>
<td>Beers, 1997</td>
<td>Older adults in the community</td>
<td>Expert consensus panel of 6 members identified 28 drugs or classes to avoid independent of diagnoses and 35 drugs or classes to avoid with any of 15 known medical conditions.</td>
</tr>
<tr>
<td>Zhan-AHRQ, 2001</td>
<td>Older adults in the community</td>
<td>Expert panel of 7 members classified 33 drugs from the 1997 Beers list into 3 categories irrespective of dose, frequency of administration, or duration: (a) Always Avoid (11 drugs, including dicyclomine, chlorpropramide, flurazepam, meprobamate, and meperidine); (b) Rarely Appropriate (some indications for appropriate use: 8 drugs including propoxyphene, diazepam, cyclobenzaprine, carisoprodol, methocarbamol, and chloridiazepoxide); or (c) Some Indications (most use is considered inappropriate: 14 drugs including amitriptyline, promethazine, indomethacin, oxybutynin, hydroxyzine, and dipyridamole).</td>
</tr>
<tr>
<td>Beers, 2003</td>
<td>Older adults in the community</td>
<td>Expert consensus panel of 12 members identified 48 individual drugs or classes to avoid regardless of diagnoses or conditions plus 20 diseases/conditions for which certain drugs should be avoided.</td>
</tr>
<tr>
<td>NCQA-HEDIS. 2006</td>
<td>Older adults in the community</td>
<td>Expert consensus panel classified the 2003 Beers list into 3 categories: Always Avoid, Rarely Appropriate, and Some Indications.</td>
</tr>
</tbody>
</table>

**Notes:**
- Developed in part from Pugh et al. (2006). AHRQ = Agency for Healthcare Research and Quality; HEDIS = Healthcare Effectiveness and Data Information Set; NCQA = National Committee for Quality Assurance.

In 2002, Gurwitz and Rochon suggested that the Beers criteria may be inappropriate to measure PIM use in the elderly because the list includes many drugs that were once common but no longer considered by many prescribers, such as flurazepam (Dalmane), pentazocine (Talwin) and meprobamate (Equanil/Equagesic). More than 8 years later, these drugs and most of the Beers criteria drugs accounted for much of the NCQA-HEDIS 2009 and 2010 lists of DAE “high-risk medications.” Missing from this current list of DAE-PIMs are common opioids that perhaps pose greater threat to patient safety among older adults; for example, codeine (e.g., with acetaminophen) is not included except in combination with antihistamines or skeletal muscle relaxants.

Skepticism about the degree to which PIMs are truly harmful, or perhaps provider perceptions that PIMs meet therapeutic needs that could not otherwise be addressed, are suggested by examination of trend data for use of PIMs. For example, resistance to reduction in use of PIMs in older adults is evident in the data reported by NCQA for Medicare beneficiaries. NCQA tracking of the prevalence of use of DAE high-risk medications shows no change over the 4-year period from 2005 to 2008 (Table 2). Approximately 23%-24% of Medicare beneficiaries...
TABLE 2 Summary of Results of Selected Studies of PIM Utilization in Older Adults

<table>
<thead>
<tr>
<th>Authors (Publication Date)</th>
<th>Description of Sample and Study Period</th>
<th>Definition of PIM</th>
<th>% (n) Receiving PIM</th>
<th>% Receiving Propoxyphene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fick et al. (2001)25</td>
<td>1 HMO; n = 2,336; June 1, 1997 - October 31, 1998</td>
<td>Beers list (1997)</td>
<td>23.2 (n = 541)</td>
<td>9.6 (n = 224)</td>
</tr>
<tr>
<td>Pugh et al. (2005)26</td>
<td>National VA; n = 1,265,434; October 1, 1999-September 30, 2000</td>
<td>Zhan (2001) plus dose-limited drugs</td>
<td>23.0 [17.5]-d</td>
<td>4.1</td>
</tr>
<tr>
<td>Pugh et al. (2006)19</td>
<td>National VA; n = 1,896,361; October 1, 1999-September 30, 2000</td>
<td>HEDIS 2006</td>
<td>19.6d</td>
<td>4.5</td>
</tr>
<tr>
<td>Barnett et al. (2006)31</td>
<td>10 private HMOs; n = 157,517; January 2000-June 2001</td>
<td>Zhan (2001), 33 drugs</td>
<td>28.8 (n = 45,365)</td>
<td>7.0 (n = 11,034)f</td>
</tr>
<tr>
<td>Barnett et al. (2006)31</td>
<td>VA (10 regions); n = 123,633; April 2002 - September 2003</td>
<td>Zhan (2001), 33 drugs</td>
<td>21.3 (n = 26,339)</td>
<td>3.0 (n = 3,692)g</td>
</tr>
<tr>
<td>NCQA 200523</td>
<td>National reporting - 2005</td>
<td>HEDIS DAE</td>
<td>23.9 [6.6]d</td>
<td>NR</td>
</tr>
<tr>
<td>NCQA 200623</td>
<td>National reporting - 2006</td>
<td>HEDIS DAE</td>
<td>23.1 [5.9]d</td>
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<tr>
<td>NCQA 200823</td>
<td>National reporting - 2008</td>
<td>HEDIS DAE</td>
<td>23.4 [6.0]d</td>
<td>NR</td>
</tr>
<tr>
<td>Zhang et al. (2010)24</td>
<td>Medicare Part D beneficiaries (n = 533,170) in calendar year 2007</td>
<td>HEDIS DAEh</td>
<td>25.8</td>
<td>-</td>
</tr>
<tr>
<td>NDHCRI33</td>
<td>Medicare Part D beneficiaries in North Dakota who filled at least 1 prescription during the 6 months from April 1, 2008, through September 30, 2008</td>
<td>CMS 2008</td>
<td>14.8</td>
<td>5.1</td>
</tr>
<tr>
<td>SDFMC33</td>
<td>Medicare Part D beneficiaries in South Dakota who filled at least 1 prescription during the 6 months from April 1, 2008, through September 30, 2008</td>
<td>CMS 2008</td>
<td>16.4</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Intervention to Reduce PIM Utilization

