Which Triptan?—
Opportunity for Same or Better Outcomes at Lower Cost

With 7 triptans on the market in the United States, there is considerable opportunity for managed care plans to negotiate significant price reductions from manufacturers for preferred formulary status, particularly under 3-tier benefit designs or in closed formularies (i.e., 100% member cost-share for nonformulary drugs). Last year, the Department of Defense and Veterans Affairs released a request for (price) proposal from manufacturers of 4 triptans (the newest triptan, eletriptan [Relpax], was apparently introduced after the RFP was prepared). The drugs under consideration by DOD/VA were almotriptan (Axert), sumatriptan (Imitrex), rizatriptan (Maxalt), and zolmitriptan (Zomig), based, in part, on prices bid in an RFP in October 2002. The RFP found the 4 triptans to be therapeutically equivalent, based on “similar outcomes, similar side-effect profiles, and sufficient safety data.”1 Naratriptan (Amerge) and frovatriptan (Frova) “should not be considered front-line agents” according to the VA “because of less favorable pain-free results at two hours as compared to the other triptans.” On April 7, 2003, the comptroller general denied a protest from the manufacturer of sumatriptan that claimed “discrepancies in the meta-analyses” and alleged superiority of sumatriptan; the comptroller general said, “Even accepting that sumatriptan could be considered superior, the agency’s determination that the differences between the drugs were not material for its purposes has not been shown to be unreasonable.”

In a previous article in this Journal, a meta-analysis showed that the number needed to treat to achieve 1 patient pain free at 2 hours was 3.2 patients for rizatriptan 10 mg, 4.2 patients for zolmitriptan 5 mg, 4.7 patients for either almotriptan 12.5 mg or sumatriptan 100 mg, and 5.9 patients for sumatriptan 50 mg. Naratriptan 2.5 mg required 8.2 patients, and frovatriptan 2.5 mg required 11.3 patients treated to achieve 1 patient pain free at 2 hours.2 In this issue of the Journal, Williams and Reeder found in their base-case analysis that the average cost-effectiveness ratios, using March 2004 prices, were $82, $133, and $138 per composite end point defined as Sustained pain-free and No Adverse Events (SNAE) for migraine attacks for almotriptan 12.5 mg, sumatriptan 50 mg, and sumatriptan 100 mg, respectively.3 In other words, sumatriptan had a price premium of 62% to 68% compared with almotriptan. The incremental cost-effectiveness ratios for almotriptan 12.5 mg were $12 and $16 (compared with sumatriptan 50 mg and sumatriptan 100 mg, respectively) per incremental attack at which SNAE is achieved. This research has significant value for managed care pharmacists by determining cost for the combined outcomes of efficacy and safety. Readers should note that this analysis by Williams and Reeder included the 67% price increase for almotriptan (from $10.99 average wholesale price per unit to $18.44 per unit) that was imposed in late 2003 when the drug was transferred from one manufacturer to another.

Does Member Cost Sharing Pose a Threat to Desirable Patient Outcomes?

Cost sharing by health plan beneficiaries is on the way up, both in dollar amounts or percentages and in the proportion of beneficiaries affected by cost sharing. In 2003, 96% of workers and dependents with health benefits sponsored by employers had either copay or coinsurance requirements for medical office visits, 92% were required to contribute to payment of the monthly family premium, 63% had 3-tier cost sharing for prescription drugs (up from 55% in 2002, 42% in 2001, and 27% in 2000), 79% had an annual deductible, 76% were required to contribute to the monthly premium for individual (single) coverage, 44% had a separate hospital deductible, and 8% had a separate prescription drug deductible.

Research published in late 2003 claimed that the introduction of 3-tier copay designs for prescription drug benefits resulted in patients discontinuing drug therapy.4 However, careful examination of the data in that study showed mixed and even contradictory results, including the finding that the discontinuation rate for angiotensin-converting enzyme (ACE) inhibitors was twice as high in the comparison (control) group compared with one of the employer 3-tier plans in the study.5 Wogen and Frech pointed out that there is, in fact, no consensus regarding the impact of patient copay on therapy persistence and adherence.

