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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 cost 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.

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Offering the Panal to the Bullfighter (1872-73) — Mary Cassatt

As the only American exhibitor to accompany the revolutionary painters known as the French Impressionists or independents, Mary Cassatt demonstrated her finesse with lighting on and off canvas. On canvas, Cassatt’s studies of Gérôme, Velázquez, and Correggio helped her to discover her own prolific characteristics. Off canvas, she defied traditional subservient views of women. Cassatt’s achievements exfoliated the conventional gender-based limitations deemed appropriate for women of her time.

During Mary’s childhood, the Cassatt family spent two years living in France and Germany. After returning home to Pennsylvania, Cassatt attended the Pennsylvania Academy of the Fine Arts. Her emancipated lifestyle began shortly thereafter when, at the age of 22, she opted to live and study in Paris. Although she left France briefly due to the 1870 Franco-Prussian War, Paris remained her permanent home. Her move proved to be an excellent decision, as three years after this relocation, she was invited by Edgar Degas to join the Impressionists. By taking this political and social stance, Cassatt alerted the art community that her work would mirror her personal signature instead of public preference.

Cassatt was a translator and diplomat for American collectors of French Impressionism. Her first-hand knowledge and persuasiveness combined with her family’s prominence in Pennsylvania made her an ardent promoter.

Cassatt’s studies were influenced by her exposure to painters from France, Italy, Belgium and the Netherlands; however, her time in Spain led to “Offering the Panal to the Bullfighter.” Each year from spring to fall, Spanish culture abounds with ferias and bullfights. It is a succession of colorful celebrations that are embraced by most cities and villages throughout the country. Laymen and aficionados are entranced with the ceremonial drama surrounding the bullfight. Our cover image unveils a seductive, behind-the-scenes look into this theatrical activity. The Spanish term for honeycomb is panal. When the panal is dipped in water, it becomes an enticing, sugary drink. While Cassatt does not use dark hues in this work, her admiration of Velázquez is nonetheless apparent, most notably in the bullfighter’s costume. Some critics suggested the piece lacked technical advancement; nevertheless, the painting was accepted at the annual official Paris showing in 1873. Although Cassatt’s popularity throughout Europe did not transfer easily to America, other venues for exhibition of this work were the Cincinnati Industrial Exposition, the National Academy of Design in New York, and in 1878 Cassatt’s alma mater, the Pennsylvania Academy of the Fine Arts.

In deference to her contributions to art, Cassatt received the French Legion of Honor Award in 1904. Whether she was painting domestic scenes (in which she used members of her family as subjects) or exotic activities of the time, Cassatt’s visualizations were a passage to and from idealism and realism. She lost her eyesight at the age of 70, but her incredible insight continued until her death in 1926.

As an Impressionist, Mary Cassatt used reflections of light to affect her painting. As a woman, she used forward thinking and a tenacious demeanor to lighten the stoic views and lack of acceptance for progressive women.
### PERSPECTIVES

#### Drugs, PPOs, Tiered Cost-Share for Beneficiaries, and Consumer Preferences

Two-tier copay drug benefit plans have been in existence for nearly 20 years; three-tier copay drug benefit plans emerged at least 10 years ago. PacifiCare of Oklahoma began offering a three-tier copay drug plan in 1992. The most common three-tier drug benefit design at that time required a $3 copay for a generic drug, an $8 copay for a “formulary” brand drug, and 50% cost-share for a nonformulary drug, all in a maximum 30-day supply. Ultimately, the three-tier copay drug plan became the predominant form of drug benefit design in the state of Oklahoma, but it took more than two years in the early 1990s for PacifiCare to convince a significant number of employers to adopt the “new” benefit design. Marketing and sales people did not embrace it: “Formularies” and percentage cost-share were “hard to sell.”

By 2002, multiple-tier-copay drug benefit plans had become dominant among private employers, HMOs, and other managed care plans. Full choice is one of the valuable features of these three-, four-, and even five-tier drug copay plans. While tier-copays provide financial incentives for use of preferred drugs, members generally have full choice of drugs. Properly administered, tier-copay drug plans obviate the need for online edits that require pharmacist intervention for prior authorization (PA), step therapy, or other administrative controls.

The concept of charging eligible beneficiaries different cost-share amounts based upon the cost-effectiveness of the therapy applies beyond prescription drugs. After nearly 10 years of multiple-tier copay plans for prescription drug benefits, PacifiCare Health Systems (Cypress, Calif.) launched its Select Hospitals tier-copay plan in the fall of 2001. Member use of preferred (lower-cost) hospitals was associated with $0 per day copay, while member use of other, network hospitals had copays of $100, $250, or $400 per day.1 The multiple copayment options by provider were packaged by other health plans in 2002, including Humana in its SmartSuite of options.2

As with drug benefit tier-copays, the tiered cost-share method for hospitals is designed to (a) make beneficiaries more aware of the cost differences among alternate therapy choices and (b) encourage the use of lower-cost therapeutic alternatives. HMOs and other managed care plans will likely embrace this tier cost-share method for hospitals and physicians, perhaps as enthusiastically as drug benefit managers have done for prescription drugs. The pressure on employers from medical and hospital cost increases that rose dramatically, first in 2000 and for three consecutive years through 2002, make this tier-copay health benefit design a timely addition to managed care.

Health plan members often cite provider choice over many other health plan features as the most important factor when they select a particular health plan, second only to out-of-pocket cost-share amounts. Yet, the survey results are mixed. Health plan members who select IPA-HMOs appear to rate coverage of pharmacy benefits as highly as out-of-pocket cost-share amounts.3 Commonly, price factors outweigh quality factors when individual purchasers select a health plan.4 In a prescription drug benefit, the drug is probably the metaphor for the provider in the medical portion of the health benefit. In other words, the provider-equivalent in a prescription drug benefit may be the drug itself. Work by Holdford and Carroll in this issue of the Journal supports this notion: “Product choice was the most important attribute in selecting a drug benefit plan.”5

These results are not surprising; they may even be obvious. Yet the findings of the research by Holdford and Carroll are not generalizable due to several factors, including the higher average income and other atypical characteristics of the study population as well as its small size. The sample size is particularly small compared to the sample sizes typical of marketing surveys. Further, the question is perhaps more complex than it appears. Survey research has suggested an inverse relationship between member knowledge of drug plan coverage and member satisfaction.6 Earlier survey research found nearly equivalent member satisfaction in closed formulary (66%) and open formulary plans (70%)—a counter-intuitive finding without further examination. Beneath the finding in this earlier research is a subgroup analysis that found the degree of member satisfaction to be related to the absolute amount of the copayment: 71% of drug plan members were highly satisfied in the $1 to $5 copay plans (for branded drugs) versus 61% highly satisfied in drug plans with an $11 or higher branded drug copayment.7

#### Adherence, Compliance, and Persistence in Drug Therapy

Patient compliance with prescribed treatment, adherence to the regimen, and persistence in continuing behavior adherent to therapy are influenced by many factors, including the costs of drug therapy. Patients can measure “cost” in the incidence and severity of side effects as well as the out-of-pocket payment for the drug. White et al. in this issue of the Journal8 address the question of the influence of pharmacy provider type, mail service versus community pharmacy, on medication adherence and persistence. As the authors note, this study did not show that mail-service pharmacy has a causal effect on adherence to HMG antilipid therapy. Rather, the authors suggest that users of mail-service pharmacy may be more adherent to HMG therapy. We do not know if the underlying factor is the convenience of mail service, the provision of a 90-day supply of medication, or self-selection of mail service versus community pharmacy.

At least two other points are important for readers: (1) This MCO, like many others, owns the mail-service pharmacy, which earns revenue and profit for the enterprise and thereby “competes” with community pharmacies, and (2) The authors did not include the effects of out-of-pocket payments in their research model or statistical analyses of the data. In fact, the authors did not describe precisely the differences in drug benefit design and out-of-pocket costs between the mail-service pharmacy benefit and the community pharmacy benefit. Including variables for out-of-pocket costs
and the amount of the annual maximum dollar benefit for the Medicare+Choice members in the list of independent variables would have made this research and its results more robust and resistant to alternate explanations for the findings.

Drs. Johnsnud and Schafermeyer7 provide a useful review on adherence and persistence in the Subject Reviews section in this issue to help readers interpret the work by White et al. Particularly intriguing in considering methods of improving patient adherence to drug therapy is the complex interaction of severity of disease, number of concomitant drugs used by each patient, and perception of susceptibility. White et al. expressed surprise that mail-service users appeared to be more adherent to HMG drug therapy despite their higher average age and a larger number of co-existing illnesses as measured by the chronic disease score (CDS). It would be equally plausible to hypothesize that these patients would be expected to be more adherent to HMG therapy due to greater perceived susceptibility to adverse outcomes arising from nonadherence. More insight into this question could have been obtained had the authors measured the number of concomitant drugs for each patient and included this measure in their analyses.

### Effects of Medicare+Choice Annual Maximum Dollar Prescription Drug Benefits

About 73% of Medicare beneficiaries had some form of prescription drug coverage in calendar year 1998,8 the time period of the study reported by White et al. Medicare HMOs (Medicare+Choice) plans accounted for about 15% (about one-fifth of third-party coverage) of prescription drug benefits for Medicare beneficiaries in 1998. The share of Medicare+Choice members with prescription drug coverage declined from 84% in 1999 to 67% in 2001, contributing to a decline in the share of prescription drug coverage accounted for by Medicare HMOs to just 10% of the entire Medicare population in 2001.9 Annual dollar maximum limits for Medicare+Choice prescription drug benefits are common, with an average $1,149 annual maximum limit in 1997 and some as low as $600 per year. By 2000, 38% of Medicare+Choice members with prescription drug benefits had an annual maximum of $750 or less.

Data from the Kaiser Family Foundation also show that 13% of Medicare beneficiaries spent $2,000 or more on prescription drugs in 2001, accounting for 52% of total prescription drug spending for all Medicare beneficiaries. Spending of $1,000 or more was found among 28% of Medicare beneficiaries, equalling 76% of total expenditures for prescription drugs. Yet an amazing 17% of Medicare beneficiaries had no ($0) spending on prescription drugs in 2001. White et al. reported that only 0.01% (two members) in their Medicare+Choice population exceeded the annual drug benefit maximum, which can be as low as $500. They report that 25% of Medicare beneficiaries in this California HMO had an annual maximum of $1,000 or less.

These data are difficult to reconcile. The annual cost of HMG therapy alone could meet or exceed the $1,000 annual maximum. For example, the annual cost of pravastatin, before member copay, was in the range of $800 to $850 for 1998 and in the range of $875 to $925 for 1999. The authors of this study did not measure the incidence or effects of an annual dollar maximum on Medicare member utilization of prescription drugs. They did report that Medicare+Choice members accounted for 56% of the study subjects in the community pharmacy cohort and 85% in the mail-order cohort, making these two groups significantly different by this measure.

### DUR Messages—Better Data Needed for Making Better Decisions

Every day, we are bombarded by advertisers competing for the attention of prospective buyers. Marketing messages are everywhere, adding to the blizzard of data that threatens to overload our senses. We struggle to filter information from the noise. Pharmacists are also bombarded at work with electronic alert messages, ranging from requests for preferred drugs to drug-drug interaction messages that could be clinically significant, even life-threatening, for some patients. There is a real need to increase the ratio of true-positive and clinically significant electronic messages to the total number of messages sent to pharmacists by third-party claims processing systems.

The work by Heaton, Hansten, Martin, et al.12 in this issue of the Journal does little to help us cross the quality chasm that exists between what we do today and what we should be doing to improve the quality of care and reduce the incidence of clinically significant, avoidable adverse events attributable to drug interactions. This is yet another report of potential problems in prescription drug therapy. We do not know from this work the number and ratio of drug-interaction alert messages that were communicated to the dispensing pharmacists by the third-party claims processor for these alleged drug-interaction pairs or the pharmacists’ responses to these electronic messages.

Drug claim processors have the capability, in the transaction standard (NCPDP version 3.2) that has been effective for more than five years in pharmacy software systems as well as claims processors, to capture information in the claim record regarding electronic messages sent to pharmacies. The current v3.2 electronic claims transaction standard, to be updated and expanded further in version 5.1 for HIPAA compliance later this year, can also capture pharmacist response codes. The authors presumably could have also reported what pharmacists reported as actions taken in response to the drug interaction conflict alert messages. The electronic transaction standard in effect at the time of the study by Heaton et al. permitted at least four response codes: (a) “reason for service code” (e.g., “DD=drug-drug interaction”), (b) “professional service code” (e.g., “MO=prescriber consulted”), (c) “result of service code” (e.g., “1G=filled, with prescriber consulted”), and (d) DUR/PPS level of effort (e.g., how much time was required for the intervention, such as “12=Level 2,” indicating 0.25 hours). The presentation of these data would have shed additional light on
the magnitude of the alleged potential problem associated with apparent dispensing of drug-drug interaction pairs.

The authors do note that they measured no health outcomes in their study. We need better data to permit us to make better decisions to avoid clinically significant drug interactions. Additional perspectives on the path to better data for preventing adverse events caused by drug-drug interactions is provided by Christensen, Fulda, Lyles, and Pugh13 in this issue of the Journal.

Frederic R. Curtiss, Ph.D., R.Ph., CEBS
Editor-in-Chief

REFERENCES

Triptan Quality Limits

Dear Editor,

I am writing in response to Dr. Culley's and Dr. Wanovich's article in JMCP November/December 2001 regarding triptan limits. While I commend their efforts to seek answers on how to judiciously utilize these medications, I have some rather fundamental questions:

1. How many of the 105 study patients who were denied a triptan either remained at home, skipped work, missed school, or did not perform life's routine tasks but rather suffered through a migraine attack?
2. How many people actually had medication-induced headache (MIH) as opposed to poorly controlled migraine?
3. Who pays the "dispensing pharmacist" to call the MCO?
4. How many patients paid for a triptan out of their own pocket?
5. Does decreased cost of care equate to improved and/or quality care?

Taking a triptan more often than prescribed is not a natural act. Frustrated patients do this because migraine tends to be an insidious, forever worsening, condition; yet patients are rarely offered adequate treatment and/or proper medication counseling. The multiple barriers migraine individuals must overcome to find effective treatment have been documented. In my experience working at one of this country's two tertiary headache clinics' hospital units (where MIH is a leading admission diagnosis), patients self-discover relief with daily or near-daily triptan use. Once this discovery is made, it is difficult to convince these skeptical patients to do otherwise (I know because I try every day) since they have already endured years and even decades of countless inappropriate and/or ineffective therapies.

Far too many migraine patients ultimately succumb to the notion that modern medical science cannot help them. Patients don't seek help at the emergency room or other points of the health care system because those places have rarely helped in the past. This may partly or wholly explain why this study's patients did not utilize other health services. People just give up and suffer. Where are the outcomes regarding these patients, especially the 105 denied triptan prescription refills?

As the authors point out, over-use of triptans can cause MIH, but they do not say how many individuals in their study actually had this condition. Clinicians who work exclusively with headache patients agree, in principle, that frequent triptan use should be discouraged. However, how frequent is too frequent? Nobody knows for sure. Case reports, clinical experience, and other anecdotal evidence have shown that daily triptan use is not always detrimental and may in fact be beneficial for select patients, for up to three years. Additionally, we safely and effectively prescribe short courses (3–5 days) of daily triptans for predictable migraine situations such as menstrual migraine. The U.S. Headache Consortium's evidence-based migraine treatment guidelines, the most authoritative document on migraine therapy, recommends that acute medications such as triptans not be used more than two days per week. However, they also note that this recommendation is not absolute and further research is needed.

In the next few months frovatriptan will become available on the U.S. market. This drug's half-life is more than 24 hours, far exceeding the half-lives of existing triptans. Some headache specialists speculate that this long half-life may yield a triptan that can, and should, be utilized on a daily basis for chronic headaches. Also, I know from personal communications that there are ongoing controlled trials of daily use with already-marketed triptans. I eagerly await the results of these researchers' efforts.