<table>
<thead>
<tr>
<th>Authors (Publication Date)</th>
<th>Description of Sample and Study Period</th>
<th>Definition of PIM</th>
<th>% (n) Receiving PIM</th>
<th>% Receiving Propoxyphene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman et al. (2005)**</td>
<td>1 HMO (New York); n = 90,000-100,000 1999 Q4 - 2001 Q4</td>
<td>8 contraindicated drugsi</td>
<td>5.3 (n = 2,871) in 1999 Q4 (baseline); 4.3 (n = 2,713) in 2001 Q4</td>
<td>NR</td>
</tr>
<tr>
<td>Kaufman et al. (2005)**</td>
<td>1 HMO (New York); n = 100,000-110,000 2002 Q1 - 2003 Q4</td>
<td>10 contraindicated drugsi</td>
<td>2.4 (n = 1,495) in 2002 Q1; 2.2 (n = 1,451) in 2003 Q4</td>
<td>NR</td>
</tr>
</tbody>
</table>

*All studies selected persons aged 65 years or older.

**6.2% received at least 1 of 11 Always Avoid drugs; 9.1% received at least 1 of 8 Rarely Appropriate drugs; and 13.3% received at least 1 of 14 Some Indications drugs.

+PIMs in this study included 7 drugs (digoxin and 6 short-acting benzodiazepines, such as alprazolam) defined by the Zhan-AHRQ panel as dose-limited, and 16.1% received at least 1 dose-limited drug, and the prevalence was 4.6% after adjustment for diagnosis, dose, and duration. Prevalence rates before (after) adjustment for diagnosis, dose, and duration for the 3 Zhan categories were: 0.8% (0.8%) of beneficiaries received 1 or more of 11 Always Avoid drugs, 8.9% (8.0%) received at least 1 Rarely Appropriate drug, and 15.5% (13.3%) received at least 1 Some Indications drug.

The denominator in these proportions was the count of utilizing members, approximately 65% of eligible members, by calendar quarter.

The numbers in [ ] are the proportions of health plan members who received 2 or more DAES.

Pugh et al. (2006) excluded the HEDIS 2006 estrogen drugs because their study period (1999-2000) preceded publication of the Women's Health Initiative study results which changed recommendations for use of estrogens in certain women. Even with the exclusion of estrogens, 23.3% of women versus 19.2% of men had received at least 1 drug on the HEDIS 2006 list of DAES.

The rate of propoxyphene use among females was 8.5% versus 5.0% among males; this private sector HMO population was 56.5% female (n = 88,970 of 157,517 members).

The rate of propoxyphene use among females was 4.9% versus 2.0% among males; this VA sample was 2.7% female (n = 3,311 of 123,633 beneficiaries).

Zhang et al. did not include the “narcotics” (propoxyphene, meperidine, pentazocine, opium, and naloxone) from the HEDIS 2009 list. Result shown is the mean value for hospital referral regions.

The 8 drugs defined as contraindicated based on the Beers list (1997) were: amitriptyline, cyclobenzaprine, diazepam, indomethacin, meprobamate, methocarbamol, methyldopa, and propoxyphene (including combinations).

The denominator in these proportions was the count of utilizing members, approximately 65% of eligible members, by calendar quarter.

The 10 drugs defined as contraindicated based on Zhan (2001) were: amitriptyline (in doses 50 mg per day or more), cyclobenzaprine, diazepam, indomethacin (2 or more pharmacy claims in the calendar quarter), meprobamate, methocarbamol, methylpap, diclofenac, disopyramide, and hyoscine (i.e., excluding propoxyphene and combinations).