In this issue of the Journal, Meissner, Moore, Shinogle, Reeder, and Little found that an average $10 (47%) increase in copayment per prescription in a 3-tier drug benefit design for a public employer was associated with no statistically significant change in drug utilization per patient for 2 classes of drugs used to treat allergic rhinitis.6 The actual average copayment increase was $10.98 (71%) for nasal steroids (NSs), which was associated with an 11.3% decrease in utilization of NSs, primarily the result of a 10.2% decrease in the number of users of NSs in the year following the copay increase. However, the number of NS prescriptions per patient per year was unchanged at 2.05 versus 2.07 in the year prior to the copay increase (P = 0.842).

The combined utilization of low-sedating antihistamines (LSAs) and NS prescriptions increased by 8.9% following the increase in copayments for these 2 therapeutically interchangeable drugs for allergic rhinitis. Rather than causing a reduction in the utilization of LSAs, the imposition of a 3-tier copay drug benefit design and an average $7.23 (41%) increase in copayment per prescription was associated with a 14.8% increase in the use of LSAs, including an 11.8% increase in the number of patients using LSAs. The number of LSA prescriptions per patient per year was unchanged at 2.68 in the year following the increase in copayment compared with 2.61 in the year prior to the copay increase; P = 0.429. While not adversely affecting patient use of drugs to treat allergic rhinitis, implementation of the increase in copayment in the 3-tier drug benefit design was associated with the intended outcome of producing cost savings for the health plan. Health plan savings were 16.3% per patient, and these health plan savings would have been larger if the costs had been adjusted for inflation. The health plan costs for all drugs for these allergic rhinitis patients fell by 13%, also understated since the costs were not adjusted for inflation.
Alternate Managed Care Approaches to Disease Management of Allergic Rhinitis

Research in this issue of the *Journal* calls into question several claims for cost-effective disease management of allergic rhinitis. Szeinbach, Williams, Munterdam, and O’Connor found that nearly two thirds of users of low-sedating antihistamines (LSAs) with a medical diagnosis of allergy did not test positive for serum immunoglobulin E (IgE) specific to allergens for allergic rhinitis. Of the 66% of patients defined as frequent users of LSAs (3 or more LSA prescriptions in the 1-year study period), the proportion who tested negative for serum IgE was 62%.

Allergic rhinitis is the fifth most common chronic disease in the United States, affecting 10% to 30% of adults annually and up to 40% of children and contributing to sleep interruptions, lower quality of life, and reduced productivity. Disease-specific patient surveys have been developed and marketed to help measure the magnitude of adverse effect on quality of life and productivity and to guide disease management interventions for allergic rhinitis; the SF-36 and short form SF-12 have been criticized as imprecise for this disease. It is fairly easy to make a case for the use of LSAs or nasal steroids to reduce the social burden of allergic rhinitis, but what is the optimal approach to obtain the most favorable clinical and service outcomes at the lowest cost?

The advent of over-the-counter (OTC) loratadine reduced by more than 90% the average cost to treat allergic rhinitis symptoms with an LSA, now as little as $6.50 per month of therapy with OTC loratadine. Yet, many drug benefit plans have not realized the full value of this dramatic price reduction because they have not implemented managed care tools to steer members to this cost-effective alternative. Most prescription drug benefit plans do not cover OTC drugs, and most drug benefit plans in 2004 included coverage of either fexofenadine (Allegra) or cetirizine (Zyrtec) as a formulary drug (i.e., tier-2 copayment).

Therefore, the work of Szeinbach et al. remains relevant for several reasons. A reasonable argument could be made that unnecessary exposure to any drug, no matter how safe in the incidence of side effects, should be avoided. The use of a serum IgE test to rule out a false diagnosis of allergy would appear to be important if the test is not expensive. Examination of the usual and customary (U&C) charges of a private third-party administrator for Common Procedural Terminology code 86005 (allergen-specific IgE) in March 2004 revealed an allowed price of $140.65 in zip code 80262 (Denver, Colorado) and $121.65 in zip code 30606 (Athens, Georgia). Adding a physician office visit would push the allowed charge to more than $200 to test a patient for serum allergy, more than the net plan cost for 3 LSA prescriptions. However, a countervailing argument would count the costs of repeated physician office visits plus LSA costs for as many as two thirds of patients who may not benefit from LSAs due to the absence of true allergy.

