Effective Cholesterol Management With Fewer Dollars

Employers, government, and health plans look to managed care pharmacists for ideas and programs to deliver the same or better outcomes at lower cost. Managed care pharmacists can look to the experience at Kaiser in Northern California in 2002 for a combination of methods to improve the efficiency of cholesterol reduction within coronary risk management. Kaiser and its 3 million members in North California use a computerized (electronic) medical record (EMR) and generic lovastatin to achieve superior clinical outcomes at lower cost for members with elevated cholesterol. In advance of the December 2001 introduction of generic lovastatin, Kaiser revised its cholesterol management strategy to start all new patients on generic lovastatin and dose lovastatin to target goal of low-density lipoprotein (LDL); atorvastatin is used only in patients who cannot tolerate lovastatin or cannot reach LDL target goal. Kaiser found that it can treat 5 patients with lovastatin for the same drug cost as just one patient on atorvastatin. The EMR and clinical practice guideline yield superior clinical results, with 60% to 70% of new patients still taking the statin drug at one year compared to the national benchmark of about 30%. About 85% of Kaiser Northern California members on a statin drug have LDL cholesterol below 130mg/dL, nearly twice the national average of 45% and nearly 4 times Kaiser’s 22% rate in 1997. The value-for-money interventions at Kaiser extend to the use of generic beta-blockers and generic lisinopril in patients with or at high-risk of heart failure. Kaiser data also appeared to show that longer-term outcomes are superior, as measured by a 30% lower risk of death due to heart disease among Kaiser members compared to other Californians.

Tablet Splitting to Improve the Value-for-Money Equation in Cholesterol Management

In a previous issue of the Journal, Calabrese and Baldinger described a dose optimization program using pharmacy claims data to target patients in 15 drug categories to achieve $1.67 per-member-per-year (PMPY) or $0.14 per-member-per-month (PMPM) savings, in 2001 dollars, across the entire population of 234,000 members. This intervention included 3 statin drugs. In this issue of the Journal, Gee, Hasson, Hahn, and Ryono describe another value-for-money intervention involving tablet splitting of 3 statin drugs. Conducted prior to the market introduction of generic lovastatin, the researchers found that tablet splitting was associated with favorable clinical (laboratory) outcomes and humanistic-service outcomes while creating the opportunity to treat nearly twice as many patients for the same cost.

This work by Gee, Hasson, Hahn, and Ryono is at least the third published study of tablet-splitting interventions that has found favorable clinical or service outcomes attendant to significant improvement in cost outcomes. There are 2 studies that have measured the effects of tablet splitting on clinical outcomes. As noted by the authors, their work was preceded by a small study that found no significant difference in blood pressure among patients who took whole tablets of lisinopril compared to the same patients who crossed over to split tablets of lisinopril. A second study was conducted among patients who split tablets of the anticholesterol drugs simvastatin and atorvastatin, 2 of the 3 statin drugs studied by Gee, Hasson, Hahn, and Ryono. As with the current study, there was statistically significant but not clinically significant improvement in intermediate outcomes (i.e., serum lipid levels). However, unlike the work of Gee, Hasson, Hahn, and Ryono, the earlier study involved a small number of patients (N=125) and did not measure humanistic outcomes (e.g., service perception or patient satisfaction).