AHRQ = Agency for Healthcare Research and Quality; CMS = Centers for Medicare & Medicaid Services; DAE = Drugs to Avoid in the Elderly; HEDIS = Healthcare Effectiveness Data and Information Set; HMO = health maintenance organization; MCBS = Medicare Current Beneficiary Survey; MEPS = Medical Expenditure Panel Survey; mg = milligrams; NDHCRI = North Dakota Health Care Review, Inc., the Medicare QIO for North Dakota; NMCES = National Medical Care Expenditure Survey; NR = not reported; PIM = potentially inappropriate medication; QIO = quality improvement organization; SDFMC = South Dakota Foundation for Medical Care, the Medicare QIO for South Dakota; VA = Veterans Affairs.
received at least 1 of the DAEs each year, and approximately 6% received 2 or more DAEs each year. But, there is apparently some geographic variation in DAE use. In November 2010, Zhang et al. reported that the rates of utilization of DAEs varied by nearly 4-fold from 11.4% of Medicare Part D beneficiaries in the Bronx, New York, to as much as 44.0% of beneficiaries in Alexandria, Louisiana. This research also found that variation in DAE utilization was not related to overall spending on drugs (Pearson correlation \( r = 0.02, P = 0.78 \), meaning that the quality of prescribing, assessed via the use of DAEs, was not associated with higher use and spending for all drugs. Additionally, DAEs accounted for less than 1% of total drug expenditures. However, DAE use was associated with higher medical expense \( r = 0.30, P < 0.001 \). Utilization rates of PIMs in older adults have remained high for nearly 2 decades even though the composition of the lists of PIMs has changed; and most research has found high rates of PIM use for members of managed care organizations. Based on the original (1997) Beers criteria for ambulatory care, Fick et al. found that 541 of 2,336 continuously enrolled beneficiaries (23.2%) in a managed Medicare health maintenance organization (HMO) received 1 or more PIMs during the 17-month period from June 1, 1997, through October 31, 1998 (Table 2). Propoxyphene (and its combination products, primarily with acetaminophen) was received by 41.4% (n = 224) of the 541 beneficiaries who received 1 or more PIMs; other commonly used PIMs were amitriptyline (n = 73), cyclobenzaprine (n = 49), hydroxyzine (n = 37), diazepam (n = 36), promethazine (n = 33), carisoprodol (n = 31), and indomethacin (n = 29). Data from 2 years later in a national sample of nearly 1.3 million Veterans Affairs (VA) beneficiaries aged 65 years or older for the period from October 1, 1999, through September 30, 2000, found a 23.0% overall prevalence of PIMs defined by the Zhan (2001) criteria, including 0.8% Always Avoid, 8.9% Rarely Appropriate, and 15.5% Some Indications. A separate study of nearly 1.1 million VA beneficiaries aged 65 years or older for the same 12-month period from October 1, 1999, through September 30, 2000, found a 19.6% overall prevalence of PIM use using the NCQA-HEDIS 2006 list of DAEs to define PIMs. In both VA samples, propoxyphene was the highest use PIM (Table 2). In the study of approximately 1.1 million VA beneficiaries (98% male), 4.5% received propoxyphene at least once in the 12-month period (5.7% of females and 4.5% of males). A nearly identical rate of propoxyphene use (4.1%) was found in the study of nearly 1.3 million VA beneficiaries (also 98% male) for the same 12-month period. In the latter study, 51.9% of the VA beneficiaries who received propoxyphene had also received the drug in the preceding year.

Aside from propoxyphene being the most common PIM in the managed Medicare study described Fick et al. and in the 2 studies approximately 2 years later in VA beneficiary samples, there was more discrepancy than overlap in the prevalence of use of specific PIMs. There was similarity in the prevalence of use of diazepam (1.2% and 1.5% in the 2 VA samples and 1.5% in the Medicare HMO) but wide variation for most other PIMs. For example, the second most common PIM in the VA sample of 1.1 million beneficiaries was diphenhydramine, received by 3.5% of male and 4.7% of female beneficiaries, versus 0.1% of Medicare HMO members studied by Fick et al. Chlorpheniramine, another common antihistamine, was received by 2.1% of the VA population versus 0.3% of the Medicare HMO members. The disparity in use of these PIMs among VA beneficiaries versus Medicare HMO members may be attributed to differences in coverage (e.g., diphenhydramine and chlorpheniramine may have been excluded from coverage as over-the-counter drugs in the Medicare HMO and therefore not captured in pharmacy claims data). These examples suggest that caution is warranted when attempting to evaluate prevalence of use of specific PIMs across samples and that factors other than prescribing practices may explain variation in PIM use (e.g., drug coverage policies, formulary management, or nuances in claims administration or record-keeping practices).