The study did discuss a mechanism for patients to exceed triptan limits by having the "dispensing pharmacist" call the MCO in order to seek a "justified" (not defined) reason. However, is creating additional work for an already overwhelmed retail pharmacist an ideal intervention? Where are the costs of these phone calls reported? Being placed on hold after calling an MCO for an hour or more happens on an alarmingly regular basis. And how many study patients, once denied, simply opened their wallets and got the triptan drug anyway? The study's results do not comment on this. My patients tell me they routinely do this.

Under-utilization of migraine prophylactic drugs is seen frequently in practice. The study's results show that use of prophylactic drugs increased, but only slightly, 22,433 versus 23,201 prescriptions filled. This meager increase does not demonstrate that people who would benefit from prophylactic drugs received them because of enforcing triptan limits.

I also strongly question the authors' expectations that "limitations on the triptans could cause an increase in the use of acute pain medications (analgesics, etc.)." Step care (prescribing a non-specific drug such as an analgesic and progressing towards migraine-specific drugs such as triptans only after nonspecific drugs fail) is the most commonly utilized migraine treatment strategy in this country, even though it has been shown inferior to stratified care. Thus, for the comparatively few migraine patients who are prescribed a triptan, the majority have already tried and failed analgesics. Most patients and doctors are unwilling to go back to unsuccessful treatments.

I give continuing education lectures to pharmacists about migraines. It is obvious that migraine and medication-induced headaches are illnesses surrounded by mystery, misunderstanding, and improper treatment. Lack of education may be one reason for this confusion. Research shows that the typical pharmacy student receives only one contact hour of classroom education per year regarding headache disorders, and only two schools in the entire country offer clerkships dedicated exclusively to headaches.

The American Migraine II study shows migraine headaches profoundly affect the lives of at least 28 million people (not 23 million as reported by the authors), only 48% of whom are diagnosed by a physician. Worse, up to 82% of people who present to tertiary headache centers are experiencing MIH. The leading cause of chronic daily headaches (CDH) is MIH, and CDH consume a disproportionate amount of all the resources devoted to treatment of primary headache disorders.

While the authors noted a figure of $17.2 billion, this number should be quantified to illustrate that up to $17.2 billion annually
is lost to decreased productivity. The direct medical costs of migraine have been calculated at $1 billion annually. Thus dis-ability, not direct care costs (i.e., triptans), imposes the greatest economic burden. Effective migraine therapies must be aimed at reducing disability, not merely limiting the costs of drugs. Get people back to work, back to school, back to life’s daily tasks, and you will save society a lot of money.

As a result of their acquisition cost and often inappropriate utilization, triptans are targets for MCO scrutiny. As with any discussion of pharmacoeconomics the definition of “cost” must be explained. Obviously if a patient does not use a triptan the MCO has no cost. However, the Panel on Cost-Effectiveness in Health and Medicine endorses a society perspective. What is the cost to society of a patient suffering at home (thus not at work) with a migraine? Also the poorly treated patient, who has already paid an insurance premium, pays yet again in terms of pain, disability, and actual dollars. Denying people access to care to reduce expenses does not automatically equate to quality care. Such an approach may actually raise costs for patients and society as a whole.

Rather than limiting triptan access, why not attempt to direct these patients to appropriate therapy, i.e., find out why they are taking frequent triptans in the first place and fix THAT? There are validated tools including the migraine-disability assessment questionnaire (MIDAS) and the Headache Impact Test (HIT-6) that can help quantify the onus of headaches on patients’ lives as well as guide treatment. The Consortium’s evidence-based guidelines advocate stratified care, not step care, as the premium approach to migraine therapy. There are over 200 specialized headache centers in this country where patients can be referred. Get the poorly managed patient to a knowledgeable clinician who will properly prescribe demonstrated effective drugs and the resulting migraine expenses will not be excessive.

Pharmacists are well positioned to make positive changes for migraine sufferers. A recommendation of an OTC “headache product” is the number one OTC product suggestion pharmacists perform, occurring over 53,000 times per day. Also, as illustrated by the study, MCOs employ pharmacists who create policies that can have a positive (or negative) impact on patients.

The results of this study do not show that triptan limits, though well-intentioned, were beneficial for patients. The results only demonstrate a benefit for “the bottom line.” Triptan limits are just one more barrier for patients to find effective help. Since most patients have already dealt with numerous barriers before, the poorly managed, defeated, and in this study unreported migraine
patients will quietly tolerate yet another barrier.
I speak on their behalf.
Richard Wenzel, Pharm.D., Diamond Headache Clinic Inpatient Unit, National Headache Foundation, Member and Therapeutic Guide Committee Member; American Headache Society – Member; Adjunct Professor, University of Illinois-Chicago, College of Pharmacy
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LETTERS

A Neurologist’s Perspective on Quantity Limits
Dear Editor,
Perhaps we could put them in barrels—to be placed strategically on street corners. Those who pass may take what they “need.” All would be happy.
Shift, momentarily, to narcotics. If it is true that we, doctors, do patients a disservice by restraining our use of narcotics, perhaps the responsibility should be lifted from physicians. Perhaps narcotics, which are largely inexpensive to manufacture, should be made widely available. Thus none would “go hungry.”
Or is it that we limit such access for another reason? Is it that we have found a “dark side” to access without restraint? Is it that limitation is an act of kindness?
Narcotics are clearly acknowledged to have “a dark side.” Used wisely and appropriately, with reasonable restraint, they serve the patient—relieving both pain and anguish. Yet they may also enslave the patient. When “pain” is a metaphor for anguish, and when narcotics are used to escape angst (a form of “pain” with similar vocabulary), then narcotics enslave. They serve not to build effectiveness nor to capture capacity, but to encourage dissolution. Thus, sanguine medical care calls upon physicians to provide narcotics with restraint—recognizing that correction of the illness is really the ultimate goal.
In this same vein we must, in my opinion, use triptans with recognition that they produce a temporary relief, and not a correction of the underlying proclivity to migraine. If they are used wisely, and with restraint, they serve the patient—providing much-needed relief with comparative safety. Yet if headaches are frequent and triptans are used only as a temporary escape, then surely the illness shall exact a greater cost. And this is not the goal of optimal medical care.
We may debate what we would call “reasonable” or “excessive” use of triptans. However, for me the issue is simple. I simply ask myself, “Is my prescription of triptans resulting in a maximally functioning human being?” If I encourage the patient to turn repeatedly and frequently to triptans I believe I am only serving to encourage the enslavement of the patient. Alternatively, if I provide these valuable medications for the patient to use occasionally, with other agents serving to control an ongoing headache tendency, then I believe I am serving the patient’s overall best interests.

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The Authors’ Response
Dear Dr. Wenzel,
We are responding to your comments in your letter to the editor of JMCP. We thank you for your comments and will address as many of your issues as possible. The objective of our study was to examine the overall impact of the quantity level limit on all triptans users in our managed care lines of business (nearly 12,000 members), not specifically the 105 patients that were denied additional quantities of medication.1 We would like to clarify that the members who were denied additional quantities of medication were still eligible for the

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amounts listed in the article and we would not deny a refill that was within those limits. We are concerned about our members and any adverse impact this quantity limit may have had. There are questions that remain regarding the impact on productivity and quality of life that our study does not address. To date, there is a paucity of literature that adequately addresses this subject, to which there are no adequate answers. Although the quality of life issues are certainly important, they are far outside the scope of our study.

We agree that people who suffer from migraines have a devastating disease and there is no one-size-fits-all way to manage them. That is precisely the reason we created an exception process. We realize there are members in our population that experience more frequent migraines than most others. Please keep in mind that in our study, 56% of all requests for additional quantities of triptans were approved; in December 2001, our approval rate was 88%. Interestingly 18% of all requests required a clinical review. For the remaining 82% of calls that were handled, no additional quantities were requested, typically because the physician agreed the edit limits were sufficient for their patients. This suggests that many members were obtaining prescriptions for large quantities, not because they needed to, rather because they could. Stockpiling, prescription sharing, and other fraudulent practices happen on a daily basis and only serve to increase the cost of health care for all insured people.

As you stated, rebound or medication-induced headaches (MIH) are a serious problem. In your reference, 82% of people who present to a tertiary headache center experience MIH. Clearly this illustrates that physicians, pharmacists, and patients are having difficulty with the proper use of these medications and the management of this debilitating condition. By implementing a quantity limit, we hoped to identify these highest uses and hopefully prevent our members from ever reaching that state of poor migraine control. Also, because of our exception review process, we frequently had discussions with physicians about their patients who use more than our limits and made exceptions for those members while also encouraging the use of prophylactic medications and referrals to specialists when necessary.

There were many cases of medication-induced headache that were brought to our attention, but we did not specifically track individual cases. In our population, we discovered cases where physicians did not know how many tablets their patients were taking on a monthly basis, patients obtained prescriptions from multiple physicians and, in some cases, physicians requested quantities sufficient for continual twice-daily dosing of the triptans. Continuing to pay for this daily use of medication does not encourage the patient to break the rebound cycle. We work very closely with our physician community and neurologists who specialize in headache and migraine therapy. We are well aware of the problems patients encounter when they are experiencing a cycle of medication-induced headaches/migraines.

We agree that one of the limitations of our study was not being able to account for therapies that did not create an insurance claim. We did not have the necessary resources available to adequately study this issue to determine its frequency and impact.

Regarding your question about our choosing to analyze the use of acute pain medication (analgesics), our claims data indicated that most of our triptan-using population (over 92%) are also currently taking analgesics. You cite a study in your letter that suggested that only a few migraineurs are actually taking triptans. At that point (1994), the triptans as a class were relatively new and sumatriptan was the only triptan available on the market. Prescribing habits have changed since the introduction of four (soon to be five) additional drugs in this class. We used our claims history to analyze the utilization of other analgesics, realizing that the quantity limit on the triptans may have encouraged the use of other pain medications. However, as stated in our study, this was not the case.

Lastly, we never would want to be the cause of any harm to our members. We too took oaths as pharmacists to take care of the people we serve. In health care, there are limited dollars that can be spent, and our challenge is to make sure our resources are being used appropriately. By conducting this study, we attempted through all our possible means, to evaluate the overall impact of the edit on all our 12,000 members who use triptans. For those who suffered from frequent migraine episodes, we have the exception process in place to allow coverage for appropriately prescribed therapy.

We encourage you and others to continue to add to the body of knowledge regarding this disease and outcomes from various management programs. We thank you for your comments.

Dear Dr. Barbuto,

It was the dichotomy of outcomes related to medication use that you so poetically describe that was the impetus for our management program. The triptan edit was meant to promote the potential beneficial effects while minimizing the opportunity for negative outcomes, especially in our population, which demonstrated wide variations in usage patterns. We appreciate your comments and thank you for your insight.

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REFERENCES
PATIENT ADHERENCE WITH HMG REDUCTASE INHIBITOR THERAPY AMONG USERS OF TWO TYPES OF PRESCRIPTION SERVICES

OBJECTIVE: The primary objective of this study was to compare patient adherence with HMG reductase inhibitor drug therapy (HMG) between two types of prescription service: mail-service pharmacy and community pharmacies.

METHODS: This study was a retrospective database analysis of pharmacy and medical claims for 14,826 commercial (40.9%) and Medicare + Choice (59.1%) members of a large HMO in California who were newly started on HMG therapy during the identification period, continuously enrolled during the review period (defined as each member’s 6-month pre-index period through the review period), and 75 years of age. Members who exclusively used only the mail-service pharmacy and those who used only community pharmacies for HMG prescriptions were compared to members who used only community pharmacies for HMG prescriptions. The main outcome measures were adherence, medication possession ratio (MPR), persistence, prescription count, and duration of therapy.

RESULTS: All outcome measures were significantly greater for the mail-service system compared to the community pharmacy system, including adherence with HMG therapy compared to 75% with the bile acid sequestrants.3 In chronic disease conditions such as dyslipidemia, long-term adherence to lipid-lowering medication therapy is of particular importance. Several published studies have reported the frequency of discontinuation and/or percentage of adherence with lipid-lowering drug therapy. Schectman2 et al. report that among patients attending a Veterans Administration medical clinic during the period 1988 to 1991, the frequency of lipid-lowering drug discontinuation or percentage of nonadherence with lovastatin was significantly greater for the mail-service pharmacy and 65% with the bile acid sequestrants.

CONCLUSION: This analysis suggests that patients who use mail-service systems to fill prescriptions exhibit a higher degree of adherence with HMG therapy compared to those who use community pharmacies.

KEYWORDS: Dyslipidemia, HMG therapy, compliance, adherence, managed care, prescription mail service, mail-service pharmacy, community pharmacies.

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MEDICATION NONCOMPLIANCE IS RECOGNIZED AS A COMPLEX PROBLEM THAT IS A SIGNIFICANT CAUSE OF PREVENTABLE RELAPSE, DISEASE PROGRESSION, AND MORBIDITY. Failure to adhere to medication instructions has been associated with increased hospital and nursing home admissions, loss of productivity, premature deaths, and increased treatment costs.1 In chronic disease conditions such as dyslipidemia, long-term adherence to lipid-lowering medication therapy is of particular importance. Several published studies have reported the frequency of discontinuation and/or percentage of adherence with lipid-lowering drug therapy. Schectman2 et al. report that among patients attending a Veterans Administration medical clinic during the period 1988 to 1991, the frequency of lipid-lowering drug discontinuation or percentage of nonadherence with lovastatin was 2% compared to 37% with the bile acid sequestrants. In this same medical center, patients attending clinic during the period 1988 to 1994 reported the frequency of discontinuation was 4% with statins, 52% with niacin, 61% with gemfibrozil, and 65% with the bile acid sequestrants.3

Patients attending a military medical-center cardiology clinic reported discontinuation or non-adherence rates of between 13% to 37% for lipid-lowering drugs. The same investigators reported percentages of patients discontinuing therapy as high as 50% for lovastatin in a civilian population.4 Andrade5 and associates, using computerized HMO pharmacy files and medical charts of 2,369 new users of lipid-lowering agents, estimated the one-year probability of discontinuation of lipid-lowering drugs at two HMOs to be 38% for all drugs combined.

Evidence indicates that treatment with lipid-lowering drugs to decrease low-density lipoprotein cholesterol reduces the incidence of coronary heart disease, estimated to cost $111 billion dollars annually in the United States.7 Based on guidelines from the Adult Panel of the National Cholesterol Education Program (NCEP), an estimated 36 million of U.S. adults require drug therapy to reach the proposed low-density lipoprotein level goals.9 Due to the prevalence of dyslipidemia, difficulty in achieving NCEP proposed lipoprotein goals and documented poor adherence to lipid lowering ther-
apy, there is a need to explore methods which may improve medication adherence. A recent study found greater adherence to HMG therapy among patients that utilized mail service to fill prescriptions.10 More research is needed to determine if mail-service pharmacy utilization is associated with improved medication adherence. This study utilized various techniques to examine medication adherence and persistence. Medication adherence was measured by the total number of days for which a patient possessed medication as prescribed during the study timeframe. Persistence was measured by the duration, in days, of continuous therapy during the study timeframe.

**Objectives**

The primary objective of this study was to examine the relationship between patient adherence with HMG reductase inhibitor therapy and type of prescription service used—mail service compared to community pharmacies. The researchers hypothesized that patients receiving their prescriptions through mail service have a greater adherence rate and medication possession ratio than those receiving prescriptions through community pharmacies.