Another point regarding the study of Gee, Hasson, Hahn, and Ryono is remarkable. These authors recognize the important distinction between clinical analysis and statistical analysis. The relatively large study population, 519 patients in their Phase III analysis of laboratory values, contributed to findings of statistical significance for key intermediate clinical outcomes, lipid serum levels, for the tablet-splitting period compared to the prior period. Low-density lipoprotein (LDL) improved to an average 97 mg/dL in the tablet-splitting period from an average 102 md/dL prior to tablet splitting, a relative improvement of 5% (P<0.001). While the authors correctly point out that this finding is not clinically significant, it could be of practical significance since the change could be described and construed as significant improvement according to internal and external reviews of health plan performance for quality-of-care measures. For example, the performance measure for “Cholesterol Management—Control” within the HEDIS (Health Plan and Employer Data Information Set) is defined as “the percentage of health plan members aged 18 to 75 who had evidence of an acute cardiovascular event (hospitalization for acute myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty) and whose LDL-C was screened and controlled to less than 130 mg/dL in the year following the event.” The Adult Treatment Panel III guidelines of the National Cholesterol Education Program of the National Heart, Lung, and Blood Institute released in May 2001 lowered the ideal LDL level to below 100mg/dL for “high-risk” patients. According to a standard of 100mg/dL LDL-C, the tablet-splitting intervention described by Gee, Hasson, Hahn, and Ryono, could make the difference between success and failure in the determination of a “high-performing” health plan and “failure” to manage cholesterol successfully.

Single-Patient Trial (SPT) Method—Substitute for Expert Opinion?

A remarkable 40% of patients with gastroesophageal reflux disease (GERD) treated with proton pump inhibitors (PPIs) were found by the single-patient trial (SPT) method to achieve the same or better outcomes as these patients treated with ranitidine. This work by Wolfe, del Rio, Weiss, et al. suggests that spending on drug treatment for GERD could be reduced by more than one third since histamine-2 receptor antagonists such as ranitidine cost managed care organizations (MCOs) $.50 or less per day of therapy versus $4 or more per day of therapy with a PPI. All of the H2-antagonists (cimetidine, ranitidine,
famotidine, and nizatidine) were available from generic manufacturers by mid-2002. The availability of generic omeprazole, anticipated at year-end 2002 or early in 2003, would, of course, mitigate the impact of this SPT research on H₂-antagonists versus PPIs in 2003 and thereafter. However, the research method itself is intriguing and may have application for other disease conditions.

Readers will note that the authors used the Federal Supply Schedule to make their cost comparison for omeprazole versus generic ranitidine. While the prices in this schedule are not relevant to most MCOs, the relative cost difference is representative of the experience of most MCOs. Actual MCO cost-savings net of copay for the use of generic ranitidine versus (brand) omeprazole would generally exceed $2.50 per day of therapy or about $912.50 per year, greater than the $718.44 absolute savings per patient per year estimated by the authors.

### Paying for Value in the Management of Multiple Sclerosis

In mid-May 2002, federal health officials announced that Medicare would cover interferon beta-1a (Avonex, Biogen) for multiple sclerosis (MS) but not 3 other commonly prescribed MS disease-modifying medications. The policy change was disclosed in a memo sent to the private health plans that are under contract to process Medicare Part B claims for the government. Effective August 1, 2002, Medicare would pay for injectable drugs that beneficiaries self-administer less than 50% of the time, according to the Centers for Medicare and Medicaid Services (CMS). The new guidance clarifies Medicare policy for determining whether a drug is “not usually self-administered” and therefore eligible for coverage under federal law. By this time, Medicare contractors had interpreted past guidance in varying ways, and, at the time of the announcement, CMS reported that fewer than half of Medicare carriers were paying for Avonex. The logic used by CMS in making the new coverage determination for Avonex but not the other 3 products was that Avonex is injected into muscle, allowing the presumption that it is usually not self-administered, meeting the criteria for Medicare coverage. Rival MS therapies, on the other hand, are not covered because they are administered subcutaneously and therefore eligible for coverage under federal law. Up to this time, according to the Centers for Medicare and Medicaid Services (CMS). The new guidance clarifies Medicare policy for determining whether a drug is “not usually self-administered” and therefore eligible for coverage under federal law. By this time, Medicare contractors had interpreted past guidance in varying ways, and, at the time of the announcement, CMS reported that fewer than half of Medicare carriers were paying for Avonex. The logic used by CMS in making the new coverage determination for Avonex but not the other 3 products was that Avonex is injected into muscle, allowing the presumption that it is usually not self-administered, meeting the criteria for Medicare coverage. Rival MS therapies, on the other hand, are not covered because they are administered subcutaneously and could typically be self-administered by the patient.