Resilient Use of Propoxyphene

The survival of propoxyphene on the U.S. market through decades of controversy over its safety underscores the challenge in identifying drugs that are truly inappropriate and should not be prescribed, particularly for older adults. The Zhan criteria (2001), developed by a 7-member expert panel including geriatricians, a pharmacoepidemiologist, and a pharmacist under funding from the Agency for Healthcare Research and Quality (AHRQ), classified propoxyphene as “rarely appropriate” rather than “always avoid” because although it was judged never appropriate as a new drug for pain, it may be appropriate for continued use by a patient who has demonstrated tolerance for the drug, “is not abusing it, and expresses a strong preference” for continued use. The Beers criteria expert panel in 1997 classified the severity of adverse effects associated with propoxyphene as “not high,” and the Beers 2003 criteria classified propoxyphene severity of adverse effects as “low.” The prevalence of propoxyphene use in older adults has been persistent despite its inclusion in the HEDIS list of DAEs from the NCQA since 2006 and assessment of the DAE utilization rate as a quality measure for health plans including all Medicare managed care contractors.

The analyses of PIM prevalence reported by Zhan et al. as part of the AHRQ-funded development of a 3-category, 33-PIM list found that propoxyphene utilization, measured as the percentage of community-dwelling elderly receiving propoxyphene, rose from 4.8% in the 1987 National Medical Care Expenditure Survey, to 5.6% in the 1992 Medicare Current Beneficiary Survey, and 6.2% in the 1996 Medical Expenditure...
Panel Survey (Table 2). Over an 18-month study period from January 2000 to through June 2001, Barnett et al. found that 7.0% (n = 11,034) of 157,517 Medicare beneficiaries enrolled in 10 private HMOs received at least 1 prescription for a propoxyphene product.\textsuperscript{31} Propoxyphene was the highest-use PIM in this study of older adults in managed care, and more women (8.5%) than men (5.0%) had records of propoxyphene use. In a later 18-month period from April 2002 through September 2003, 3.0% (n = 3,692) of 123,633 VA beneficiaries aged 65 years or older in 10 regions of the country received at least 1 prescription for propoxyphene, with similar rates of propoxyphene use among males (3.0%) and females (3.6%).\textsuperscript{31} The lower rate of propoxyphene use in this VA sample of older adults in 2002-2003 is likely attributable to the nonformulary status of propoxyphene (information about propoxyphene's formulary status in the Medicare HMOs was not available). However, despite its nonformulary status, propoxyphene was dispensed to at least 3.0% of VA beneficiaries, and the actual utilization of propoxyphene was probably much higher because medications dispensed by non-VA pharmacies were not recorded in the VA database.

More recent data show that propoxyphene continued to account for a large share of PIM use in the Medicare Part D program. For example, the quality improvement organization (QIO) for Florida reported that propoxyphene including combination with acetaminophen accounted for almost one-third of all PIMs in Medicare Part D claims in Florida in the last 6 months of 2007,\textsuperscript{32} and the QIO for North and South Dakota reported that propoxyphene was received by approximately 5% of Medicare Part D beneficiaries or 35% of all PIMs in North Dakota in the 6 months through September 30, 2008.\textsuperscript{33} In South Dakota, propoxyphene was received by approximately 7.2% of Medicare Part D beneficiaries or 44% of all PIMs, nearly the same proportion as the 41% of PIMs reported by Fick et al. in a managed Medicare population 10 years earlier.\textsuperscript{25}

**Actual Harm Versus Predicted Harm – High Noise-to-Signal Ratio**

There is a distinct lack of consensus on which drugs pose an increased risk of harm, and the dissonance can be large. For example, previous research showed that 59% of 46 preventable drug-related morbidity (PDRM) factors accepted by expert panels in the U.S. were rejected by expert panels in the U.K.\textsuperscript{34} Such disagreement among experts is understandable because new evidence is constantly emerging, and circumstances differ among practice settings. Among the 27 PDRM factors accepted by panel experts in the U.S. but rejected in the U.K. were (a) use of a tricyclic antidepressant; and (b) the risk of liver toxicity associated with troglitazone (Rezulin), the latter because troglitazone had already been withdrawn from the market in the U.K.\textsuperscript{35} From this perspective, lists such as DAE from NCQA and PIMs should not be viewed as definitive indicators of population-level harm, but instead provide guidance for evaluation of the appropriateness of use in individual cases and opportunities for continuous evaluation of the evidence that supports the association between PIM exposure and actual patient harm. As suggested in the 2 reports from Solomon et al. in December 2010 and the recent evidence of unexpected harm associated with rosiglitazone and bisphosphonates, studying the relationship between suspected and actual harm associated with drug therapy should be an ongoing, continuous quality improvement process.