One is left pondering the value of a placebo response in patients without true allergy, but the conclusion is clear for disease management of allergic rhinitis. Stratification of patients by severity of disease, including persistent symptoms, would seem to help define when a serum IgE test to determine true allergy may be warranted and prove to be cost effective when clinical, humanistic, and cost outcomes are considered in total.

Methods to Attain Optimal Outcomes With Lipid-Lowering Drug Therapy

Realizing value-for-money in lipid-lowering drug therapy involves more than selecting the drug with the greatest reduction in low-density lipoprotein cholesterol (LDL-C) per dollar of drug cost. In a previous issue of the *Journal*, Hay eloquently explored the relationship between cost per quality-adjusted life-year (QALY) and the percentage of annual coronary event risk in the range of less than 1% to more than 9%—cost per QALY drops significantly as the annual coronary risk increases. Hay noted the relative cost-effectiveness of generic lovastatin but also cited the model developed by Stinnett, Mittleman, Weinstein, et al. and concluded that niacin dominates lovastatin as a first-line therapy for hypercholesterolemia. In this issue of the *Journal*, Armstrong, Zachry, and Malone find, via cost-effectiveness analysis, that lovastatin with extended-release niacin (Advicor) is more successful and less costly than simvastatin for persons with LDL-C goals <130 mg/dL and <100mg/dL (and high-density lipoprotein >40mg/dL); i.e., the majority of Americans.

The market introduction of rosvuastatin in late 2003 increased the attention to ever more powerful statins and the relative cost-effectiveness among these drugs. Yet, managed care pharmacists should not lose sight of the cost per outcome in disease management of coronary heart disease (CHD). For example, comparison of 5 alternative prevention strategies in a patient at 10% coronary risk over 5 years showed that aspirin 75 mg per day is the most cost effective at £3,500 (British) pounds per CHD event prevented; 72% lower cost compared with initial treatment for hypertension with a diuretic (benzofluazide 2.5 mg per day) and beta-blocker (50 mg atenolol per day; 12,500 pounds); 81% lower cost compared with the £18,300 for the initial thiazide + beta-blocker combination + enalapril (angiotensin-converting enzyme inhibitor) 20 mg per day; 94% lower cost than the £60,000 for clopidogrel 75 mg per day or the £61,400 for simvastatin 40 mg per day. In other words, about 20 patients could be treated with aspirin to prevent CHD events for every 1 patient treated with either clopidogrel or simvastatin. Among the many aspects of this thorough analysis, calculation of the costs per outcome recognized that patients taking thiazide diuretics require annual measurement of serum electrolytes and uric acid, patients taking statins require annual measurement of serum lipid concentrations and liver function tests, and major bleeding attributable to aspirin.
had an estimated incidence of 0.3% over 5 years of treatment (0.3% was subtracted from the reduction in absolute coronary risk to account for major adverse effects).

Ohsfeldt observed that the Stinnett, Mittleman, Weinstein, et al. model assumes nearly “ideal” compliance (i.e., the discontinuation rates reported in randomized controlled trials) with niacin, an outcome rarely found in the real world. The oft-reported study of 2,369 new users of lipid-lowering drug therapy in 2 HMOs from 1988 through 1990 found the 1-year probability of discontinuation to be 46% for niacin, 41% for bile acid sequestrants, 37% for gemfibrozil, and 15% for lovastatin, the only statin on the market at the time of the study. Subsequent studies have found lower rates of adherence to lipid-lowering therapy—50% or even much lower. In a study of 29,534 managed care members aged 18 years or older who had CHD or atherosclerosis and were continuously enrolled from January 1, 1998, through December 31, 1999, only 5,943 (46%) continued statin therapy through study end. Only 59% (17,402 patients) had 1 or more cholesterol-monitoring tests during the 2-year study period. For a subgroup of 641 patients with at least 1 coronary event in 1998 and who had LDL-C data available for 1999, only 48% (308) reached National Cholesterol Education Program (NCEP) goal for LDL-C in 1999. In other words, less than one half of the patients on statin therapy were still on the therapy at the end of the 2-year study period, only 59% had at least 1 cholesterol-monitoring test, and only 48% of those on secondary prophylaxis with a statin had reached NCEP goal for LDL-C.