The competing products for treatment of MS at the time of the federal ruling included interferon beta-1a (Rebif, Serono SA), glatiramer acetate (Copaxone, Teva Pharmaceutical Industries, Ltd.), and interferon beta-1b (Betaseron, Chiron Corp., marketed by Schering AG’s Berlex Laboratories).

There is no cure for MS, and the treatment goal centers on prevention of relapses and retarding progression of the disease. There are 4 categories of disease: relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive relapsing (PRMS). As with many diseases, MS patients respond selectively to drug therapy. Disease-modifying therapy available today is most effective for the RRMS form, the type of MS most common early in the disease process. All 3 of the beta interferons and glatiramer are approved by the U.S. Food and Drug Administration only for the RRMS form of MS.

In this issue of the Journal, Ollendorf, Jilinskaia, and Oleen-Burkey found a small but measurable advantage in clinical outcomes (i.e., incidence of relapse) and cost outcomes (i.e., drug cost and total direct costs of MS-related care) for glatiramer compared to 2 beta interferon products. Glatiramer requires daily dosing, while beta-1b is administered every other day, and beta-1a (Rebif) is administered subcutaneously 3 times per week. Beta-1a (Avonex) is dosed less frequently, just once per week, but is administered intramuscularly. The study by Ollendorf, Jilinskaia, and Oleen-Burkey appears to find some advantage in cost of care with glatiramer, but, interestingly, the cost savings did not stem from less laboratory testing for liver function, thyroid, and complete blood counts, an outcome that might be expected based upon product labeling. However, as the authors note, utilization of laboratory tests was low across all 3 disease-modifying agents in their study.

### New Generic and OTC Drugs Provide Opportunities for Drug Benefit Managers

At year-end 2002, for the first time in history, the same strength and dose of a prescription drug was near approval by the FDA for over-the-counter (OTC) use. This milestone was made more significant by the coincident consideration of not one but 2 blockbuster prescription drugs. A decision from the FDA regarding OTC sale of loratadine 10 mg was expected on or before the end of November 2002, and the FDA was expected to approve omeprazole 20 mg for OTC sale late in 2002 or early in 2003. Both developments are significant. For loratadine, the OTC approval of the 10 mg strength could eliminate the prescription version, because under arcane FDA rules, a prescription drug cannot coexist with an OTC drug of the same dose and strength for the same indication. For omeprazole, the market effects would be presumably different since prescription omeprazole is indicated for gastrointestinal ulcers, gastroesophageal reflux disease (GERD), and “other symptoms associated with GERD,” while the OTC version of omeprazole has a narrow, tentative approval for short-term relief of “heartburn.” In the world of high-stakes marketing of prescription drugs, these are unprecedented events. At the same time, Congress was strenuously debating ways to reduce the burden of prescription drug costs for federal programs and the uninsured. The strategic acts by the maker of loratadine and desloratadine could have a negative impact on generic prescription drug competition. Harrington and Shepherd provide a comprehensive review of the regulations and developments in the marketing of OTC drugs that were previously available only by prescription.

Generic omeprazole was still not available to U.S. consumers in October 2002, one year after the patent on omeprazole expired. The manufacturer of omeprazole had reportedly invested 7 years in developing a strategy to negate the market erosion curve expected for omeprazole. The preferred method involved development of a replacement drug with superior...
properties, but the strategic planning process reportedly resulted in the creation of nearly 50 possible solutions, including legal challenges to the introduction of generic competitors. By the measure of influence on the market erosion curve of omeprazole, the investment in strategic planning was successful, as evidenced by the absence of generic omeprazole one year after the expiration of the patent on omeprazole. (The omeprazole patent expired in April 2001 but was extended to October 2001 by the conduct of a clinical study in pediatric patients.) The generic introduction of the first proton pump inhibitor (PPI) in the United States is much anticipated by pharmacy benefit managers, and the effects of the patent lawsuits are acutely obvious to managed care pharmacists. The legal challenges developed by the manufacturer of omeprazole began in 1985, 4 years before the drug was launched in the United States.17 Such legal challenges may not delay generic competition but have the minimum effect of ensuring that, when the patent lawsuits are resolved by the courts, one generic manufacturer has market exclusivity for the first 6 months. A 1984 federal law stipulates that a generic manufacturer that is challenged by a brand manufacturer in court is permitted 6 months of market exclusivity for the generic drug once the patent challenges are resolved.18