**Methods**

This was a retrospective database analysis using pharmacy and medical claims from a pharmacy benefit and medical management company serving a large managed care organization in California that provides health care coverage for approximately 1.9 million members. Members were included in the analysis if they were newly started on HMG therapy during the Identification Period between January 1, 1998, and December 31, 1998, continuously enrolled in the health plan during the entire study period (defined as each member’s 6-month pre-index period through 360 days of follow-up) and between 18 and 75 years of age. All patients on all HMG therapies were included in this study. A washout period of 6 months prior to the Identification Period was used to identify newly started patients. The date of first HMG prescription was marked as the index date from which each patient was followed for up to 360 days during the Follow-up Period.

Two types of prescription services used to obtain HMG prescriptions were compared in this study. Members who exclusively filled all of their prescriptions during the Follow-up Period through the mail service were assigned to the mail service cohort. Members who utilized only community pharmacies during the Follow-up Period to fill all their HMG prescriptions were assigned to the community pharmacy cohort. Members were excluded from the study if they utilized a combination of mail service and community pharmacies for their HMG therapy. We also determined if patients had met their drug benefit maximum. In this health plan, a maximum drug benefit existed for some within the Medicare+Choice population. The maximum drug benefit varied by county, and not all counties had a maximum limit for prescription drugs. Of the counties with a maximum drug benefit, the dollar amount of the maximum ranged from $500 to $1,600 per year.

Approximately 37.7% of the Medicare+Choice beneficiaries had an unlimited annual maximum, 3.2% had an annual maximum benefit of $500, 21.8% had $1,000, 10.9% had $1,500, and 26.4% had a $1,600 annual maximum benefit. An example of the impact of a maximum benefit follows. If a patient has a maximum benefit of $1,500 and is taking a Proton Pump Inhibitor (PPI), an HMG, and a Metered Dose Inhaler (MDI), he may reach his maximum benefit 6 months after treatment. This patient may elect to: (1) ration medications or selectively refill prescriptions; (2) pay out-of-pocket for medications; or (3) stop taking medications. Therefore, if a patient was taking a more expensive HMG, he may have reached his maximum benefit early during the year compared to a patient prescribed a less expensive HMG. Of the community pharmacy cohort, 0.18% (n=26) reached their maximum drug benefit and 0.01% (n=2) of the mail-service cohort did. It was determined that these patients would not have significant impact on study outcomes and therefore they were not excluded from the final study cohorts.

Outcome measures evaluated in this study include adherence, medication possession ratio (MPR), persistence, prescription count, and duration of therapy.

**Adherence:** For each study participant the adherence rate for drug therapy was defined as the total number of covered days (days for which the patient possessed medication) during the study period divided by the total days in the study period (360 days).

**Medication possession ratio (MPR):** MPR was a proxy measure of patient adherence and was defined as the sum of the days supply for all prescription fills divided by the number of days of therapy between the first prescription fill and last fill, plus the days supply for the last prescription fill. In the event that this calculation resulted in an MPR that was greater than 1.0, the MPR value was reduced to 1.0.

**Persistence of therapy:** A patient was deemed persistent if they refilled a prescription within 60 days from the end of days supply of the previous prescription. However, each patient was credited only for the actual days of supply from the last prescription when determining the end of persistent therapy. For example, if a patient had a 30-day supply prescription at index date and refilled it 89 days from the index date with another 30-day supply, this patient would be persistent for 119 days. However, if the same patient had a 30-day supply prescription at index and refilled it 91 days post index, she would be counted as persistent for 30 days only. Survival analysis was performed to compare persistence between the two cohorts, where persistence was measured as time to HMG discontinuation.

**Prescription count:** In order to calculate the total number of prescriptions filled, a weighted category was created using the days supply. A days supply of less than or equal to 30 represented one prescription, 31 to 60 represented two prescriptions, and greater than or equal to 61 represented three prescriptions.

**Duration of therapy:** Determined as the length of time between
Data conversion and statistical analyses were performed using the SAS System, Version 8.1. Cohorts were compared by using F-tests, two sample t-tests, or chi-square tests, as appropriate. For the prescription level analysis, prescriptions were standardized by days of medication supplied. For the patient level analysis, HMG prescriptions were used to calculate adherence, MPR, duration of therapy, persistence, and number of transactions. Comorbidities and disease severity were estimated by using the Chronic Disease Score (CDS) method of Von Koreff et al., and the CDS was based on all prescriptions received in the Follow-up Period. Adherence and MPR were measured for an abbreviated treatment interval, rather than the entire Follow-up Period, where the first 90 days supply were deleted for each patient. Excluding the first three fills with the traditional community system and the first fill of HMG medications with the mail system (both equivalent to a 90-day supply) was believed to yield a better comparison of the two cohorts. Truncating the treatment interval may minimize a potential adherence bias whereby patients that are generally more compliant may be inclined to utilize mail service to obtain their prescription medications. These HMG prescriptions were therefore not counted toward assessment of patients' adherence. Adherence and MPR were calculated using this truncated treatment interval and compared to the initial adherence and MPR measures. To control for the possible confounding factors of age, gender, and patient comorbidity, analysis of covariance (ANCOVA) was conducted to compare adherence, MPR, duration of therapy, and persistence between the mail-service and community pharmacy cohorts. Adjusted means (least squares means) and 95% confidence intervals were calculated under the assumption that the distribution of each covariate was similar to the overall distribution across the two groups.

Results

Study Population Characteristics

The demographic characteristics of all patients who met the inclusion criteria are shown in Table 1. There were 14,826 patients included in the study. Among the identified patients, 13,254 (89.4%) utilized community pharmacies to receive their HMG therapy and 1,572 (10.6%) utilized the mail-service pharmacy. Overall, the majority of patients were male (51.2%), with a mean age of 62.1 years and mean CDS of 4.65. While 40.9% of the patients had commercial insurance, 59.1% of patients had Medicare+Choice coverage.

As noted in Table 1, patients in the mail-service cohort were older than patients in the community pharmacy cohort by more than six years (68.0 +/- 6.6 vs. 61.4 +/- 11.4, p<0.0001). There was also a significantly higher proportion of females in the mail-service cohort (53.2% vs. 48.2%, p=0.0002) and the majority of patients in the mail-service cohort were Medicare+Choice members (87.0% vs. 55.8%, p<0.0001). In addition, patients in the mail-service cohort showed a significantly higher CDS when compared to patients in the community pharmacy cohort (5.34 +/- 2.87 vs. 4.57 +/- 3.07, p<0.0001).

Outcome Measures (Unadjusted Means)

All outcome measures were significantly greater for the mail-service cohort than the community pharmacy cohort (p<0.0001) (see Table 2). Survival analysis showed a statistically significant differ-
ence in persistence between the two cohorts (p<0.0001) (see Figure 1). The survival curves appear parallel after approximately 150 days showing that the mail-service cohort continues to maintain higher persistence throughout the remaining study time period. The number of transactions was significantly less for patients in the mail-service group, as would be expected since they received 90-day supplies, when compared to the community pharmacy cohort (3.72 +/- 1.35 vs. 6.46 +/- 4.08, p<0.0001) (see Table 2). The truncated adherence and medication possession ratio, which excluded the first supply, were higher in the mail-service cohort when compared to the community pharmacy cohort (p<0.0001) (see Table 3).

Analysis of Covariance to Adjust for Baseline Differences
To compare outcome measures, analysis of covariance (ANCOVA) was conducted to control for significant baseline characteristic differences between the mail-service and community pharmacy cohorts (see Table 4, next page). The covariates included in the model were age group, gender, and CDS. Results of the adjusted analysis showed that patients in the mail-service cohort continued to show higher adherence, MPR, duration of therapy, and persistence when compared to patients in the community pharmacy cohort (see Table 5, next page).

Discussion
Adjusted outcome measures revealed that patients from the mail-service group had higher adherence, MPR, duration of therapy, and persistence when compared to patients in the community pharmacy cohort although patients were older and had more illnesses (per Chronic Disease Score). This finding was somewhat surprising since older patients and those taking multiple therapies for different conditions may tend to be less compliant with their medications. Adherence in elderly patients may be of particular concern because of increased susceptibility to adverse drug reactions; differential response to side effects; deficits in physical dexterity, cognitive skills, and memory; and the larger number of medications prescribed.13-15 The higher adherence observed in the mail-service cohort in this study may be attributable to the greater convenience of mail service for filling prescriptions. This convenient process of refilling HMG drug therapy may remove barriers to reordering and may contribute to and enhance patient adherence with their chronic medications, especially if they have multiple therapies for different conditions. Mail service allows patients to refill prescriptions without relying on transportation or physically being at a community pharmacy to pick up the medications. An argument could be made that elderly patients or those on multiple medications would particularly benefit from the convenience of mail service.

After truncating the treatment interval, the differences between the two cohorts decreased, but the mail-service cohort continued to demonstrate greater adherence and MPR rates. Further investigation may be required to determine if patients who are generally more compliant are those who would utilize a mail service to refill prescriptions, thus resulting in greater adherence patterns.

Since the standard number of days supply is 90 days with the mail service compared to 30 days with the traditional community service, it was also not surprising that the duration of therapy and persistence were higher in patients with the mail-service group versus the traditional service group. Again, for a chronic medication such as HMG therapy, providing a 90-day supply was appropriate and minimized patients’ effort to have to refill their medication every 30 days. Further research is needed to investigate the
impact of a 90-day supply of HMG therapy dispensed in the community pharmacy setting.

While the methodology utilized for this study differs from the methodology utilized in a previous study examining mail-service use among various medication classes, certain results corroborate our findings.10 Mail service was utilized more frequently by females and those of more advanced age. Medications used to treat chronic conditions, for example HMGs, were more likely to be filled through mail service and showed greater adherence.

As with all studies, limitations exist that may have influenced the findings. While most prescription claims are available within 45 days of submission, we could not be certain all claims were captured. Additionally, patients may have paid for prescription drugs out of pocket, and therefore no claim would have been generated and captured in the database. We also cannot assume that although patients’ prescription claims were submitted, and therefore represent apparent use of HMG therapy, the patient actually consumed the medication at all or consumed the medication as prescribed. Additionally, the association between adherence, medication possession ratio, persistence and duration of therapy as process measures may not necessarily result in improved clinical outcomes.

This pharmacy benefit management company offered a financial incentive that may have drawn patients to mail service. There were 14 specific drug copay plans among the patients of this study. The most common copay plan at the time of this study for both the commercial population and the Medicare+Choice population was a $5 generic copay and $10 brand copay for a 30-day supply at a community pharmacy and a $10 generic and $20 brand copay for 90-day supply from mail service. We did not measure the extent to which financial incentives in copay differences affected utilization. Moreover, it is possible that patients who elect to fill prescriptions through mail service possess different characteristics than patients who elect to fill prescriptions at community pharmacies.

Patients were eligible for this study if they were newly treated with HMG therapy; however, this may have influenced the study findings. It was not determined if patients who were newly treated with HMG therapy were previously using mail service to obtain their other medications or if patients started using mail service at the point when HMG therapy was initiated. Finally, we did not determine if patients experienced negative side effects or adverse

### TABLE 4
Parameter Estimates from ANCOVA

<table>
<thead>
<tr>
<th>OUTCOME VARIABLE</th>
<th>ADHERENCE</th>
<th>MPR</th>
<th>DURATION</th>
<th>PERSISTENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>Pr &gt;</td>
<td>Estimate</td>
<td>Pr &gt;</td>
</tr>
<tr>
<td>Intercept</td>
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<td>0.820</td>
<td>&lt;0.0001</td>
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<tr>
<td>age 18-64</td>
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<td>0.4191</td>
<td>-0.003</td>
<td>0.6768</td>
</tr>
<tr>
<td>age 65-69</td>
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<td>0.5028</td>
<td>0.006</td>
<td>0.5317</td>
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<td>gender F</td>
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<td>0.0585</td>
<td>-0.009</td>
<td>0.1223</td>
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<tr>
<td>CDS</td>
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<td>&lt;0.0001</td>
<td>0.002</td>
<td>0.0142</td>
</tr>
<tr>
<td>Age*gender 18-64 F</td>
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<td>0.0309</td>
<td>0.004</td>
<td>0.6105</td>
</tr>
<tr>
<td>Age*gender 65-69 F</td>
<td>-0.011</td>
<td>0.4453</td>
<td>0.008</td>
<td>0.3723</td>
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<tr>
<td>CDS*age 18-64</td>
<td>0.004</td>
<td>0.0302</td>
<td>-0.001</td>
<td>0.4665</td>
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<tr>
<td>CDS*age 65-69</td>
<td>-0.001</td>
<td>0.5882</td>
<td>-0.001</td>
<td>0.3450</td>
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<td>cohort: mail service</td>
<td>0.227</td>
<td>&lt;0.0001</td>
<td>0.100</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Referent Groups: Age group = 70-75; Gender = Male; Cohort = Community; CDS = Chronic disease score

### TABLE 5
Outcome Measures (Adjusted Means)

<table>
<thead>
<tr>
<th>OUTCOME VARIABLE</th>
<th>COHORT</th>
<th>Lower 95% CI</th>
<th>MEAN</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
<td>Mail service</td>
<td>0.784</td>
<td>0.800</td>
<td>0.816</td>
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<tr>
<td>Community</td>
<td>0.568</td>
<td>0.574</td>
<td>0.579</td>
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<tr>
<td>MPR</td>
<td>Mail service</td>
<td>0.915</td>
<td>0.926</td>
<td>0.936</td>
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<tr>
<td>Community</td>
<td>0.822</td>
<td>0.825</td>
<td>0.829</td>
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</tr>
<tr>
<td>Duration (days)</td>
<td>Mail service</td>
<td>307</td>
<td>313</td>
<td>320</td>
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<tr>
<td>Community</td>
<td>259</td>
<td>261</td>
<td>263</td>
<td></td>
</tr>
<tr>
<td>Persistence (days)</td>
<td>Mail service</td>
<td>271</td>
<td>278</td>
<td>285</td>
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<tr>
<td>Community</td>
<td>212</td>
<td>214</td>
<td>217</td>
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</tr>
</tbody>
</table>

CI = Confidence Interval
events leading to their discontinuation of HMG therapy, since medical record review was not performed.

### Conclusion

In this managed care population, through retrospective database analysis, patients who used mail service to fill HMG prescriptions exhibited a higher degree of adherence compared to those who used community pharmacies. Even after adjusting for potential confounding factors such as age, gender, and chronic disease score (CDS), patients utilizing mail service to receive their HMG therapy continued to show greater adherence, MPR, duration of therapy, and persistence when compared to patients utilizing community pharmacies. More research must be conducted to further explore the relative impact of mail service on medication adherence versus the relative contribution of a 90-day supply compared to a 30-day supply limit for medications for chronic conditions.

### DISCLOSURES

The authors disclose that their employer, Prescription Solutions, has mail-service capabilities, potentially biasing the findings. Funding for this study was provided by Bristol-Myers Squibb and obtained by Christopher Dezii. The principal investigator of this study was T. Jeffrey White. White, Eunice Chang, and Dezii were responsible for the study concept and design. Analysis and interpretation of data were contributed primarily by White, Chang, Dezii, Scott Leslie, David Berenbeim, and Alex Gilderman. Drafting of the manuscript was conducted by Caron Melikian. Critical revision of the manuscript was done by White and Melikian. Statistical expertise was contributed primarily by Chang and Leslie. Administrative, technical, and material support was provided by Sheri Hopson.

### REFERENCES

Consumer Preferences for Types of Cost Containment in Prescription Drug Programs

OBJECTIVE: To estimate (1) the relative importance of three major attributes of prescription drug benefit plans—level of copayment, pharmacy access, and access to products—that health plans use to control prescription drug expenditures and (2) the trade-offs that consumers make among these attributes.

DESIGN: Self-administered survey and conjoint analysis of consumer preference data.

PARTICIPANTS: A convenience sample of 130 consumers in Richmond, Va.

MAIN OUTCOME MEASURES: Consumer preference ratings for 11 hypothetical drug benefit plans; relative importance consumers attributed to level of copayment, pharmacy access, and access to products in selecting drug benefit plans; trade-offs consumers made among these attributes.