In fact, the real-world adherence to lipid-lowering therapy and attainment of target LDL-C goals appear to be much worse than predicted by the studies noted above. In 454 patients who received care at a preventive cardiology clinic in Cleveland and were prescribed a statin for the first time, 367 (81%) returned for follow-up LDL testing. The observed LDL reduction was less than expected for 3 statins (atorvastatin, simvastatin, and pravastatin), an average of 26% reduction versus 34% expected, and 27% of the patients had less than one half the expected LDL decrease. Analysis of 477 patients who were discharged from the hospital without lipid-lowering medication compared with 175 matched patients who were discharged on lipid-lowering medication found that 81% of the patients discharged on lipid-lowering drug therapy reported taking a lipid-lowering drug at 30 days postdischarge and 77% at 6 months. However, for the patients who started lipid-lowering therapy after hospital discharge, only 25% reported using the lipid-lowering medication after 30 days and only 13% at 6 months.

Even with patient adherence to statin therapy, the value-for-money equation shows a low return on investment for indications other than primary or secondary prophylaxis of coronary events. For example, while pravastatin and simvastatin are approved for secondary and primary prevention of stroke, respectively, the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial showed no effect on stroke in high-risk elderly patients (i.e., secondary prophylaxis) after an average of 3.2 years of therapy with pravastatin 40 mg per day: 4.7% incidence of fatal or nonfatal stroke in the pravastatin group versus 4.5% in the placebo group ($P = 0.81$). It was only in combination with the end point of death from CHD or nonfatal myocardial infarction (MI) that the pravastatin group was favored over placebo, an absolute incidence of 10.1% versus 12.2% ($P = 0.014$). This absolute difference of 2.1% translates into 48, the number needed to treat to prevent 1 either fatal or nonfatal MI or stroke or coronary death. At a total discounted drug cost of $4 per day, it would cost $224,256 of pravastatin in 2004 dollars to prevent 1 fatal or nonfatal MI or stroke.

In early March 2004, the Heart Protection Study Collaborative Group authored an article that trumpeted the importance of treating patients at risk of stroke with simvastatin. The recommendation was based upon analysis of outcomes data from 3,280 adults with cerebrovascular disease and an additional 17,256 with occlusive arterial disease or diabetes. Based upon the 5-year treatment period, there was an average 39 mg/dL reduction in LDL-C. There was a 1.4% absolute reduction in the first-event rate for all stroke (fatal and nonfatal), 4.3% in the simvastatin group compared with 5.7% in the placebo group. The authors touted the “highly significant 25% proportional reduction in the first-event rate for stroke.” This study involved a large number of patients; even this relatively small absolute difference (1.4%) would be statistically significant, and 25% sounds like a large proportion.

From a value-for-money perspective, the investment in simvastatin to prevent stroke does not appear to be terribly appealing. Setting aside the direct and indirect costs associated with adverse drug events in high-risk patients taking 40 mg of simvastatin per day for 5 years, the direct drug cost is large. Using discounted drug prices available in the United States at the time this study was published (March 2004), and the number needed to treat (NNT) (71.4) calculated from the Heart Protection Study, it would be necessary to spend between $520,000 and $540,000 on simvastatin to prevent 1 nonfatal stroke.

The results of the Heart Protection Study were preceded by publication in 2000 of a study of the effects of pravastatin in 9,014 high-risk patients with a history of MI or unstable angina. In that study, which was used to obtain U.S. Food and Drug Administration (FDA) approval of pravastatin for a stroke indication, there was an absolute 3.7% incidence of fatal and nonfatal stroke in the treatment groups versus 4.5% in the placebo group. This 0.8% absolute difference was touted as a 19% reduction in stroke. Translated into the NNT and the actual cost of pravastatin at discounted prices in March 2004, it would require nearly $1.1 million in drug (pravastatin) cost to prevent 1 nonfatal stroke. This cost estimate is conservative since it does not include the direct and indirect costs of adverse drug events associated with the use of pravastatin 40 mg per day for an
average of 6 years in patients with CHD. Expert observers later pointed out shortcomings in the research design, statistical analyses, and interpretation of the data that could undermine even the modest apparent favorable effect of pravastatin in the risk of stroke in CHD patients.\(^{33}\)