Managed care pharmacists might be interested in some of the legal arguments made in the course of the 17-year history of patent challenges regarding omeprazole. For example, a patent complaint was filed by the manufacturer for the use of omeprazole in combination with antibiotics for the eradication of Helicobacter pylori. The argument was that physicians could not prescribe omeprazole in combination with the use of antibiotics for heartburn because this practice would violate the patent.17 A patent dispute in New York commenced in December 2001, and the trial was concluded in June 2002. Four months later, on October 11, 2002, the U.S. District Court ruled that 3 of the 4 generic manufacturers had infringed on patents related to the subcoating formulation for omeprazole.19 The court found that the fourth generic manufacturer had its own patented method for a subcoating formulation for generic omeprazole, and this manufacturer had FDA approval to market its generic omeprazole, but this was not the generic company that held the original abbreviated new-drug application and the 6 months of market exclusivity for generic omeprazole. Therefore, the U.S. District Court decision in October 2002 made the date for the introduction of generic omeprazole in the U.S. market uncertain.20 Every day that the legal dispute continued earned another $10 million in omeprazole sales.

### Direct-to-Patient Advertising (DTPA) and Direct-to-Consumer Advertising (DTCA) of Prescription Drugs

A publishing company in St. Louis reported in mid-2002 that 17,000 community pharmacies were participating in “direct-to-patient-advertising” (DTPA) in 2002 compared to just 3,000 3 years earlier.21 The pharmacy chains that contracted with the company in 2002 included some of the largest chain drug stores in the United States. The practice of DTPA involves generation of a patient-specific “health newsletter” that is based primarily on the drug prescribed but is customized to the patient name, age, gender, and whether the patient has drug insurance coverage. While the fine print in the health newsletters identifies the drug company sponsor, this practice could undermine the ability of the pharmacist to provide unbiased counseling to patients. For the drug companies, the practice permits marketing messages to be wrapped in the patient-pharmacist interaction. Marketing promotions in the “health newsletters” sometimes included recommendations for patients using low-cost generic drugs to switch to higher-cost sustained-release versions of the same drugs. In other cases, these patient-specific newsletters targeted users of a competing company’s drug, urging patients to switch to the drug manufactured by the drug company that sponsored production of the newsletter. One billion such DTPA newsletters were expected to be produced in pharmacies in 2002, sponsored by 18 of the 20 largest U.S. drug companies, each paying as much as $10M to produce the health newsletters.

Eighteen months after the publication of federal rules that relaxed direct-to-consumer advertising (DTCA) of prescription drugs, IMS Health reported there were 40 brand-prescription drugs being advertised on television and about 100 brand drugs advertised to consumers in print and other media.22 TV advertisements accounted for $825M (55% of the total $1.5 billion) compared to $686 million for consumer-targeted print advertising. In this issue of the Journal, Glasgow, Schommer, Gupta, and Pierson report case-specific results of DTCA that support the results of consumer surveys.23 At least 5 consumer surveys conducted from 1998 through the first-half of 2002 have found a remarkably high reported rate of success in converting DTCA of prescription drugs into prescriptions written by physicians. By a measure that we might call the ad-to-Rx (ATR) ratio, DTCA of prescription drugs is very effective at generating new prescriptions. The ATR ratio ranges from 9% to 24%, with a modal value of about 15%.