RESULTS: Product choice was the most important attribute in selecting a drug benefit plan. The importance rating was 42.1%. Consumers indicated strong preferences for open formularies. Level of copay received an importance rating of 31.9%. Higher copays were associated with lower consumer preference. Choice of pharmacy had an importance value of 26.0%. Consumers preferred plans that allowed either free choice of pharmacy or that included their current pharmacy. A market segmentation analysis yielded similar results.

CONCLUSIONS: Conjoint analysis provides useful consumer preference and trade-off information that health plans could use to minimize consumer dissatisfaction with drug benefit plans.

KEYWORDS: Conjoint analysis, Cost control, Cost sharing, Copayment, Formulary, Network, Consumer preference, Trade off analysis.

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The escalating cost of outpatient prescription drugs has caused concern for employers and other payers for pharmaceutical products and services. The Health Care Financing Administration (now Center for Medicare and Medicaid Studies) reported that the rate of growth in prescription expenditures in the United States has increased each year since 1994, to an average annual increase of 15.4% in 1998. By comparison, the annual growth in total health care expenditures in 1998 was only 5.6%. As a result, prescription drugs have become a primary target for cost containment efforts.

Managed care organizations (MCOs) have employed a variety of types of efforts to control the costs of prescription drugs. These efforts can be categorized into three general groups: increased patient cost sharing, restrictions on choice of products, and restrictions on choice of pharmacy. These efforts are usually implemented through use of copayments, formulary policies that encourage substitution of generic or therapeutically equivalent drugs for brand-name prescription drugs, and use of closed pharmacy networks.

Despite the widespread and increasing use of such techniques, MCOs may implement cost containment strategies without a clear understanding of their consequences on consumer satisfaction. For instance, little is known about how consumers perceive and respond to restrictions on access to drugs or pharmacies. This may lead managers of drug benefit plans to design programs based upon preconceived and potentially incorrect assumptions about consumer preferences. The outcome of this situation may be dissatisfied consumers who switch to health care plans that better meet their needs and wants.

This study was designed to address the question, “What attributes are important to consumers when designing pharmacy benefit plans?” Specifically, the objectives of this study were to: estimate the relative importance of three major attributes of prescription drug benefit plans, estimate the trade-offs that consumers make in selecting among different pharmacy benefit attributes, and identify segments of consumers based on their preferences for drug benefit plan attributes.

Methods

Satisfaction surveys are the most common technique used by managed care researchers to understand consumer choices.
for various elements of health care plans (e.g., accessibility, price). A complaint about consumer satisfaction surveys in managed care is that they are typically conducted to promote the plan to new enrollees rather than to understand consumer perceptions of plan services. Another problem with satisfaction surveys, as with other uses of rating scales and ranking procedures, is that they ask respondents to evaluate individual attributes of plans one at a time, in isolation from other plan attributes. This approach fails to frame questions in a manner that will elicit the trade-offs made in actual consumer decisions. For example, consumers do not evaluate the quality of a health benefit plan independent of cost and accessibility. Preferences for plan quality are affected by the size of the premiums and breadth of the provider network.

To avoid these problems, this study used conjoint analysis to elicit consumer preferences for different attributes of drug benefit programs. Conjoint analysis (CA), a commonly used marketing research method, is designed specifically to mimic the decision process that consumers use in choosing products and services. Consumers are asked to assess all elements of a product or service simultaneously instead of independently, as seen with other techniques such as satisfaction surveys. CA has been used to study consumer preferences for drug therapies, pharmaceutical services, health outcomes, and health insurance.

With CA, respondents are asked to evaluate a hypothetical product profile (i.e., a description of the product or service being evaluated) and give an overall preference for that product profile based upon the individual attributes used to describe it. The process is repeated for other profiles that alter the levels of the product's attributes. The respondent's profile preferences are then analyzed to determine the relative importance of each attribute in determining the respondent's overall preference for the product or service. In this study, consumers' preferences for different drug benefit plans were used to determine the relative importance placed on patient cost sharing, pharmacy restrictions, and product choice limitations.

Our study employed a part-worth function model. This model assumes that a consumer's overall preference for a multi-attribute product is the sum of the importance the consumer places on each of the product's attributes. This model is flexible in its assumptions, widely used, and widely accepted by academics and industry researchers in marketing.

Each drug benefit plan in our study was described by three attributes—cost-sharing, access to pharmacy, and formulary (drug list) restrictiveness. The attributes were chosen after a thorough review of the literature on pharmacy patronage, patient satisfaction, and prescription drug benefit plans. Each attribute represents a different method of cost containment and together they allow consumers to trade off cost, service, and access.

Three levels of each attribute were specified (see Table 1). The levels were selected to capture the full range of values for each attribute that consumers might see in the market and to vary sufficiently so that respondents can detect differences.

We used a fractional factorial design to reduce the number of different drug benefit plans viewed by respondents. Eleven plans were presented to consumers. Nine were used to develop importance estimates. The other two were used as a holdout sample to assess the accuracy of the estimates.

Plans were presented as written descriptions of benefits and restrictions for prescription copayment, choice of pharmacy, and limitations of formulary. A full profile approach to data collection was used in this research. Profiles were pretested on students and university employees to identify unclear or ambiguous choices. A copy of a profile is provided in Figure 1 (next page). Consumers were asked to rate each plan on a 10-point scale. A score of “1” indicated that they would be unlikely to choose that benefit plan and a score of “10” indicated they would be likely to choose that plan. Intermediate points in the scale were not defined.

The drug benefit plans were presented to consumers as part of self-administered written questionnaires. Responses were collected from a convenience sample of consumers in the Richmond, Virginia, area.

### Table 1 Attributes and Levels Used in the Analysis

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to pharmacy</td>
<td>1. Can use any pharmacy</td>
</tr>
<tr>
<td></td>
<td>2. Insurance plan has a restricted network but patient’s usual pharmacy is included</td>
</tr>
<tr>
<td></td>
<td>3. Insurance plan has a restricted network and patient must switch to a new pharmacy</td>
</tr>
<tr>
<td>Patient cost-sharing</td>
<td>1. No copay</td>
</tr>
<tr>
<td></td>
<td>2. $8 copay per prescription</td>
</tr>
<tr>
<td></td>
<td>3. $15 copay per prescription</td>
</tr>
<tr>
<td>Formulary restrictiveness</td>
<td>1. Open formulary — the plan covers any medicine the physician prescribes</td>
</tr>
<tr>
<td></td>
<td>2. Mandatory generics — the plan covers only generic products if they are available</td>
</tr>
<tr>
<td></td>
<td>3. Closed formulary — the plan has a limited and restricted list of drugs that it will cover Any drugs not on the list must be switched to a similar drug on the list or the patient must pay out of pocket</td>
</tr>
</tbody>
</table>

### Estimation of Utilities and Importance Values

The PC-SAS program TRANSREG was used to estimate part-worth utility values for each consumer. The metric conjoint option was used. The TRANSREG program uses OLS regression analysis to estimate part-worths. The output of the program was a part-worth utility score for each level of each attribute for each respondent.

### Market Segmentation Analysis

The CA results also were used to conduct a segmentation analysis. This analysis assigned respondents to segments based on the

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Please look over the prescription drug plan below and then circle the number on the scale at the bottom of the page to indicate how likely you would be to choose the plan.

**PLAN 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription copayment</td>
<td>You must pay 8 dollars for every prescription you have filled. Your insurance plan will pay for any cost above 8 dollars.</td>
</tr>
<tr>
<td>Choice of pharmacy</td>
<td>You are restricted to a network of only a few pharmacies in your area, and the pharmacy you usually visit is not a part of the network.</td>
</tr>
<tr>
<td>Presence of a formulary (drug list)</td>
<td>Your insurance permits your pharmacy to dispense any medicine your doctor prescribes for you.</td>
</tr>
</tbody>
</table>

1 2 3 4 5 6 7 8 9 10

Unlikely to choose | Likely to choose

---

**TABLE 2** Demographic Description of Sample

<table>
<thead>
<tr>
<th>Sex</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>86</td>
<td>66.7</td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
<td>33.3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Income</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than $10,000</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>$10,000 to $29,999</td>
<td>25</td>
<td>23.6</td>
</tr>
<tr>
<td>$30,000 to $49,999</td>
<td>23</td>
<td>21.7</td>
</tr>
<tr>
<td>$50,000 to $74,999</td>
<td>32</td>
<td>30.2</td>
</tr>
<tr>
<td>$75,000 or more</td>
<td>23</td>
<td>21.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescription payer</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Government</td>
<td>3</td>
<td>2.4</td>
</tr>
<tr>
<td>Private insurance</td>
<td>28</td>
<td>22.4</td>
</tr>
<tr>
<td>HMO</td>
<td>71</td>
<td>56.8</td>
</tr>
<tr>
<td>Self</td>
<td>16</td>
<td>12.8</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>5.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>18 to 24</td>
<td>10</td>
<td>7.8</td>
</tr>
<tr>
<td>25 to 44</td>
<td>72</td>
<td>56.2</td>
</tr>
<tr>
<td>45 to 64</td>
<td>39</td>
<td>30.5</td>
</tr>
<tr>
<td>65 or over</td>
<td>7</td>
<td>5.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marital status</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Never married</td>
<td>32</td>
<td>24.8</td>
</tr>
<tr>
<td>Married</td>
<td>81</td>
<td>62.7</td>
</tr>
<tr>
<td>Divorced</td>
<td>9</td>
<td>7.0</td>
</tr>
<tr>
<td>Separated</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Widowed</td>
<td>5</td>
<td>3.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Highest level of education</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Postgraduate</td>
<td>37</td>
<td>28.7</td>
</tr>
<tr>
<td>College graduate</td>
<td>40</td>
<td>31.0</td>
</tr>
<tr>
<td>High school</td>
<td>49</td>
<td>38.0</td>
</tr>
<tr>
<td>Less than high school</td>
<td>3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Strength of their preferences for the attributes. Consumers were assigned to either copayment, formulary, or pharmacist choice segments if their importance values for one of these attributes was at least 40% and if it was at least 10 percentage points greater than the importance they placed on the other attributes. Those individuals who did not fall into any of these single preference categories were considered to have mixed preferences.

Respondents with mixed preferences were further assessed to determine which two attributes they most preferred. These respondents were assigned to a segment based on cumulative importance values of at least 70% for at least two attributes when the importance values for attributes were within 10 percentage points of each other.

**Assessment of the Conjoint Model**

The internal reliability of responses was assessed by measuring the CA model’s goodness of fit. The validity of the data was assessed using a method suggested by Acito and Jain. The method tests whether the predicted values calculated from the CA estimates are more accurate predictors of the actual values of the holdout profile than are random values.

**Results**

Data were collected from 130 consumers. A demographic description of respondents is shown in Table 2. Responses for three consumers could not be used in calculating utilities due to incomplete responses on the survey. The sample was predominantly female and married. Most were college graduates with family incomes of greater than $50,000 per year. Most received prescription benefits through an HMO. On average, respondents purchased 6.0 (+/- 7.1 SD) prescriptions per year for themselves or other family members. The range of purchases was from 0 to 40 prescriptions per year.

Part-worth utility values (UVs) are shown in Table 3 (next page). The importance values estimated from the CA model indicated that formulary status was the most important attribute (42.1% out of a possible 100%) in determining a consumer’s preference for a prescription benefit plan. Consumers strongly preferred open formularies. As formulary restrictiveness increased, preferences decreased. The change in preference was more than twice as great for a change from a mandatory generic policy to a restricted drug list than for a change from no formulary to a mandatory generic policy.

The next most important attribute was the amount of the copayment (31.9%). Increasing the copayment from $8 to $15 had about three times more impact on consumer preference than increasing it from no copayment to an $8 copayment.

Restricting access to pharmacies had an importance value of 26.0%. Consumers had approximately equal preferences for an open network and a closed network that included their usual pharmacy. That is, they saw no disadvantage to a restricted network if it included the pharmacy at which they usually purchased...
prescriptions. Preferences were only affected if the restricted network did not include their usual pharmacies.

**Market Segmentation Analysis**

The results of the market segmentation analysis are shown in Figure 2. Forty-four percent of respondents based their decisions primarily on formulary choice, 23% based their decisions primarily on copayment, and the smallest number (10%) on pharmacy access. Of the 30 respondents who expressed mixed preferences, 21 (70%) indicated that formulary choice was a major determinant of their choice.

**Correlation Analysis**

No significant relationships between the importance of pharmacy choice or formulary status were indicated for either the demographic variables or annual prescription purchases. Results did indicate that level of copay was less important to higher income groups (F with 4,98 df = 2.96, p=0.0234) and married respondents (F with 1,124 df = 4.3, p=0.040). While there were significant differences among age groups in the importance of copay (F with 5,119 df = 3.64, p=0.004), there was no clear pattern.

**Assessment of the Conjoint Model**

The goodness of fit of the conjoint model (R²) was 0.88, indicating a good fit of the data to the model. The mean (SD) absolute value of the differences between predicted and actual values for the two holdout profiles were 3.0 (1.9) and 2.2 (1.6). By comparison, the mean absolute value of the differences between the actual values and randomly selected values was 3.6 (2.6). A Z-test indicated that the values predicted from the conjoint results were significantly (p<0.05) more accurate than random values.

**Discussion**

The purpose of this study was to determine the relative importance of prescription drug benefit attributes in consumer selection of drug benefit plans. The results indicated that, given the levels of attributes specified in this study, preferences for drug benefit plans were most influenced by formulary restrictions for this sample of respondents. Respondents strongly opposed closed formularies and, to a much lesser extent, mandatory generic policies. This is particularly noteworthy in light of the increasing use of formulary restrictions on branded products. Use of restricted formularies has increased from 23% of HMOs in 1992 to 49% in 1999.23-24 Use of closed formularies in employer-sponsored plans has remained relatively stable since 1995, but use of incentive formularies has grown from “a few plans” in 1996 to 25% of responding plans in 1999.25-26

As expected, consumers most preferred to have no copay and least preferred the $15 (highest) copay. They also indicated that the change from an $8 copay to an $15 copay was three times more important than a change from no copay to an $8 copay. This may suggest that consumers have become accustomed to paying small copays, but that they are resistant to paying larger copays.

Access to their usual pharmacy was much less important to consumers than formulary restrictions and somewhat less important than copay amount. To explain the relative importance of the attributes in another way, a change in formulary status from open to closed (restricted drug list) had nearly as much effect on consumer preference as both the implementation of a closed network that did not include the consumer’s usual pharmacy and the implementation of a $15 copayment.

The market segmentation analysis provided similar results as to
Consumer Preferences for Types of Cost Containment in Prescription Drug Programs

the relative importance of attributes. Most consumers made their choice of plan based primarily on formulary status, fewer based their choice primarily on copay level, and the fewest based their choice on pharmacy access. Figure 2 shows that over 75% of respondents made their plan choices based on a single plan attribute while the remaining respondents made their choice based upon multiple attributes.

The segmentation analysis also provides insight into individual preferences for plan attributes. Although formulary status and copay are clearly preferred by most respondents when choosing a plan, 21 respondents placed great emphasis on pharmacy access in choosing plans (i.e., 13 with most important and 8 with mixed preference for one other attribute). This consumer segment might be likely to respond negatively to restricted pharmacy networks.

Our study did not specifically examine consumer preferences for three-tier copay plans. To some extent, this is a limitation because of the wide use of three-tier copay design in drug benefit plans today. Recent surveys indicate that three-tier copays covered 40% of HMO enrollees27,28 and 50% of enrollees of health plans sponsored by large employers in fall 2000.29 This is up from only 5% of enrollees in three-tier plans in the spring of 1998 and is expected to continue to grow.27,28 A recent report also indicates that insurers and PBMs are beginning to offer plans with more than three tiers.29 Consequently, information on consumer preferences for these features would be important information for those designing drug benefit programs.