Steinman et al. (2009) assessed the appropriateness of drug use at the Iowa VA Medical Center in 256 elderly outpatients using 5 or more medications, finding little concordance between PIM criteria and actual “problematic” drug use as assessed by a physician-pharmacist team.\textsuperscript{36} The team identified 563 of 3,678 drugs (15.3%) received by the 256 elderly outpatients as “problematic;” versus 214 PIMs (5.8%) according to the Beers criteria and 91 (2.5%) by the Zhan criteria. The expert reviewers rejected as nonproblematic 61% of the Beers criteria PIMs and 49% of the Zhan criteria PIMs. In other words, this analysis found false-positive rates for Beers and Zhan criteria of 61% and 49%, respectively, and both lists had large false-negative rates for “problematic prescribing.”

**Beers PIMs Do Not Predict ER Visits for ADEs in Older Adults**

Although there is considerable research reported for the use of PIMs, there is surprisingly little reported on actual harm manifest as adverse drug events (ADEs). The disparity between noise and true signal in PIMs was investigated by Budnitz et al. (2007) using a national public surveillance sample of hospital emergency room (ER) visits in 2004 and 2005 for persons aged 65 years or older. Based on a sample of 4,492 ER visits for ADEs, Budnitz et al. estimated that 177,504 ER visits associated with ADEs in elderly patients occurred in the United States in each of the 2 study years.\textsuperscript{37} Of the total estimated ADE-related ER visits per year, only 6,452 (3.6%) were attributed to the 41 drugs defined as “always potentially inappropriate” in the most recent (2003) list (e.g., indomethacin, cyclobenzaprine, propoxyphene). A higher estimated number of ER visits (n = 9,308) was associated with the 7 Beers list drugs defined as “potentially inappropriate in certain circumstances” (e.g., daily fluoxetine, naproxen, short-acting benzodiazepines such as alprazolam at doses of more than 2 milligrams [mg]). In contrast, 3 drugs not on the Beers list of drugs defined as always potentially inappropriate accounted for 33.3% of the ADE-related ER visits: warfarin (17.3%), insulin (13.0%), and digoxin (3.2%). Although lower in severity than the digoxin-associated ADE-related ER visits (80% of which resulted in hospitalization), an additional 10.4% of ER visits were associated with aspirin (5.7%) or clodigorel (4.7%). In the context of actual outpatient use of all drugs, the risk of ADE-associated ER visits was 35 times higher for warfarin,
insulin, and digoxin combined than for the Beers list of PIMs considered to be always potentially inappropriate (206 versus 5.6 per 100,000 outpatient prescription visits).37 This evidence suggests that efforts to improve patient safety in drug therapy in older adults would be better spent in diligent monitoring of drugs known to be associated with harmful ADEs rather than “prescriber education” about PIMs.

The important work reported by Budnitz et al. substantiates the risk of potential harm posed by propoxyphene, but the risk is small from a population perspective. The 0.5% of ER visits associated with propoxyphene ADEs, and the same rate for nitrofurantoin, placed these 2 drugs behind the anticholinergics and antihistamines (0.9%) in the proportion of ADE-related ER visits attributable to the 41 Beers list PIMs that are defined as always potentially inappropriate.37 However, this rate for propoxyphene means that it accounted for only about 1 in 200 ADE-related ER visits in 2004-2005, less than the 0.6% of ER visits attributed to naproxen and piroxicam combined. In other words, the market withdrawal of propoxyphene will have a large impact on the proportion of patients who receive PIMs, but it will probably not have a perceptible effect on the number of ADE-related ER visits.

Specific Drugs Related to Hospital Admissions

There is surprisingly little published research regarding the specific drugs that are most commonly responsible for drug-related hospital admissions. In a systematic review, Howard et al. (2006) found 17 prospective observational studies that described the proportion of hospital admissions that were drug-related and preventable and either the types of medications or underlying causes associated with preventable drug-related admissions.38 A median 3.7% (range 1.4%-15.4% in 13 studies) of hospital admissions were found to be drug-related and preventable, and 51% of the preventable drug-related admissions involved 4 classes of drugs (9 studies): antiplatelets (16.0%), diuretics (15.9%), NSAIDs (11.0%), anticoagulants (8.3%), or opioid analgesics (4.9%). Four of the studies evaluated by Howard et al. included patients aged 65 years or older, and 2 small studies of elderly patients found 12.0% of 150 hospital admissions39 and 15.4% of 240 hospital admissions40 to be drug-related and preventable, but an additional larger study found 4.3% of 1,011 hospital admissions to be drug-related and preventable.41

The systematic review by Howard et al. also provides some information regarding the underlying causes of hospital admissions attributable to preventable ADEs. Across 5 studies in which ADE-related hospital admissions were examined for underlying cause, a median 33.3% were attributed to problems with patient adherence, 22.2% to inadequate monitoring, and 30.6% to problematic prescribing; 12.5% of ADE-related admissions were unclassified as to cause.38 The work reported by Gandhi et al. for ADEs reported by ambulatory care patients suggests that there is considerable opportunity for clinicians to be more attentive to medication-related symptoms for the 11.0% of ADEs that were deemed preventable.42

One Step Forward or 2 Steps Backward in Protecting Patients from ADEs?