An early study in 1998 found that 28% of the elderly who saw a drug advertised on television spoke to their physician about the drug, and 33% received a prescription for the requested drug, an ATR ratio of 9%.24 A telephone survey of 1,205 adults of all ages conducted in the first half of 1999 found that 81% of respondents had seen, read, or heard an ad for a prescription drug (versus 63% in late 1997). 28% of those who had seen, read, or heard an ad asked their physician for the advertised drug, and an amazing 84% who reported asking their physician for the drug claimed to have received the requested drug, an ATR ratio of 24%.25 A survey of 1,093 persons conducted in 2001 found that 32% of respondents had talked to their physician about an advertised drug, 26% had actually requested a prescription for the advertised drugs, and 71% reported receiving the requested drug, an ATR ratio of...
a dizzying array of drug benefit designs among health plans and drug plans were feasible and even practical. Today, there exists 2-tier copay plans were common, and percentage cost-share member cost-share in plan design. By the end of the 1980s, spread implementation after 1985 permitted reconsideration of expectations did not exist. The adoption of electronic process- period before 1980, electronic claims processing of prescription charge in third-party payer vernacular) was not known. In the third-party prescription drug plans because the price (allowable nomenclature to use in defining these plans. To begin to answer these questions, we first need a common healthful for consumers and for the U.S. health care system? To begin to answer these questions, we first need a common language to define these plans.

Measuring Outcomes of 3-Tier Copay Drug Benefit Plans

The dramatic increase in drug benefit costs in the period beginning in 1998 and continuing through 2002 caused a very rapid uptake of the 3- and 4-tier copay drug benefit plan designs among private health benefit plans, including Medicare+Choice plans. Languishing among 2-tier copay and closed formulary drug plans for 6 to 7 years, health plans, PBMs, and employers embraced these multi-tier copay plans with new vigor in 1999 and thereafter. But are these “new” drug benefit designs healthful for consumers and for the U.S. health care system? To begin to answer these questions, we first need a common nomenclature to use in defining these plans.

Single copay plans were used early in the administration of third-party prescription drug plans because the price (allowable charge in third-party payer vernacular) was not known. In the period before 1980, electronic claims processing of prescription claims and the precision and accuracy that we have come to expect today did not exist. The adoption of electronic processing for prescription drug claims in the early 1980s and its widespread implementation after 1985 permitted reconsideration of member cost-share in plan design. By the end of the 1980s, 2-tier copay plans were common, and percentage cost-share drug plans were feasible and even practical. Today, there exists a dizzying array of drug benefit designs among health plans and self-insured employers. Specified dollar copayments are overlaid with coinsurance, sometimes with deductibles or benefit (dollar) maximums. There are 3-, 4-, and even 5-tier plans. Research on the effects of these plans on cost, utilization, member satisfaction, and medication adherence, as well as other outcomes, demands that we have a nomenclature to define drug benefit plan design. Terms such as “multi-tier” or “3-tier” are not sufficiently specific to permit effective communication among managed care pharmacists and interested parties. For example, a 3-tier copay design may have 2 copay amounts (tiers) for brand formulary drugs while another 3-tier copay design may have only one copay amount (tier) for formulary drugs (i.e., nonformulary drugs would be assigned to the third-copay tier). Most 3-, 4-, and 5-tier copay designs assign the lowest (tier-1) copay to generic drugs, but even this is not always true.

Thus far, there have been few reliable results produced from efforts to measure clinical, service (humanistic), or cost outcomes of the multi-tier-copay drug plan designs. In this issue of the Journal, Nair, Ganther, Valuck et al., report that 3-tier drug plan members had less favorable attitudes toward their plans compared to those in 2-tier plans. This work advances our inspection of the effects of 3-tier copay drug benefit plans versus 2-tier plans, but the results should be interpreted cautiously and the discussion evaluated critically. While the authors attempted to measure the effects of age as an independent variable, their study groups were dramatically different. The 2-tier copay group (N=2,316) had 11.7% of its members over age 65 versus 54.7% for the 3-tier copay group (N=1,499). Not surprisingly, higher out-of-pocket copayment costs are incurred by persons over age 65 due to higher prescription utilization. Also, only 10% of the tier-2 plan members were enrolled in Medicare+Choice versus 61.4% of the tier-3 plan members. All Medicare+Choice members had a $1,000 annual benefit maximum, a variable that would be expected to affect member attitudes, particularly for the members with chronic diseases that were the subjects in their study.