While our study did not specifically address multiple-tier copay programs, the results may shed some light on consumer preference for them. The results indicated that consumers were willing to pay significantly higher copays to avoid closed formularies. This is basically what tier copay plans allow them to do—pay higher copayments for drugs otherwise not covered (100% cost-share). As such, our results indicate that consumers would prefer tier copay programs to closed formularies.

In addition, the results suggest the ranges of copay differences within which consumers would prefer tier-copay benefit plans. Specifically, the utility value associated with the change from a mandatory generic policy to a closed formulary was 1.09. This is substantially larger than the utility value of a change in copay from $8 to $15 (0.703) and a little larger than the utility value of a change from $0 to $15 (0.921). This can be interpreted to indicate that consumers would almost surely be willing to pay $7 more per prescription, and probably would be willing to pay $15 more, to have their choice of drug products as opposed to being subject to a closed formulary. This suggests that copay differences between the brand-name drug on the formulary and the brand-name drug not on formulary tiers need to be substantially higher than $15 to induce consumers to switch from nonformulary to formulary products.

**Limitations**

The results of the study are subject to several limitations. First, the results are based on a small, convenience sample from one area of the country. It is not known whether similar results would be obtained from a larger, more nationally representative sample. The respondents in our sample do differ slightly from national averages on prescription use. Sample respondents reported mean prescription purchases of about six prescriptions per year. These purchases included prescriptions the respondent purchased for his or her own use as well as ones purchased for family members. National statistics from HMOs indicate higher usage rates of about eight prescriptions per member per year for younger consumers and 22.5 prescriptions per member per year for Medicare recipients.23

Second, the results apply only to the particular levels of attributes specified in the study. For example, the results can only indicate preferences for the copayment levels specified. No conclusions can be made for copayments of $25, $35, or any other levels that were not explicitly assessed. Third, the results do not allow for linear extrapolation. The utility weights indicate that a change in copay from $0 to $8 has less effect on consumer preference than a change from $8 to $15. If the utilities were linear these two changes should have about equal effect. Finally, the study did not attempt to model all possible attributes associated with pharmacy benefit plans, such as the use of mail-service pharmacy or three-tier copays.

These limitations do not affect the internal validity of the study's results. They do, however, limit the extent to which the results can be generalized.

**Implications**

When designing plans, pharmaceutical benefit managers need to balance the issues of drug availability, provider access, and cost. The use of conjoint analysis can help identify plan features that consumers prefer and the extent of those preferences. The consumers in this study indicate that the freedom to choose drugs was more important than out-of-pocket cost or pharmacy access. However, preference for this attribute was influenced by other elements of the plan.

Plan designers can use information from CA to decide whether potential savings in plan design can be balanced with the impact on consumer preferences for the plan. For example, restricting pharmacist access for this sample will have the least impact on consumer preferences but also will have the least potential for savings—pharmacy compensation is already very low. The greatest potential for cost savings in pharmacy plans lies in controlling drug costs through mechanisms such as the use of a formulary—the attribute with the greatest impact on consumer preferences.

Drug benefit designers can use CA results to model the trade-off between preferences and cost savings. Benefit managers can combine forecasts of estimated savings for plan changes (e.g., a restricted pharmacy network) with the results of consumer preferences for those changes in order to identify which plan design will produce the greatest savings with the least impact on preferences. This can provide benefit plans with an additional method
for predicting the impact of changes in drug benefit design on consumer satisfaction.

It is also interesting to contrast the findings of this study with research on preferences for health plans. The attribute patients most preferred in choosing health plans is access to the physician.\(^3\) For this study of prescription drug benefit plans, the most preferred attribute is the freedom to have the drug chosen for you by your physician. Therefore, it appears that the determinant attribute in choosing medical and pharmacy benefit plans may both be an extension of the physician's expertise and decision for the patient.

**Future Research**

It would be valuable to conduct a more detailed benefit plan assessment with a more geographically diverse population and using a different group of attributes and attribute levels. It would also be useful to assess how pharmacy benefits are chosen in relation to other medical plan criteria.

**Conclusion**

Health plans use a number of different methods of cost containment to control the costs of prescription drugs. Typically, these include restrictions on which products will be reimbursed, which pharmacies consumers may patronize, or the imposition of higher copays. Implementing any type of restriction will result in some degree of consumer dissatisfaction. The results of this exploratory survey indicate that health plans can expect the most dissatisfaction to result from restrictions on product choice, especially when the restrictions involve therapeutic (as opposed to generic) interchange. Health plans can expect somewhat less dissatisfaction from increasing consumer cost-sharing and less still from restricting access to pharmacies. These results indicate the potential usefulness of considering consumer preferences and trade-offs in the design of drug benefit plans.

**DISCLOSURES**

This research was funded by the National Community Pharmacists Association, formerly the National Association of Retail Druggists. Author David Holford discloses that he received funding for unrelated research in pharmacoeconomics from PhRMA. Author Norman V. Carroll discloses that he has received research funding from Pfizer for unrelated cost of illness research. Both authors assert that neither funding source exerted any influence on the results of this research. Holdford served as principal author on this paper. Study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, and statistical expertise was conducted jointly and equally by the authors. Administrative, technical, and/or material support was provided by Virginia Commonwealth University School of Pharmacy.

**REFERENCES**

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High Frequency of Itraconazole Prescriptions with Potentially Interacting Medications in a Large Health Care Plan

OBJECTIVE: The objective of this study was to determine the frequency with which potentially interacting medications are prescribed. Patients in a large Midwestern U.S. managed care health plan who received prescriptions for itraconazole, an antifungal medication, and at least one concomitant interacting medication were identified. These exposures were classified by the seriousness of the potential interaction.

METHODS: A retrospective database analysis was performed on pharmacy claims data to identify patients who had received itraconazole and an interacting medication at any time during the course of itraconazole therapy. Medications that are known to interact with itraconazole were categorized into three subgroups based on the nature or severity of their potential interaction: (1) “severe,” because of the serious or life-threatening nature of the potential interaction; (2) “avoidance,” because interactions with these medications may lead to a suboptimal antifungal effect; and (3) “precautionary,” because monitoring of patients is warranted and the benefits of itraconazole therapy may outweigh the potential risk of an interaction.

RESULTS: Of 2,034 patients prescribed itraconazole, 23.1% had at least one interacting medication prescribed concurrently. Itraconazole was prescribed with a potentially interacting medication in 683 instances; medications in the “severe” interaction category were dispensed in 155 instances; medications in the “avoidance” category were dispensed in 371 instances; and medications in the “precautionary” category were dispensed in 157 instances.

CONCLUSIONS: A substantial number of patients in a large managed care health plan were concurrently prescribed itraconazole and medication with a potential for interaction. These data suggest that systems need to be implemented to help avert such potential interactions.

KEYWORDS: Itraconazole, Drug interactions, Drug use review.

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nychomycosis is a fungal nail infection that takes a significant toll on the quality of life of patients. It affects from 2% to 13% of adults and children. Although the prevalence of onychomycosis in the managed care setting is not known, the advent of dynamic new oral therapies has brought new attention to onychomycosis. The treatment options for onychomycosis vary widely, as do the costs incurred with these different treatments. Since there is no standardized treatment algorithm for this medical problem, room exists for improved management.

When choosing among medications for onychomycosis, the potential for drug interactions in patients using other medications is an important and well-recognized issue. Drug interactions and other adverse events can lead to considerable health problems and/or inconvenience to patients and drastically increase the cost of medical treatment. These interactions can result in treatment failures if the bioavailability of antifungal therapy is altered or in toxic effects associated with inhibition of drug metabolism. In either case, further treatment may be required, thus increasing the cost of treatment and the risk of additional drug interactions. Thus, the treatment of onychomycosis presents an opportunity to examine the frequency with which drug interactions might compromise optimal patient care.

Among the azole antifungal agents, itraconazole is a highly regarded treatment option. Desirable qualities of this antifungal include its active metabolites, long half-life, and high tissue penetration. Furthermore, it is well tolerated, with adverse effects consisting mainly of nausea, headache, rash, and, on rare occasions, abnormal hepatic function. However, itraconazole has significant potential for drug interactions. It acts by inhibiting reactions catalyzed by cytochrome P450 within the fungal cell membrane, including the synthesis of ergosterol, an essential component of fungal membranes. Itraconazole also inhibits mammalian cytochrome P450 enzyme (CYP) 3A4 and, as a result, can significantly affect the pharmacokinetics of drugs that are metabolized through this system. This interaction may lead to serious, possibly life-threatening, toxicities when itraconazole is administered with medications that are metabolized through this P450 isozyme.
Medications with the potential to interact with itraconazole can be classified as severe, avoidance, or precautionary on the basis of the extent to which coadministration might compromise the patient's health or the efficacy of itraconazole in treating a fungal infection. Among the medications that potentially result in severe interactions with itraconazole is the contraindicated drug, cisapride, which is only available through a limited use program (cisapride was available without restrictions at the time of this study). Co-administration of itraconazole with the oral benzodiazipines, midazolam or triazolam, may, through inhibition of the P450-mediated metabolism of these drugs, heighten and prolong sedative and hypnotic effects. In a similar manner, again involving cytochrome P450 (CYP) 3A4 isoform, administration of itraconazole with either lovastatin or simvastatin may result in rhabdomyolysis.

Interacting medications that effectively reduce the bioavailability of itraconazole should be avoided. Since the absorption of itraconazole requires an acidic environment, drugs or conditions that increase gastric pH (such as H2-receptor antagonists) can decrease the serum levels of the drug. In fact, foods or beverages (e.g., cola) that lower pH have been exploited to counteract this effect. However, it should be noted that grapefruit juice, which is an acidic beverage, has been shown to unexpectedly decrease the absorption of itraconazole. Enzyme inducers (phenytoin, rifampin, and phenobarbital) can increase the metabolism of itraconazole, resulting in decreased drug levels and possible therapeutic failures.

Finally, there is a group of “precautionary” drugs, including warfarin, oral hypoglycemics, dihydropyridine calcium channel blockers, cyclosporine, digoxin, and quinidine. Prescribers must weigh the benefits and risks of prescribing these medications and itraconazole concurrently. Dosages of concomitant drugs may be adjusted downward to avoid toxicity.

Although the potential for drug interactions with itraconazole is well known, we are unaware of any studies documenting the frequency with which potentially interacting medications are prescribed. Pharmacy claims databases can be used to analyze prescriptions for large numbers of patients. Given the large number of agents that interact with itraconazole and the many patients receiving concurrent medications, we hypothesized that the frequency of prescription of potentially interacting medications would be high. Therefore, we undertook the current study to identify patients who were prescribed itraconazole in a managed care setting and to quantify the number of patients who had received concurrent prescriptions for potentially interacting medications.

Methods

This was a retrospective database analysis. The database consisted of drug claims for 1.375 million members of a large Midwest U.S. health care plan. The study population was limited to patients who had been continuously enrolled in the plan for at least 2 years, from January 1, 1996, to December 31, 1997. All fee-for-service (65% of total population) and health maintenance organization patients were included. No exclusion of patients was made on the basis of age or gender. Patients were included in the analysis if they were diagnosed with onychomycosis (ICD-9 code 110.1) and were prescribed itraconazole. Patients were excluded if they either did not have a diagnosis of onychomycosis or were not prescribed itraconazole. Any claims that were reversed (screened from fill date to end of study) or stopped by pharmacy point-of-service edits were excluded. Only those claims that could have actually been dispensed to patients were included in the analysis. Additionally, when possible, refill patterns were used to verify receipt (and continual exposure) of medication.

This subset was subsequently sorted on a single criterion: prescription of a potentially interacting medication at any time during the course of itraconazole therapy. Interacting medications and potential consequences were identified from the itraconazole prescribing information. Finally, these prescriptions were subdivided into one of three categories based on the nature or severity of potential interactions associated with the use of each medication and itraconazole concurrently. The first category, “severe,” consists of medications with potentially life-threatening consequences secondary to itraconazole-induced inhibition of CYP3A4 activity. The second category, “avoidance,” includes medications that could cause a suboptimal antifungal efficacy due to altered absorption or metabolism of itraconazole. Although specific proton pump inhibitors (PPIs) are not listed in the prescribing information as “avoidance medications,” the prescribing information does indicate that itraconazole absorption is decreased in the presence of gastric acid suppressors. For this reason, PPIs were included in this category. The third category, “precautionary,” describes medications with a potential for interactions that are not life-threatening and that do not necessitate drug avoidance, but do warrant monitoring. Here, the benefits of itraconazole may outweigh the risks of potential interactions with concurrent medications. It should be noted that whether serious or other consequences actually occurred from the drug interactions was not within the scope of this study.

All frequency reporting was done with SAS 6.12 software.

Results

A substantial percentage of the patients receiving itraconazole were prescribed an interacting medication. During the time frame of the study, there were 2,034 patients who were both diagnosed with onychomycosis and prescribed itraconazole. Of this group, 470 patients (23.1%) had at least one potentially interacting medication prescribed and filled at some time during their course of itraconazole therapy. The total number of potential interactions was 683, since many patients received more than one potentially interacting medication. For example, 311 (66%) patients had one interacting pair, 118 (25%) had two interacting pairs, 30 (6%) had three interacting pairs, 9 (2%) had four interacting pairs, and two (1%) had five interacting pairs.
High Frequency of Itraconazole Prescriptions With Potentially Interacting Medications in a Large Health Care Plan

Medications with potentially severe interactions were dispensed in 155 instances (see Table 1). Because of itraconazole’s inhibitory effects on CYP3A4, interactions in this group could lead to a pronounced pharmacologic, possibly toxic, effect of the concurrent medication. Simvastatin, prescribed in 59 instances, was the most common concurrent medication in this group. Although itraconazole interacts with several 3-hydroxy-3-methylglutarylcoenzyme A reductase inhibitors, simvastatin was the most commonly coadministered because it was on formulary at the time of this study.

Medications in the avoidance group have a potential for decreasing the absorption or increasing the metabolism of itraconazole. Both mechanisms lead to reduced efficacy of the antifungal agent because of suboptimal plasma levels of itraconazole. There were 371 instances in which patients received these medications along with itraconazole (see Table 2). The majority of these instances (341) involved histamine H2-receptor antagonists or proton pump inhibitors.

Medications in the precautionary group include those for whom the benefits of itraconazole may exceed the potential risks from the interaction. However, some of the interactions do have clinical consequences, and, therefore, monitoring is warranted. There were 157 instances in which patients received medications of this sort while taking itraconazole (see Table 3). Oral hypoglycemic agents constituted the most common class of “precautionary” interacting medications.

**Table 1**

Concomitant Prescription of Medications With “Severe” (Potentially Life-Threatening) Itraconazole Drug Interactions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number of Instances Prescribed Concurrently With Itraconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terfenadine*</td>
<td>35</td>
</tr>
<tr>
<td>Azetidizole*</td>
<td>14</td>
</tr>
<tr>
<td>Cisapride†</td>
<td>5</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0</td>
</tr>
<tr>
<td>Triazolam</td>
<td>10</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>32</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>59</td>
</tr>
<tr>
<td>Total</td>
<td>155</td>
</tr>
</tbody>
</table>

*These agents are no longer marketed. †A limited-access program for this agent began May 1, 2000; it is no longer widely available in the United States.