Collectively, the 2 studies reported by Solomon et al. in December 2010 advance knowledge of the relative harms and benefits of 3 classes of drug therapy commonly used in older adults and for individual drugs in the opioid class. One study challenges the theory that opioid analgesics are safer than non-opioid analgesics in the elderly,8 and the second study suggests that the individual opioids pose different risks across the spectrum of adverse events. Compared with hydrocodone, codeine was associated with increased risk of cardiovascular events, and tramadol and propoxyphene may pose less risk of fracture compared with hydrocodone.9 The latter finding contradicts research now nearly 20 years old that found a similar risk for hip fracture for propoxyphene and hydrocodone.10 The action by the FDA in November 2010 to remove propoxyphene from the U.S. market will seemingly have uncertain effects in protecting patient safety. We do know from the work of Budnitz et al., however, that hydrocodone-acetaminophen accounted for 1.7% of ADE-related ER visits, more than 3 times the number of ER visits associated with propoxyphene ADEs.

From one perspective, it can be argued that the recent research reported by Solomon et al. in 2 studies raises more questions than it answers. On the other hand, although we don’t necessarily know with a degree of certainty which drugs are less harmful in older adults, it seems that we now know more about the magnitude of what we don’t know in this regard. And importantly, it is increasingly inescapable that the rewards in improved patient safety will derive from increased attention from pharmacists and physicians to continuous monitoring of patient response to drug therapy, particularly for chronic drug therapy in older adults.

Managed Care Interventions to Reduce Prevalence of PIMs

Among the managed care interventions that have been conducted with the intent to reduce the use of PIMs in older adults was a 4-year, 3-pronged effort reported in JMCP in 2005 by Kaufman et al.44 This intervention was conducted in a large HMO that included approximately 100,000 Medicare members with pharmacy benefits. After each calendar quarter over 4 years of the intervention, prescribers of certain PIM drugs received lists of their patients, the specific drugs dispensed to these patients, and suggestions for formulary therapeutic alternatives. In addition to the letters and patient drug profiles sent by mail, a clinical pharmacist called high-volume prescribers (i.e., those with 4 or more patients with PIMs in a given calendar quarter) by telephone to discuss therapeutic alternatives. The third prong of the intervention involved a 1-time general...
mailing to all network physicians and pharmacists of an article in the HMO's pharmacy and therapeutics committee's newsletter on the subject of “inappropriate prescribing in the elderly.” The mail and telephone interventions involved 8 target drugs defined as contraindicated based on the Beers list in calendar years 2000 and 2001 and 10 target drugs based on the Zhan list in calendar years 2002 and 2003 (Table 2). Although the authors had an ambitious goal of 0% use of the 8-10 contraindicated drugs, the first 2 years of the intervention were associated with little change, from 5.3% (n = 2,871) of 54,211 pharmacy benefit users receiving 1 or more contraindicated drugs in the base period in 1999 Q4, to 4.3% (n = 2,713) of 62,883 pharmacy benefit users receiving 1 or more contraindicated drugs in 2001 Q4.

The most noticeable change in the count of patients who received PIMs occurred after January 1, 2002, when the list of drugs was changed from 8 drugs to 10 drugs by (a) deleting propoxyphene (and combinations) from the target list, (b) increasing the threshold dose of amitriptyline to at least 50 mg per day, and (c) adding 3 drugs (dicyclomine, disopyramide, and hyoscyamine) to the target list. Although the use of propoxyphene was not reported separately in this study, the deletion of propoxyphene from the target PIMs (and addition of dicyclomine, disopyramide, and hyoscyamine), was associated with PIM use prevalence of 2.4% in the first quarter (2002 Q1) and a stable rate of 2.2% utilization of the 10 target PIMs over 4 calendar quarters in 2003. It is important to note, however, that this intervention reported by Kaufman et al. for a Medicare + Choice (now Medicare Advantage) plan captured utilization rates for calendar quarters, compared with 12-month or 18-month utilization rates for much of the other research in the literature on the prevalence of PIM use in older adults. Second, because Kaufman et al. reported utilization rates for pharmacy benefit users, these rates should be multiplied by about 0.65 to estimate utilization rates for eligible members; therefore, the pre-intervention rate in 1999 Q4 was about 3.4% for the 8 target PIMs that included propoxyphene, compared with about 2.8% in the second year of the intervention (2001), and about 1.4% in the fourth year of the intervention (2003) for the 10 target PIMs that excluded propoxyphene.