Managed care strives to obtain the same or better outcomes at lower cost, thereby creating the ability to restrain the absolute amount and relative increase in health care premiums. Lower premiums make care affordable to more persons. Higher premiums make insurance coverage affordable to fewer persons. A significant increase in the cost of health care and health care coverage in 2002 and 2003 can be expected to result in an increase in the number of uninsured. U.S. Census Bureau figures, released September 30, 2002, showed that the nation’s uninsured population grew 3.5% in 2001, from 39.8 million in 2000 to 41.2 million. Free health care would make rationing necessary. Cost sharing at the point of care reduces the cost of health care premiums and can be employed in multi-tier copayments to influence member choice of care (e.g., drug). Therefore, multi-tier copay plans represent quintessential managed care, maximum choice. It is unfortunate, but reparable,
that many managed care drug plans overcharge members for generic drugs with copays of more than $5 per 30-day supply. For example, an announcement in mid-2002 trumpeted a program to promote generic drugs to physicians, pharmacists, and consumers but was associated with a 3-tier benefit design of $12 (generic), $20 (tier-2) and $30 (tier-3) copays for a 30-day supply.\textsuperscript{37} The study by Nair, Ganther, Valuck, et al. adds to a thin literature on health plan member attitudes, other than satisfaction, related to prescription drug benefit plans. The study methods and interpretation of results should be reviewed carefully and critically. For example, the authors report statistically significant results that often appear to be an artifact of the large sample size and may have little if any practical significance, but, nevertheless, be of interest to some readers. For example, the authors reported that 3-tier plan members compared to 2-tier plan members may be more likely to consult with friends or family members to obtain information related to the purchase of prescriptions, but not the pharmacist, or that 3-tier plan members may be more likely to obtain a second opinion from another physician. In all of these cases, the absolute differences in the mean scores are very small, less than 0.25 points on a 7-point scale. In survey research, ask 100 questions, and 5 will be statistically significant simply by chance, at an a priori \( P \) value of 0.05. Survey enough respondents, and small differences in mean scores will produce statistically significant results.

\section*{JMCP Peer Review and Editorial Process}

The quality of the \emph{Journal} depends upon the collaborative work of authors, reviewers, and editors. Reviewers are often themselves authors, and more than 150 reviewers help to continuously improve the quality of the \emph{Journal}. The bias management policy of the \emph{Journal} is extensive and encompasses reviewers as well as authors. Members of the JMCP Editorial Advisory Board sometimes submit manuscripts for consideration, and these papers are treated no differently than any other manuscript.

All manuscripts submitted for consideration in the \emph{Journal} undergo a prereview screen to protect reviewers from work associated with a paper that, due to a fundamental flaw in research design or insufficient relevance to readers, cannot be revised sufficiently to earn publication in the \emph{Journal}. This prereview process is generally completed within 2 weeks of receipt of the manuscript. After passing the prereview process, each manuscript is sent to at least 3 independent reviewers, selected based upon expertise in one or more areas that are the principal subjects of the manuscript. All reviews are conducted under masking of author names and affiliations. Anonymity is the cornerstone of critical, scholarly review.

The JMCP bias management policy applies to all persons, regardless of their affiliation. In this issue of the \emph{Journal}, the chairperson of the Editorial Advisory Board, Marvin D. Shepherd, PhD, collaborated with another researcher, Patricia Harrington, to write a subject review on the very timely matter of the transition of drugs from prescription to availability over-the-counter (OTC). In this case, 3 expert peer reviewers agreed unanimously that the manuscript should be published, and the authors revised the manuscript according to all reviewer suggestions. The mission of JMCP is to provide reliable and timely information to assist managed care pharmacists in their efforts to maximize value for money and improve the quality of patient care.

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