**Table 2**

Concomitant Prescription of Medications With “Avoidance” (Suboptimal Antifungal Efficacy) Itraconazole Drug Interactions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number of Instances Prescribed Concurrently With Itraconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>12</td>
</tr>
<tr>
<td>Histamine H2-receptor antagonists</td>
<td>202</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>139</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>371</td>
</tr>
</tbody>
</table>

**Table 3**

Concomitant Prescription of Medications With “Precautionary” (Monitoring Warranted) Itraconazole Drug Interactions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number of Instances Prescribed Concurrently With Itraconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>6</td>
</tr>
<tr>
<td>Warfarin</td>
<td>50</td>
</tr>
<tr>
<td>Oral hypoglycemics</td>
<td>63</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>1</td>
</tr>
<tr>
<td>Digoxin</td>
<td>32</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0</td>
</tr>
<tr>
<td>Quinidine</td>
<td>2</td>
</tr>
<tr>
<td>Felodipine</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>157</td>
</tr>
</tbody>
</table>

Discussion

In this retrospective analysis, a large number of patients were identified as having received prescriptions for itraconazole. A high percentage of those patients (23.1%) had also been prescribed at least one potentially interacting medication at some time during the course of their itraconazole therapy.

Abundant evidence in the literature details interactions between itraconazole and drugs metabolized by CYP3A4. In addition to two double-blind randomized studies indicating that itraconazole seriously affects the pharmacokinetics of midazolam and triazolam, causing prolonged hypnotic effects and impairment of psychomotor performance, a double-blind placebo-controlled randomized two-phase study showed a marked effect of itraconazole on the pharmacokinetics of felodipine, increasing peak plasma concentration and area under the felodipine concentration-time curve. This led to a significantly larger decrease in blood pressure and a significantly greater increase in heart rate during the itraconazole phase compared with the placebo phase of the study. Indeed, one of nine subjects in the study developed nausea and headache because of low blood pressure during the itraconazole phase.
Numerous reports of “real world” experiences also suggest that interactions between itraconazole and CYP3A4-metabolized drugs can lead to toxicity. Case reports of patients administered itraconazole and cyclosporine indicate a dramatic increase in cyclosporine serum concentrations when itraconazole is added to the regimen. An interaction between itraconazole and digoxin leading to an elevated serum concentration of digoxin has also been described. An interaction between itraconazole and vincristine was found in a subset of patients with acute lymphoblastic leukemia, resulting in increased vincristine-related neurotoxicity. The absence of case reports describing harmful interactions between itraconazole and other drugs indicate that these drug interactions are clinically significant.

Several drugs have been shown to affect the pharmacokinetics of itraconazole as well. These drugs, classified in the “avoidance” category, were the most common interacting drugs in the present study. Lim and colleagues found a significant decrease in the absorption of itraconazole when intragastric acidity is decreased by administration of famotidine. Agents that induce the metabolism of itraconazole, such as phenytoin, rifampin, and isoniazid, lead to decreased plasma concentrations of itraconazole. Effects on drug metabolism could account for treatment failures in patients who receive itraconazole plus one or more of these interacting medications. A particular concern with the medications in the “avoidance” group is that a decrease in antifungal efficacy may lead to prolonged itraconazole therapy and, therefore, to a potentially greater risk of exposure to interacting medications.

Limitations
The current study is limited by its data set and design. Although we used refill patterns to assess drug use, we had no way of determining the time at which a noncompliant patient stopped taking medication. Also, we relied upon administrative data quantifying potential clinical interactions rather than actual interactions. Further research should be conducted to quantify actual patient outcomes of the potential interactions. Nonetheless, we believe the results are provocative and warrant the attention of health care providers and pharmacists. The frequencies of potential interactions do represent actual dispensed prescriptions, so it is likely that the patients were exposed to the medications discussed. The potential interactions may have been underestimated, since they were generally defined according to the package insert, which may not be up to date with current literature that describes new interactions based on experience in the community.

At the very least, these data suggest that pharmaceutical care for patients with onychomycosis may need improvement. Of the patients studied, approximately 5% (101) were prescribed potentially life-threatening drug combinations. Additionally, a large proportion (18%) of itraconazole-treated patients used medications with a potential for less serious interactions. Institution of a more systematic approach toward the treatment of onychomycotic patients that focuses on the identification of those patients taking medications that can potentially interact with itraconazole should help avoid these interactions. Communication with the patient is essential because these potential interactions may not be recognized in patients who have their prescriptions filled at different pharmacies. We suggest that pharmacists and other health care providers refer to Communication Skills in Pharmacy Practice: a Practical Guide for Students and Practitioners for ideas on how to communicate effectively with their patients. Other strategies for prevention of these interactions include educating pharmacists and prescribers, verifying the functionality of pharmacy computer systems to detect these interactions, using oral antifungal medications without significant drug interactions (e.g., terbinafine), and placing formulary restrictions on the use of itraconazole.

This issue of potential drug-drug interactions goes far beyond the specific drug interactions described in this article. While pharmacists currently employ databases such as drug use review (DUR) software systems to alert them to drug interactions, many systems do not distinguish between high-risk and low-risk interactions. Thus, pharmacists are bombarded by a flood of interaction alerts on a daily basis. The constancy of these alerts has led many pharmacists to disregard them. In addition, research has shown that even when DUR systems are in use, systems fail to identify some potentially harmful drug interactions. A study undertaken by the University of Washington School of Pharmacy investigating Washington State chain and health maintenance organization pharmacies revealed that the nine different DUR programs in use by these pharmacies failed to identify common drug interactions one-third of the time. While drug interaction data was the same on all systems, the software interpreted the data variably, among and even within software programs.

The scope and importance of the issue of drug interactions at the point of prescription dispensation has been recognized by the pharmacy industry. On April 16, 2001, the Academy of Managed Care Pharmacy and the U.S. Pharmacopeia announced an initiative to reduce medication errors at the points of dispensing and prescribing through improvements in online prospective drug utilization review (OPDUR) systems. This initiative will focus on designing OPDUR systems that enable the pharmacist to distinguish drug interactions with the potential for significant harm.

To this end, the initiative will undertake to establish evidence-based clinically significant criteria for use by health care professionals and OPDUR vendors that will classify drug interactions with a high probability of causing serious harm. The initiative calls for a consensus on which interactions meet the established criteria for causing serious harm and for the creation of a system that will enable ongoing review of drug interactions and the addition or subtraction of drugs and classes of drugs from the system. Finally, it will facilitate interaction of health professionals, pharmacy-system vendors, pharmacy benefit management companies, and health plans to ensure that DUR systems used at the point of care incorporate the criteria established by the initiative.

Severe interactions typically influence morbidity and mortality.
and have been shown to increase the risk of hospitalization. Furthermore, even non-life-threatening interactions are likely to affect health care delivery and inflate costs. For example, drug-drug interactions involving medications in the avoidance group may result in prolonged treatment, therapeutic failures, and added drug costs. Also, the additional patient counseling and increased monitoring required with the prescribing of potentially interacting medications contributes to total health expenditures. While it is difficult to ascertain the exact costs associated with preventing or managing drug-drug interactions, it is reasonable to conclude that failure to effectively manage these interactions adds to the costs of health care.

**Conclusions**

In this retrospective study, the high number of patients receiving itraconazole concomitantly with potentially interacting medications was startling and disturbing. Pharmacists must implement strategies to protect patients receiving itraconazole from potentially harmful drug interactions. Institutions responsible for training health care professionals and providers of continuing education should offer programs to educate health care professionals on preventing drug interactions. The initiative undertaken by the Academy of Managed Care Pharmacy and the US Pharmacopeia to improve OPDUR systems in an effort to reduce medication errors at the point of prescription and dispensation is a positive step toward resolving these issues.

**DISCLOSURES**

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**REFERENCES**


Measuring Adherence and Persistence in Drug Therapy

In this issue of *JMCP*, the topic of medication adherence is addressed in an article by White et al. that compares differences in prescription refill patterns of antihyperlipidemic agents between patient groups receiving medications via mail service or retail pharmacies. While the objective of this naturalistic study was to compare refill patterns between two different types of prescription services utilized by plan members, the results and discussion from this article highlight an important measurement that may directly impact the clinical and economic outcomes related to the use of medications for treating chronic diseases.

Measures of medication adherence, also termed “compliance,” add an important dimension to outcomes studies by providing decision-makers with a valuable metric for comparing the utilization patterns of selected therapeutic agents. When medications are prescribed rationally and patients follow their regimens appropriately, the likelihood of achieving positive patient outcomes increases dramatically. However, when patients don’t adhere to their regimens, which may occur for numerous reasons, the opportunity for achieving positive health outcomes may be jeopardized. Measuring levels of adherence to medication therapies can help to explain or predict which plan design, educational intervention, or particular drug product has the potential to provide optimal patient outcomes within an organized health care setting.

In the article in this issue, the authors included patients in the study who had been newly started on an HMG-CoA reductase inhibitor based on a review of pharmacy claims data from a California HMO. Claims data were analyzed for each patient for a period of one year after initiating the therapy regimen. After controlling for some demographic differences between the study groups, the authors found that patients utilizing the mail service had significantly higher rates of adherence than patients using community pharmacies.

The use of pharmacy claims data to measure patient adherence has gained widespread use within pharmacy benefit programs. Large prescription claims databases have provided researchers with convenient access to utilization patterns of large patient populations and the opportunity to investigate medication adherence.

Perhaps the most comprehensive methodological work in the area of measuring medication compliance using administrative databases comes from Steiner et al. in two widely cited articles. In an original research article and in a subsequent review piece, Steiner and his colleagues provided a rationale for using different methods to calculate the patient adherence rate. Different rates may be calculated depending upon the length of time that one chooses to observe adherence within a population.

Utilizing a measurement based on Steiner’s earlier work, Sclar et al. described the now often-used “Medication Possession Ratio” (MPR) to calculate days of therapy between refills using prescription claims histories. To calculate this ratio, the total days supply of the medication dispensed (not including the last prescription dispensed) is divided by the total number of days between the first prescription dispensed and the last prescription dispensed during an observation period. Typically, this calculated ratio is less than 1.0, owing to the fact that patients will exhibit gaps in medication days. However, if patients obtain refills before their supply has been exhausted, the calculation may exceed 1.0.

As a benefit to readers, White et al. chose to calculate rates of adherence in one or more way. For example, the authors calculated a mean MPR of 93% for patients using mail-service pharmacy and an MPR of 82% for community pharmacy patients. However, over the one-year follow-up period, mail-service patients refilled prescriptions with an average total days supply that covered only 81% of the observed days, while community pharmacy patients’ refills covered, on average, only 57% of the observed days. While mail-service patients had longer mean days of persistence compared to community pharmacy patients (280 days versus 214 days, respectively), the authors did not report rates of discontinuation within the study groups, which would have allowed for an insightful comparison. Previous research has shown discontinuation rates of 10% to 60% within this class of medications.

Relying solely on a single ratio of adherence, such as an MPR calculation, provides the decision-maker with essentially one dimension of information regarding appropriate and adequate use of a medication within a population. When measuring medication adherence, we have to be sensitive to the different dimensions that should be considered. The first dimension is one of “consistency” with the prescribed regimen. Is the patient actually taking the drug in the manner that it was prescribed? To measure this dimension, the MPR can be used to compare what we would expect utilization to be based on the submitted days supply found in the prescription claim record. The second dimension is one of “persistence” in taking the medication. Is the patient refilling the medication in a timely fashion, over a pre-defined period of time, without gaps in treatment days? Both of these dimensions are equally important in comparative evaluations of medication adherence.

Consider a patient who refills two consecutive 30-day prescriptions in a timely manner, but then discontinues the medication, without the physician’s consent, for the rest of the year. Next, consider another patient that uses the medication intermittently for a total of nine months during the year, creating gaps in treatment. The latter patient’s MPR would be significantly lower than the former patient’s calculated MPR. Of the two patients, which one is more “adherent”? Which patient would be considered more “persistent”? Is one attribute of greater importance in determining appropriate use? Further consider which dimension of adherence would affect long-term total and component health care costs for the patient.

In a recent review of the many methods used to measure medication adherence among patients, Farmer described the advan-
tages and disadvantages of techniques such as biological markers, patient diaries, pill counts, electronic monitoring, and prescription record reviews.7 The method chosen to measure adherence can significantly affect the results of the study. Using prescription refills to measure adherence, for example, has some major limitations. First, prescription refills do not provide data on the quantity of medication actually consumed or the timing of doses.8 Many patients will obtain refills when reminded even when they have medication remaining (especially when they have low cost-sharing requirements); others will stockpile medications or store them in several places for convenience.9 Second, measuring prescription refills from claim records ignores the effect of prescription samples. Third, measuring prescription claim records does not capture information on the prescriptions written but not filled. It has been asserted that about one-third of patients do not have their prescriptions filled.10 Fourth, one cannot tell from claims data whether premature discontinuance of medication represents a change in physician orders or a decision (rational or irrational) of the patient.

As with any other research, studies on adherence must avoid selection bias. In other words, the groups must be comparable. Comparing groups that differ in days supply dispensed (e.g., 90-day supply for mail-order refills versus a 30-day supply for network prescriptions) is likely to bias the results. A 90-day supply will almost always appear to have a longer duration and greater persistence than a 30-day supply. Whenever possible, confounding variables must be controlled. The authors reported a significantly higher proportion of Medicare+Choice patients in the mail-service cohort (87%) than the community pharmacy cohort (56%); however, this difference was not controlled for in the ANCOVA analyses presented in Table 4. Also, no mention was made as to how differences in copayment levels were controlled. Failure to control for type of insurance coverage (e.g., Medicare+Choice vs. commercial) or copayment level could affect the results considerably; we lose the opportunity to determine if there is, in fact, a true cause-and-effect relationship between the type of prescription service and levels of adherence and persistence.

Measurements must also be valid—they must measure what they purport to measure. If one accepts that “adherence” is a measure of the degree to which patients actually follow prescription orders when self-administering medication, then the limitations of measurements such as “duration” and “persistence” become apparent. The appropriateness of the research design and interpretation of the results cannot be over emphasized when assessing rates of adherence and persistence within a managed care population; these measurements have the potential to influence the assessment of the overall clinical and economic benefit of prescription utilization.

As we continue to measure the economic impact of medications and interventions within managed care, the consideration of adherence and persistence rates should be an integral part of the assessment process. It seems reasonable to think that poor adherence rates within patient populations would ultimately lead to greater subsequent medical costs. However, an overview of the relationship between adherence rates and medical expenditures conducted by Hughes et al.11 concluded that while poor adherence rates almost always had a negative effect on the efficacy of the drug therapy, the economic impact varied. The results were based on a review of 22 studies previously published in the literature. The most notable scenario where economic impact was least affected by poor adherence was in the case where drug costs dominated total costs within a disease state. In summary, it appears that the economic effects of poor adherence within a population are unpredictable, at best.

Insightful administrators would do well to encourage the inclusion of real-world levels of adherence into the decision-making process when considering both the potential clinical and economic outcomes related to drug therapies or interventions within a managed care patient population. As a follow-up to their earlier research, Hughes et al.12 have suggested methodologies that can account for estimated levels of adherence within patient populations.13 This recognition of varying adherence rates allows decision-makers to conduct sensitivity analyses through modeling exercises to better predict outcomes in a naturalistic setting.

In addition, more research is necessary to better determine a range of “acceptable” levels of adherence rates within therapeutic categories. We know that 100% compliance is optimal, but not likely attainable across a population. Therefore, is 90% adherence adequate and attainable? How about 75%? Authors often select an anecdotal level of 80% as an appropriate indicator of compliance, but offer no rationale for the selection of that particular rate. Studies that evaluate the relationship between different rates of adherence and their direct effect on clinical and economic outcomes should be encouraged in order to determine practical levels of acceptable adherence rates.

As these investigations continue, we may learn how to better achieve optimal levels of medication adherence, thus improving the potential for positive patient outcomes within the managed care setting. We must recognize the shortcomings of our present methods of measurement of adherence and persistence in drug therapy management.