Interventions with Prescribers Have Limited Effect in Reducing PIM Use
In theory, it should be simple to reduce the threat to all patients posed by high-risk drug therapy, particularly in older patients who are at higher risk of gastrointestinal bleeding and fractures or other injury associated with falls. After all, that is what managed care implies—managing care to improve clinical, service-humanistic, and cost outcomes. But, as Graf reminds us, there is a large demand for relief from chronic pain, reported by about 50% of the population, and this demand increases with age. The path toward optimum balance between harm and benefit must surely pass through the valley of pain relief without risk of harm from gastrointestinal erosion or falls due to orthostatic hypotension or impaired reaction time. We are still looking for “the most important strategies that the nation can use to fight” the problem of inappropriate use of drugs in the elderly, as the DHHS described 9 years ago, while proclaiming that “provider behavior must be modified through education” along with “monitoring systems and patient and caregiver empowerment.”

In addition to the limited influence of a 3-part intervention to reduce utilization of 8-10 specific PIMs reported by Kaufman et al. in a managed Medicare population, other research has suggested that PIM use is resilient to prescriber interventions. Briesacher et al. (2005) found that the use of drugs defined as PIMs by the Centers for Medicare & Medicaid Services (CMS) was common among nursing home and assisted-living residents before and after these PIMs became subject to mandatory drug use review policy in July 1999. These PIMs were found in 28.8% of nursing home residents and 22.4% of assisted-living residents before mandatory drug use review. PIM use was little changed in nursing home residents after mandatory drug use review (25.6%; 95% CI = 24.1%-27.1%) and not significantly changed among assisted-living residents (19.0%; 95% CI = 16.7%-21.3%). This research suggested that the small decline in PIMs among nursing home residents could not be attributed to the intervention, and the authors reported that “nearly all” pre-intervention use of the PIMs “came from medications with some acceptable indications.”

PIM-DAE Identification is Only a Starting Point
The term “potentially inappropriate” should remind us that determination of prescribing problems and truly inappropriate medication use requires assessment of the characteristics of individual cases. In publishing their list of PIMs in older adults in 1997, Beers et al. cautioned that the list might be used as a screening tool or starting point for evaluation of the appropriateness of PIM use in individual patients. In their later work to classify drugs into the 3 categories Always Avoid, Rarely Appropriate, and Some Indications (Table 1), the Zhan-AHRQ expert panel was split regarding classification of 5 muscle relaxants (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, and methocarbamol). Some panel members judged that these 5 drugs should never be used in older adults because of lack of efficacy and the potential for adverse effects, but others argued that their use might be appropriate in a healthy older adult for a short course for acute back pain. As we have noted previously, there is considerable disagreement among “experts” about what constitutes a potentially inappropriate drug and which drugs are truly contraindicated in older adults. Nevertheless, the current NCQA-HEDIS quality of care measures for physicians include “use of high-risk medications in the elderly.” Crownover and Unwin reminded...
Protecting Patients from Adverse Drug Events: Propoxyphene, PIMs, and Drugs to Avoid in Older Adults

us in 2005 that the path toward identifying potential threats to patient safety associated with prescription drug use in older adults began in a systematic way in 1991. Dubbed by Crownover and Unwin as BOGSAT (bunch of old guys sitting around talking), the Beers used a Delphi method with a panel of 13 experts to create the initial Beers list (1991) of PIMs for nursing home residents. Over the 20 years since this initial BOGSAT, almost all of the PIM-DAE lists have been developed by expert panels, generally using a consensus technique such as a Delphi method. However, expert consensus panels may or may not produce evidence-based guidelines for practice, leading Crownover and Unwin to opine that PIMs are not DIMs (definitely inappropriate medications) and that the PIM lists are inadequate because they do not suggest therapeutic alternatives for PIM targets, such as amitriptyline, that have an evidence base to support their use. And, given the lack of evidence of actual harm associated with much of the PIM-DAE “high-risk medication” list, it may be reasonable to raise the question of whether PIMs might be considered in the context of “no harm, no foul,” leaving a large opportunity for continuous and attentive monitoring for ADEs in all chronic drug therapy in older adults.

DISCLOSURES

The authors report no conflicts of interest related to the subjects or products discussed in this article.

REFERENCES


Protecting Patients from Adverse Drug Events: Propoxyphene, PIMs, and Drugs to Avoid in Older Adults


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A Managed Care Organization’s Initiative to Improve Patient Safety in the Use of Concentrated Insulin

As obesity becomes more prevalent, so have cases of newly diagnosed diabetes. According to 2008 estimates, more than 18 million American adults have diabetes and 12.4% of them take both insulin and oral medications to treat their disease.1,2 Patients on both insulin and oral medications commonly present a therapeutic challenge to clinicians attempting to attain tight glycemic control and hemoglobin A1c levels within a desirable range. Often, this group will develop insulin resistance, defined by Cochran et al. as a situation where a patient requires greater than 200 units of insulin daily.3 Because of this problem, an increase has occurred in the utilization of concentrated U-500 regular insulin.