In addition to considerations of drug therapy adherence, lack of attainment of target LDL-C goal and high (unfavorable) cost-effectiveness ratios for stroke and for patients at low risk of coronary events, statins are not without adverse events. Despite the high profile and oft-mentioned market recall of cerivastatin (Baycol), potential drug interactions that could cause harm similar to that reported with cerivastatin appear to go unrecognized and underappreciated. Petropoulos and Bello-Quintero in this issue of the Journal found that among 11,677 patients on simvastatin therapy, 1,231 (10.5%) were prescribed at least 1 potentially interacting medication and more than one half (57.8%) of simvastatin doses were above the maximum recommended daily dose when prescribed with potentially interacting medications.\(^{34}\)

Atorvastatin is the most prescribed statin and the number one prescription drug by sales in the United States.\(^{35,36}\) Clopidogrel is used increasingly in patients with acute coronary syndrome (unstable angina/non-Q-wave MI), including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or coronary artery bypass graft. Most of these patients also receive statin drug therapy; many no doubt receive atorvastatin. Atorvastatin has been reported to attenuate the antiplatelet activity of clopidogrel in a dose-dependent manner, hypothesized to be related to the metabolism of atorvastatin by the cytochrome P450 (CYP) 3A4 enzyme.\(^{37}\) This drug interaction was not studied by Petropoulos and Bello-Quintero in their article in this issue of the Journal.

In June 2002, the label for simvastatin was changed to warn against a potentially dangerous interaction with amiodarone.\(^{38}\) With this label change, approved May 6, 2002, by the FDA, simvastatin became the only statin available in the United States with a dose-related effect for myopathy and rhabdomyolysis. The previous labeling mentioned a dose-dependent relationship with myopathy, but not rhabdomyolysis, and did not cite the reported incidence. Also noteworthy in the label change in June 2002 was the fact that a labeling supplement (supplemental new drug application [sNDA]) was submitted by the manufacturer to the FDA on May 15, 2001, as part of its obligation to respond to new postmarketing adverse event signals. This occurred 3 months before the market withdrawal of cerivastatin.\(^{39}\)

The study conducted by Petropoulos and Bello-Quintero highlights a subject that apparently warrants increased attention. Despite the label change for simvastatin in June 2002 and the well-recognized market withdrawal of cerivastatin in August 2001, the risk posed by drug interactions with statins can be overlooked, even by experts. In an article published in April 2003, the authors attributed a case of rhabdomyolysis to high-dose (40 mg per day) simvastatin and stated confidently that the “myopathy was caused by an increase in the dosage of simvastatin and not by an interaction with another medication.”\(^{40}\) Despite concomitant use of amiodarone (100 mg per day), the authors stated, “Our patient, however, had no concomitant use of drugs historically suspected of involvement in rhabdomyolysis, nor was he immunsuppressed secondary to organ transplantation.” In addition to missing the drug interaction, this article is likely to be picked up in electronic searches as a case report of rhabdomyolysis associated with simvastatin dose rather than the drug interaction.

Where does this information leave us with respect to the use of lipid-lowering, particularly statin, therapy? The mantra in disease management cost-effectiveness is stratification of patients by relative risk of an adverse outcome. While statin therapy may be relatively safe, there are risks.\(^{41}\) Setting aside the matter of drug cost, the threats to patient safety dictate that statin therapy should be restricted to patients at defined risk of an adverse cardiac or perhaps cerebrovascular outcome. The evidence at present does not support the use of statins in primary prophylaxis of cerebrovascular events, and the link between serum cholesterol and stroke has not been established.\(^{42}\) Lower-cost therapies (e.g., aspirin) are more effective in secondary protection, and statin therapy might be offered to younger stroke patients with a history of coronary heart disease.\(^{43}\) When the risk-to-benefit ratio is sufficiently low to warrant statin therapy to prevent coronary events or in secondary prevention of stroke, there is an important opportunity and a real need for pharmacists to help improve adherence to therapy\(^{44}\) and monitor patients for potential drug interactions and adverse effects.

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Letters to the Editor
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