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(See references, next page)
Conjoint Analysis in Pharmaceutical Research

The Holdford and Carroll article1 in this issue of JMCP uses conjoint analysis, a methodology for evaluating subject preference assessment that is unfamiliar to many pharmacists, other clinicians, and health services researchers. Despite the lag in adoption of these methods in the health care field, conjoint analysis is rapidly gaining popularity as a versatile research tool that can be used in a variety of evaluation contexts. There are a number of important pharmacy and pharmaceutical research questions that naturally suggest conjoint analysis as a valuable research methodology. These include new drug development, drug benefit program design, drug treatment willingness-to-pay assessment, and medication cost effectiveness research. A current Medline search shows that while only 26 articles with the keywords “conjoint analysis” appeared in the medical literature prior to 1997, 40 articles have appeared from 1997 to date, with the citation rate increasing by roughly 30% annually.

Conjoint analysis methods were originally developed by market researchers over 40 years ago, and have been further advanced and widely used in marketing studies by academic and commercial marketing research groups.2 These methods received formal underpinnings in economic utility theory early in their development.3,4 Powerful tools for empirical evaluation of conjoint analysis applications were pioneered principally by Daniel McFadden, who shared the 2000 Nobel Prize in economics for this research.5,6 The initial application for McFadden and colleagues was evaluation of consumer preferences for alternative transportation options, specifically, the introduction of the BART subway system for northern California commuters.7

What Is Conjoint Analysis?

Conjoint analysis is a method for systematically evaluating and estimating the strength of subject (e.g., consumer, patient, clinician, decision-maker, etc.) preferences for discrete choice alternatives (e.g., different therapies, different drugs, health insurance choices, disease symptoms, treatment side-effects, etc.). The key insight behind conjoint analysis is that people systematically choose among alternatives based on observable “bundles” of attributes that each choice option represents.8 For example, consumers shopping for a new automobile would consider the vehicle size, body style, color, price, engine power, fuel efficiency, seating capacity, safety features, and other observable characteristics, including the brand name itself (e.g., Ford, BMW, Chevrolet, Honda, etc.) in making a car purchase decision. While each individual possesses idiosyncratic or unobservable tastes that contribute to observed choice, the researcher can systematically evaluate the strengths of each of these unobservable attributes in eliciting choice preferences through a conjoint analysis experiment, where a variety of vehicle profiles are ranked by potential car-buyers on the basis of varying the bundles of observable (and thus modifiable) attribute bundles.

In a conjoint analysis experiment, the potential car buyers would be asked to rank their preferences for vehicles with different combinations of the salient observable characteristics. Subjects with different demographics (e.g., income, family size, education, occupation, etc.) will almost certainly demonstrate different preference strengths for different choice attributes. This allows the car manufacturer market researchers to “segment” the market into groups of consumers that have similar tastes, and then provide a variety of vehicle choices that better match the spectrum of tastes in the consumer population.

Why Has It Taken So Long for Conjoint Analysis to Be Used in Health Care?

Conjoint analysis generally utilizes stated preference (SP) methods, rather than revealed preference (RP) methods. In SP studies, subjects are provided information on alternative choice profiles in

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an experimental, hypothetical-choice setting. They are asked to state their choice preferences “as if” they were actually going to be given their choice in the real world. In RP studies, the choices that subjects make in the real world are the units of analysis. For example, the quantity and variety of breakfast cereals people actually buy as a function of prices and other consumer characteristics could be analyzed using retrospective data from grocery stores chains, an RP method. Similarly, the amount of health care that people utilize as a function of health plan copayments and other characteristics can be observed and analyzed in a prospective RP study, such as the Rand Health Insurance Experiment.9

Many social science and health services researchers have long held strong biases against SP research methods. They have believed that subjects do not respond in hypothetical experimental settings as they really would if confronted with such choices in the real world. They think that SP subjects can easily see what answer is “best” for them, and then strategically rank their answers to give the researcher a false impression of their true preferences.

For example, subjects in a naive SP experiment on health insurance plan design might systematically overstate their preferences for freedom-of-choice of provider, generosity of coverage, or accessibility of facilities if they were not actually paying for these features. Similarly, taxpayers might systematically understate their preferences for increasing taxes to cover a new hospital, highway, or public works project if they thought that doing so would convince politicians to vote against these programs.

Conjoint analysis can overcome these problems through experimental designs that make it impossible for the SP subject to game their responses by comprehending what the “correct” answer should be. In a well-designed conjoint analysis experiment, the choice profiles vary in such a way that strategic responses aren’t possible.

From another perspective, there are many critical research questions that simply cannot be evaluated with RP methods. For example, suppose a pharmaceutical manufacturer wants to know whether a new drug in early development has efficacy or toxicity characteristics that clinicians and patients would prefer to the existing FDA-approved therapeutic alternatives. Before investing significant resources in clinical trials, the company could sponsor clinician and patient conjoint analyses of the new drug profile compared to the existing alternatives. RP data for this drug would not become available until the drug was actually approved, which would potentially require millions of additional research dollars and years of investment.

One of the key recent advances in conjoint analysis research is the insight that conjoint analysis research studies can be combined with RP data to provide results that are more useful and valid than those of either study design used separately. Thus, if researchers had a very good RP study on patient preferences for existing antihypertensive drugs, they could use that, in combination with a conjoint analysis of a new experimental antihypertensive medication to predict how well the new therapy would be accepted by various types of patients, more precisely than using just the RP study or just the conjoint analysis alone.

Validity of Conjoint Analysis
Conjoint analysis studies have been subjected to substantial validation research.8 Perhaps the strongest proof of validity of this research method is the fact that nearly all major corporations utilize either internal or external conjoint analysis market research in product design and pricing decisions. Governments and public agencies also rely heavily on conjoint analysis methods for transportation planning, environmental policy planning, and other public policy research. If the conjoint analysis techniques were not valuable, they would not be used routinely for these multimillion dollar public and private decisions.

Conducting a Conjoint Analysis
Designing a successful conjoint analysis experiment involves first establishing the important characteristics of choice that lead people to prefer one alternative to others. This is often done by assembling a focus group of representative subjects (e.g., consumers, patients, or clinicians) and with a structured interview format to elicit the most important attributes-of-choice decisions. The resulting information is then used to create a pilot data collection instrument that is administered to a small sample of subjects to ensure that the survey instrument is capturing meaningful and relevant dimensions of subject choice. A full-scale survey is then implemented using statistical power calculations to estimate necessary sample sizes and fractional factorial experimental designs to ensure that adequate data are collected on each decision attribute of interest.8,10 The data are analyzed using multinomial logit or other qualitative dependent variable estimation techniques.11 Policy analyses are then performed to (a) evaluate and rank the strengths of each attribute in determining subject choice, (b) establish how these rankings change for different demographic subgroups, (c) predict how many subjects would switch to another choice (e.g., a new drug) if specific attributes were available for that choice, (d) estimate the strength of the price or cost attribute to determine subject willingness to pay for various choice alternatives, and (e) estimate subject utility directly as a function of choice alternatives.

Use of Conjoint Analysis in Medical, Pharmaceutical and Health Services Research
Holdford and Carroll list several areas where conjoint analysis has been successfully applied in areas of clinical interest, including consumer preferences for drug therapies, pharmaceutical services, health outcomes, and health insurance.1 Additional subjects found in a Medline search include: health status preference scales,12,13 new drug development,14 patient preferences for clinical products and services,15,16 and decision-maker preferences.18

Conjoint analysis has many advantages over other health status assessment and ranking techniques. Like the standard gamble and...
time trade-off methods, it is rigorously grounded in economic utility theory. It is much less cumbersome to implement in cost-effectiveness applications and other settings than these other utility measures. In fact, any health status measurement tool can be converted into a conjoint analysis index of consumer preference. It is also rigorously grounded in econometric estimation models with testable parameter restrictions. Conjoint analysis provides direct assessment of consumer willingness-to-pay for treatment options and consumer utility, in an SP framework that is resistant to subject “response gaming.” It can be combined with data from empirical RP studies to provide results that are more precise than either method separately. It has been used and validated in numerous private-sector and public-sector studies in many different fields of preference elicitation. In short, we can expect to see conjoint analyses used increasingly in health care, pharmaceutical, and pharmacy evaluations.

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Better Data for Making Better Decisions: Finger-Pointing or Useful Drug Use Review (DUR)

The research presented by Heaton et al.1 in this issue of the Journal suggests that a significant number of patients were prescribed itraconazole concomitantly with potentially interacting medications. Another study,2 using similar retrospective database research methods, drew comparable conclusions about apparent drug interactions with cisapride. The implications of these research reports are several-fold and raise important questions about pharmacy practice in general and drug use review (DUR) specifically.

The first implication is that online prospective drug use review (OPDUR) systems are not systematically identifying specific drug-drug interactions (DDIs). This may be because the alerts generated by OPDUR systems do not have high sensitivity or specificity. Second, the results of this study and others like it, with better data and methodology, could help make prospective DUR screening more effective by focusing on only those problems characterized as clinically significant. Third, many pharmacists do not consider OPDUR to be helpful or clinically relevant to their pharmacy practice in the “real world.” A major concern of experts is that this barrage of OPDUR alerts does nothing to advance patient care and may actually desensitize pharmacy personnel to such messages. This has limited the potential of any OPDUR system to improve patient care. Lastly, OPDUR systems have practical and functional limitations that impact their utility. In this review, we explore these issues in brief and set the stage for a more thorough review of state-of-the-art DUR to be published in a future issue of JMCP.

Sensitivity and Selectivity of OPDUR Systems

Evidence of significant problems with OPDUR systems and their components has been mounting for some time. The USP (United States Pharmacopeia) Drug Utilization Review Advisory Committee (1995-2000) has pointed to problems with existing DUR criteria.3 The committee concluded that wide variation exists in the current sets of DUR criteria. A leading cause of this inconsistency has been the lack of formal methods governing the development of DUR criteria. Additionally, the group called for a shift
away from an individual patient review DUR to a more comprehensive disease-management approach. The concerns of the USP panel are illustrated by a study conducted by Hazlet et al. They tested the ability of prospective DUR systems in chain and HMO pharmacies in the state of Washington to detect 16 well-established drug-drug interactions (DDIs). These systems failed to detect the specified interactions one-third of the time. The chance of detecting important DDIs (sensitivity) ranged from 0.44 to 0.88. The specificity of these systems (few false positives) ranged from 0.71 to 1.0. The challenge in developing optimal or at least more useful OPDUR systems is to refine the criteria in such a manner that an alert message is highly predictive of an event.

**Clinical Significance of OPDUR Alerts**

The results of the Heaton et al. study and others like it could, with better data and methodology, help make prospective OPDUR screening more effective by focusing on only those problems characterized as clinically significant. Heaton and colleagues indirectly point to the difficulties associated with assessing the true magnitude of any specific DDI problem. While clinical studies well document the potential severity of DDI problems, our knowledge of the magnitude of such problems in the “real world” is relatively sparse. Experience suggests that many patients exposed to dangerous drug-drug interactions do survive them, often without using medical care services.

A fundamental goal of all DUR systems should be to safeguard patient safety at the point of service without compromising the patient’s interest. The practical task is how to accomplish this within the context of currently available electronic systems. The challenge before us is to answer basic questions, such as, what is the frequency of a specific adverse clinical consequence among patients exposed or receiving alerts (incidence).

Common clinical epidemiological techniques can help us in this respect. For example, in assessing the value of diagnostic tests, we look for measures that have high sensitivity values. Applied to a drug-drug interaction, the sensitivity score would reveal the percent of all clinical cases (e.g., bleeding episodes) that would have been detected by an alert message. An analogous and possibly more intuitively meaningful measure of “true positive” alerts is the positive predictive value. This is the percentage of all alerts that, if left unaddressed, would result in this clinical consequence. For example, of all flagged warfarin-aspirin alerts, what percentage of them would have resulted in a bleeding episode? Similar specificity and negative predictive value measures help define “rule out” criteria (true negatives).

Claims databases can help in making these types of assessments. Either sensitivity or specificity or positive/negative predictive values can and should be used as yardsticks for assessing the utility of existing or more sophisticated screening criteria as called for above. Having said that, we must hastily point out that this type of analysis is not easy to perform.

**Pharmacist Response**

Pharmacists have criticized OPDUR systems for generating alert messages that they consider to be simply “noise” in the system. Often the prescriber, the patient, and even the pharmacist are unaware of the OPDUR alerts. On-site systems may not contain comprehensive drug profiles if the patient receives prescriptions from several pharmacies or pays cash for other prescriptions. Many alerts focus on clinically insignificant problems about drugs generally regarded by the physician and pharmacist as safe in a given clinical situation. Not surprisingly, many messages are ignored or these functions are deactivated. In a study of community pharmacy practice in Indiana, Chui and Rupp report that 88% of the alerts were overridden. The reasons for the overrides included: (1) pharmacist already knew of the problem (34.2%); (2) pharmacist did not think the problem existed (33.6%); or (3) the problem was judged as not clinically significant (27.3%). The challenge in developing optimal, or at least more useful, OPDUR systems is to refine them in such a manner that an alert message is highly predictive of an event.

The workplace environment of pharmacists must also change. Today, dispensing pharmacists work in surroundings where the emphasis is on prescription productivity. Pharmacists have little or no incentive to engage in DUR activities. Moreover, constraints and expectations placed on today’s pharmacists preclude thoughtful decisions regarding questionable software-generated OPDUR alerts. When pharmacists do intervene, these activities are often not recorded or tracked in a comprehensive manner. The use of National Council on Prescription Drug Programs (NCPDP) version 3.2 transaction code sets for coding pharmacist interventions and outcomes could help remedy the deficiency in documentation.

**Practical Limits**

Lastly, OPDUR systems have practical limits. The clinical relevance of OPDUR alerts could be improved greatly if viewed from within the context provided by an electronic patient profile based on comprehensive claims data. However, either many OPDUR systems lack this capability or the necessary patient and prescriber data are missing or inconsistent. Online DUR alert systems, in contrast to in-pharmacy systems, offer a better capability for capturing a complete drug profile for patients. However, the ability to integrate these data sources is limited by demands for data processing efficiency and practical time limits in an online transaction-processing environment.

Lack of sophisticated data processing also limits the clinical relevance of OPDUR alerts. A sophisticated OPDUR system should have the capability to modify its “hits” based on previous pharmacy claims, medical history, laboratory procedures, etc. For example, if a prescriber has already acknowledged his awareness of a particular problem but considers it clinically insignificant, this response can be integrated into the OPDUR system and future alerts suppressed. Further, an ideal system would provide a link to useful information about how to manage a DDI once detected. For
example, a potential drug interaction with warfarin does not carry the same danger if warfarin is the precipitant drug and the prescriber is monitoring INRs. The goal of the sophisticated OPDUR system is to use the most precise selection criteria without sacrificing sensitivity.

Unfortunately, most present-day OPDUR systems are not state of the art and do not live up to the potential of electronic DUR. A quality chasm exists between the operation of OPDUR systems today and the need to protect patients from avoidable clinically significant drug interactions. It is time to expand DUR from individual criteria violations to a systematic review of broadly-based therapy problems. Experts in this area have called for a refocusing of the DUR process. Organizations such as the USP and the Academy of Managed Care Pharmacy (AMCP) are working to improve DUR systems. The focus of research should be on imaginative programs to increase the predictive value and selectivity of OPDUR, integration of OPDUR and retrospective DUR, data sharing with the prescriber prospectively, and improving the quality of criteria. Managed care pharmacy programs have the tools to conduct expert DUR. The time has come to expect a higher level of sophistication from our DUR systems so we can assure that patients receive the optimal benefit from their drug therapy.

Final Thoughts

A growing concern exists in the health care community that the medication use system is flawed. Systems that support effective and appropriate medication use do not exist at the population level; instead, pharmacotherapy is often a fragmented collection of independent actions. The net result is that patients are unnecessarily exposed to known hazards through interacting medications and other drug related problems.