In 1952, U-500 insulin was introduced to market in the United States as beef regular insulin. Later on, the pork version was approved in 1980, followed by the human version in 1997. From June 2007 to June 2009, utilization rates of human U-500 insulin jumped by 137%, mostly because of increases in the number of obese, clinically insulin-resistant patients with type 2 diabetes.4

Understanding of the pharmacokinetics and pharmacodynamics of U-500 insulin is increasing along with its use. Cochran et al. described that U-500 has a pharmacokinetic profile similar to that of U-100 neutral protamine Hagedorn (NPH) insulin, with slowed absorption and longer duration than U-100 regular insulin.5 In addition, although an inverse relationship generally exists between insulin concentration and absorption, the absorption curves for U-500 appear to differ in obese versus nonobese patients and with lower, subtherapeutic doses versus higher, clinically therapeutic doses.6

U-500 Insulin Is a High-Alert Medication

Because of its high concentration, U-500 insulin is generally regarded as a high-alert drug. The Institute for Safe Medication Practices (ISMP) has repeatedly reported the need for caution and the potential for medication errors when using U-500. For example, in 2001 they recommended that only tuberculin syringes—not U-100 syringes—be used to measure U-500 insulin to ensure correct dosing.7 To illustrate the problem with U-100 syringes, the ISMP safety alert described a case in which an endocrinologist wrote an order for “25 unwits of U-500 insulin” to be given in the morning. The intended insulin dose was 125 units, but because the physician did not specify the “25 unit” marking to be used on the U-100 insulin syringe scale, the patient only received one-fifth of the prescribed dose, or 25 units.8

In 2008, the manufacturer of U-500 insulin conducted a comprehensive evaluation of its database to search for potential errors associated with the medication. The evaluation came in response to a report released a few months earlier by the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System. The manufacturer identified 22 cases of medication errors in its database, with 82% of them related to administration or dispensing.4 Because reporting of medication errors to the manufacturer is voluntary, the actual numbers may be higher.

In the outpatient setting, U-100 insulin syringes are commonly used for the administration of U-500 insulin. A patient is trained to measure his or her “dose” by drawing up to a certain marking on the U-100 syringe. However, problems can arise with this approach. If a patient is hospitalized, he or she may incorrectly report the U-100 marking as his or her actual dose of insulin. In addition, when physicians order concentrated insulin in this manner, the dose is ambiguous, and the dispensing pharmacist may counsel a patient incorrectly, sometimes contradicting what the office staff previously said to the patient.

Intervention to Increase Access to Tuberculin Syringes

Thorough patient education on the use of U-500 insulin can help decrease these medication errors. The prescriber can also help by ordering the actual insulin dose with the volume. Another strategy is to avoid use of U-100 syringes and use only tuberculin syringes with U-500 insulin.

In keeping with this recommendation from the ISMP to use tuberculin syringes rather than U-100 syringes, EmblemHealth, a health plan with about 3.3 million members, undertook an initiative to increase safety with the use of U-500 insulin by improving access to tuberculin syringes. Recognizing that clinicians tend to favor U-100 syringes because of their greater availability and lower cost, EmblemHealth created a policy in which tuberculin syringes are covered under the pharmacy benefit, effective November 1, 2010. Whenever a claim for U-500 insulin is processed, the online claims adjudication process system automatically allows coverage of the tuberculin syringes at the point of service. The tuberculin syringe claims will adjudicate under either the first- or second-tier copayment of the member, depending on the pharmacy benefit rider for that member.

To increase recognition of this new policy, EmblemHealth mailed letters to all plan physicians or nurse practitioners who were identified in pharmacy claims as the prescribers of U-500 insulin for dates of service from April 1, 2010, through September, 30, 2010. The letters were also sent to all endocrinologists (n = 1,013) in EmblemHealth’s physician database system. In addition, information about the new policy was posted on EmblemHealth’s website.6

A total of 1,037 letters were mailed in October 2010. The letter described the new policy, how to properly prescribe concentrated insulin (i.e., actual U-500 insulin dose with the corresponding volume of the dose), and why ISMP recommends the use of tuberculin syringes with U-500 insulin.

A review of our paid pharmacy claims database revealed...
that U-500 regular insulin accounted for only 195 (0.2%) of all insulin claims (n = 83,470) in the 6-month period from April 1, 2010, through September 30, 2010; there were 59 prescribers of U-500 insulin for a total of 90 patients. Of the prescribers, 25 were endocrinologists (as identified by their self-reported specialty in our database) and 34 were nonendocrinology specialists (7 internal medicine, 5 family practice, 3 nurse practitioners, and 19 unknown).

Our hope is that prescriber awareness of this initiative will increase the use of tuberculin syringes in patients who are prescribed U-500 insulin, potentially decreasing medication errors and increasing medication safety.

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