Critics rightly point out the failings of current OPDUR systems or of their use by pharmacists, or both. OPDUR systems can be powerful tools to assure patient drug-related safety. The pharmacist using a comprehensive, sophisticated OPDUR system is the last line of defense for avoiding preventable drug-related morbidity. But these systems are not living up to their potential. We fervently encourage professional organizations and researchers to work collaboratively to develop the clinical and epidemiological basis for new and more sophisticated standards for OPDUR alerts.

Even the most sophisticated OPDUR system is useless if pharmacists do not respond to alerts. Better pharmacist response to alerts requires a combination of more education about improved alert systems, changed performance expectations, and removal of disincentives to respond to alert messages.

Finally, we must recognize that OPDUR systems have limits and cannot be relied upon exclusively to assure patient safety. OPDUR systems often stand alone without a strategic component designed to identify suboptimal prescribing problems or retrospective patterns. Qualitative standards of performance, such as that developed by the Institute for Safe Medication Practices, should be adopted. A strategic system that incorporates quality assurance elements is the responsibility of, and a challenge for, drug distribution system managers.

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India’s Pharmaceutical Industry: A Growing Influential Force in the World Pharmaceutical Market

BY HEMA VISWANATHAN, M.S., AND J. WARREN SALMON, PH.D.

India has been newsworthy as a result of its indigenous pharmaceutical industry selling low-cost AIDS cocktails to South Africa in direct competition with drugs manufactured by multinationals. These triple combination antiretroviral entities were thought to be protected by product patents through multilateral trade negotiations (TRIPS).

Impoverished markets offer little incentive to highly profitable multinationals to provide drugs there. The resultant controversy over intellectual property rights—patents, copyrights, trademarks, and trade secrets—and a suitable strategy to prioritize relief for the mounting suffering in Third World nations from AIDS, malaria, tuberculosis, and a dozen other causes of vast morbidity and mortality, has led AIDS activists to claim that “Patents Kill.”

The Economist has written that patents have been the preserve of western multinational companies, “allowing them to establish monopolies, drive out local competition, divert research and development away from the needs of poor countries and force up the price of everything from seeds to software. In the process, patents prevent poor people from getting life-saving drugs, interfere with age-old farming practices, and allow foreign ‘pirates’ to raid local resources, such as medicinal plants, without getting permission or paying compensation.”

At least four Indian pharmaceutical firms stand ready to sell generic AIDS drugs to governments in the least-developed nations at steep reductions (around $350 per year of therapy). Such an action (and what it has helped to prompt in multinational pharmaceutical companies’ price reductions, drug donations, and the dropping of concerted legal action in South Africa), along with the AIDS epidemic worldwide, is forcing a profound alteration in the global pharmaceutical marketplace.

Indian firms are expected to play a more pronounced role in the U.S. market as well as the developing world. It is therefore crucial that we in the United States have more information and insight into India’s pharmaceutical industry.

India’s Economy

During the time span from independence in 1947 until the early 1990s, India was a closed market, insulated from the global marketplace and characterized by Fabian socialism, central planning, and slow economic growth. In 1991, reforms initiated by the Congress Party government led to a sea change in economic activity, with foreign direct investment and exports rising phenomenally. The following decade saw a growth rate of 7% to 8% a year. In spite of a recent slowdown, India still ranks among the fastest-growing economies in Asia, second only to China, which recorded a growth of 8.1% for fiscal 2001.

There are broader forces pulling India into the global economy. Indian democracy has not historically yielded a direct forward force toward economic liberalization that would let this country run alongside the other Asian tigers. When in power, the Congress Party lowered trade barriers that had discouraged India from buying almost anything from or selling to the rest of the world. According to The Economist, “Economic growth, after a brief wobble, picked up, making India one of the world’s fastest-growing economies of the 1990s. Foreign direct investment rose from next to nothing to well over $2 billion a year. India’s share of world export of goods, which had fallen from 2% at independence to 0.4% in 1980, climbed to 0.7% in 2000.” Consumer price inflation fell and a new dynamic export industry was born, with many poor Indians being drawn from the margins of the society into jobs. Indian manufacturers of consumer goods have discovered internal rural markets and flooded them with goods—including pharmaceuticals.

Yet there remains considerable doubt about India’s competitiveness in the global economy. There are also grounds for questioning the integrity of its institutions, the quality of its infrastructure, and the present zeal for further reforms. Pressures are upon the now BJP (Bharatiya Janata Party) national government to adopt policies that rekindle the excitement in the economy of the early 1990s.
The uneven development of India is also problematic. Higher-growth Indian states tend to have higher private investment, and there are clear links between economic growth and certain kinds of infrastructure, especially electricity and telecommunications. Shortcomings in infrastructure are of two types: the traditional sort of roads, power grids, telecommunications, and so on; and what might be called the human kind, such as courts, bureaucracy, and politics. Failures in each have similar consequences, for they both raise costs, slow transactions, and deter investment. They also feed on each other, and outside observers very often maintain that the current infrastructure leaves much to be desired.9

Health care expenditures as a percentage of GDP are very low at 5.6%.6 The annual per capita drug expenditure is $3, even lower than Pakistan and Bangladesh at $7 each.7 Only 3% of the population has medical insurance, so consumers bear the brunt of a large percentage of health care expenses. Other glaring facts are that India has 16% of the world’s population, 18% of the world’s mortality, and 1% of the world’s health care investment.

India’s “new economy” has more bearing on the nation than first impressions might suggest. It extends far beyond the software industry, which has been its most visible sector internationally. Services are making a noticeable contribution to GDP, and new economy firms present an example to enterprises throughout India. The Economist claims that, “Whether you are peddling software or other services, India offers the same deal: work done to global standards, and often at a faster pace, at Indian cost.”10 Opportunities in the Indian stock market are attracting foreign capital. The past crisis brought down valuations, but investors as recently as summer 2001 sopped up low-tech companies that make their money in India and are protected from a global economic recession.9,10 The Indian pharmaceutical sector should additionally lure more attention.

## The Pharmaceutical Industry

In the early years after independence, the sole players in the industry were multinationals such as Glaxo, Pfizer, and Parke-Davis. The companies both imported and manufactured formulations. The industry saw the emergence of domestic companies after the passage of the Indian Patents Act in 1970, which offered protection against patent violation charges. Thus was born in India the phenomenon of “reverse engineering,” whereby altering some stage in the process of manufacturing a molecule made it possible to secure an Indian process patent. As a result, domestic firms copied Western products overnight. Inherent domestic advantages included the availability of skilled scientific personnel; the low cost of raw material, production, and labor; and government policy (such as exemption from excise duties) that supported indigenous production in the private small-scale industry (SSI) sector. The speed at which new product technologies were adopted and the ability of Indian companies to develop cost-effective processes and effective distribution systems has been phenomenal.11

The Indian pharmaceutical market is presently valued at U.S. $5.4 billion, of which domestic sales account for U.S. $3.8 billion and exports for U.S. $1.6 billion.12 Today, the market accounts for 8% volume of production worldwide, representing 1.8% of the global pharmaceutical industry. Over the last decade, the Indian pharmaceutical industry has recorded a compounded average growth rate (CAGR) of 15%, compared to a world industry rate of 8%.12

The industry can be divided into the organized sector and the SSI sector. The Indian pharmaceutical industry is highly fragmented, with 15,000-plus licensed manufacturing units. About 300 are in the organized sector, of which multinationals account for about 40%. Together, the top ten industry players account for only 30% of market share; the top company, Glaxo-Wellcome, has only 5.7%. The market share of multinationals has decreased from 75% in 1971 to approximately 35% at present, while that of Indian companies has increased to 65%.13 While in 2001 the top five multinationals grew at a rate of 7.2%, the top five domestic companies grew at 14%.13

A report by McKinsey predicts that the industry will further grow at a CAGR of 19% to reach $25 billion in revenue by 2010.13 It is expected that $18 billion to $19 billion will come from existing operations and the rest from new drug discovery and research services. The market capitalization of Indian pharmaceutical companies is projected to grow dramatically to $150 billion from the present $15 billion to $20 billion.13

The Organization of Pharmaceutical Producers of India (OPPI) and the Indian Drug Manufacturers Association (IDMA) are the two major associations in the industry. The OPPI has both multinational and Indian members, but is considered to reflect chiefly the multinational viewpoint. The 450 members of the IDMA—the “technocrat entrepreneurs”—on the other hand, are all Indian, so it is considered the voice of the Indian sector.

The new Indian Pharmaceutical Alliance (IPA) consists of 11 leading domestic companies, including Dr. Reddy’s Laboratories, Ranbaxy, and Cipla. They contribute about 30% of the country’s pharmaceutical exports and share over 30% of the domestic market. Their annual R&D accounts for 92% of total pharmaceutical R&D expenditure in the private sector. The alliance was formed primarily to lobby the government on policy issues, such as price regulation, evolution of a patent regime that will honor TRIPS, and upgrading the regulatory framework to prepare Indian companies for international competition.

## Products and Performance

The two main categories of Indian products are bulk drugs and formulations. India produces about 70% of its bulk drug requirement and 90% of its requirement for formulations. About 60% of total bulk drugs are exported, making them a major foreign exchange earner for the country. India is now the fourth largest bulk drug producer globally, after the United States, Western Europe, and Japan.11
Multinationals have had a strong presence in the manufacturing of formulations but some Indian companies, Reddy’s, Ranbaxy, Cipla, and Wockhardt among others, are growing steadily (see Table 1). These companies have already consolidated their domestic position and are preparing themselves to achieve the same internationally, especially in the generics market.

Price control has been a major deterrent to growth in the Indian pharmaceutical market. The Drug Price Control Order (DPCO) has been amended three times, with the latest version in 1995 reducing the number of products under price control to 76. This number is expected to decrease drastically with the passage of the New Drug Policy in 2002. Companies often withdrew certain products that fell under price control, introducing others that did not. The resultant shortages hurt consumers and triggered an increase in spurious drugs.

APPENDIX

International Market Leaders

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<tr>
<td>Glaxo-Wellcome</td>
<td>Corex (chlorpheniramine maleate) – Pfizer</td>
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<tr>
<td>Cipla</td>
<td>Taxim (celotaxime) – Alkem</td>
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<tr>
<td>Aventis Pharma</td>
<td>Becosules (vitamin B-complex) – Pfizer</td>
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<tr>
<td>Lupin Labs</td>
<td>Voveran (diclofenac sodium) – Novartis</td>
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<tr>
<td>Ranbaxy</td>
<td>Neurobion (vitamin B) – E-Merck</td>
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<tr>
<td>Pfizer</td>
<td>Betnesol (beclomethasone ) – Glaxo</td>
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<tr>
<td>Zydis Cadila</td>
<td>Rabipur (PCEC rabies vaccine) – Aventis Pharma</td>
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<tr>
<td>Sun Pharma</td>
<td>Wokadine (povidone iodine) – Wockhardt-Merind</td>
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<tr>
<td>Alkem</td>
<td>Sporidex (cephalexin) – Ranbaxy</td>
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<tr>
<td>Knoll Pharma</td>
<td>Cifran (ciprofloxacin) – Ranbaxy</td>
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Cipla, the market leader in AIDS drugs in India, intends to supply the drugs to the Cambodian, Nigerian, and South African governments and plans to gain more approvals from other African governments. Brazil has also shown keen interest in buying generics from India. According to the Wall Street Journal, “reducing prices for governments made good business sense. Other generic drug companies in India say they avoid Indian excise tax, wholesale and retail markups, and fancy packaging by selling to foreign governments. That allows the drug makers to reduce prices 40% and keep the same profit. Selling to governments also means fewer problems with defaults and possibly even with patents.”

Two other Indian firms, Hetero Drugs, Ltd., and Aurobindo Pharma, Ltd., are also pushing to export AIDS drugs through governments and international organizations.

In April 2001, 39 multinational pharmaceutical firms dropped their court challenge to prevent the South African government from importing, manufacturing, or licensing cheap copies of their patented medicines. This legal landmark may turn out to be a breakthrough in getting treatment to the 40 million AIDS sufferers worldwide. Appearing atavistic at first—up against AIDS activists and two Nobel Prize winners, Nelson Mandela and Medicine without Borders—these leading firms finally succumbed to widespread public pressure. Continuing the suit in Pretoria would have subjected the firms to an inspection of their books and records to prove their profits, and research would have been affected by the competition from Indian manufacturers.

AIDS activists and African trade ministers have taken their patent challenge against the multinational drug companies to the World Trade Organization (WTO), where developing nations represent 80% of the membership. After WTO negotiations in Seattle collapsed, it appears that prescription medicines were “the big sticking point,” according to the Wall Street Journal. U.S. Trade Representative Robert Zoellick may concede the intellectual property rights issue to win African support on other issues, since a large number of trade allies want to import cheaper drugs to fight rampant AIDS epidemics. In Africa 22 million people have AIDS; 14 million have already died from the disease.

There remain legitimate concerns about whether human drug trials in India are adequate, and whether drug-manufacturing factories in India and other less developed countries pass full international quality checks. If the United Nations goals for battling AIDS are to be met, health ministries and faculties of medicine and pharmacy in Asia, Africa, and Latin America must begin to play a greater role in ensuring that spurious pharmaceuticals are not allowed to create unlimited resistance to AIDS and other disease. Here policies to restrict importation to a few select Indian firms may be preferable so that they can be monitored by local and international organizations.

The Changing Scenario and Future: Post-GATT

Dramatic changes are inevitable as India moves toward 2005, when the country may be committed to honoring product patents...
India’s Pharmaceutical Industry: A Growing Influential Force in the World Pharmaceutical Market

by virtue of becoming a member of WTO and a signatory to the General Agreement on Tariffs and Trade (GATT). Indian companies have recognized that innovation and research are vital for success and survival. Current Indian R&D investment is 1.9% of industry turnover, far below that of multinationals.2 It is impossible at present for any Indian company to command sufficient resources to take a product from discovery all the way to market. The government has expressed support by granting a 10-year tax holiday on profits for companies investing in R&D.

Top companies are slowly gearing up, with R&D investment rapidly increasing. A recent success story is Dr. Reddy’s licensing of two of its antidiabetic molecules to Novo Nordisk, a Dutch company, and the sublicensing of one to Novartis for distribution in the United States, Canada, and Mexico. The proceeds are expected to be pumped back into R&D. This strategy appears to be the foundation for a slow progression from novel drug delivery systems and analog research, including combinatorial and chiral chemistry, up the value chain to basic research.

The post-GATT scenario will witness a reduction in the number of companies, with many smaller companies shutting down. Multinational interest in India is bound to be rekindled, especially with the government now allowing 100% foreign direct investment (FDI) and making a commitment to honor intellectual property rights. Several Indian firms are preparing to turn into contract research organizations (CROs) and contract manufacturing organizations (CMOs). Skilled professionals can be hired in India for one-fifth to one-tenth the cost in the West, making outsourcing a profitable option for multinationals. Thirty manufacturing facilities have already been approved by organizations such as the U.S. Food and Drug Administration, the Medicines Control Agency in the United Kingdom, and the Australian Therapeutic Goods Administration.

Another strategy in the post-GATT era is the building of strategic alliances with global giants for marketing and distribution as well as licensing. The established marketing networks and distribution systems of Indian companies have potential to be a valuable resource for multinationals. The industry in India will also make opportunities to offer technical service, such as analytical and toxicology services. An additional area with potential is the development of international clinical trial centers based on good clinical practice (GCP).

**Summary and Conclusions**

The market for pharmaceuticals in India has immense potential. Decreased price controls and changing patent regulations will soon make conditions in India much more favorable to multinational corporations. Alliances with Indian manufacturers for marketing networks and contract research are ripe for exploration. Indian drug companies are gearing up their R&D investment. Their thrust will be on exports, especially in the generics market, and licensing of new discoveries to larger multinationals in an effort to fuel expansion and further growth.

Although scientific skill and entrepreneurship are already proven ingredients in the success of the Indian pharmaceutical industry, catalysts such as upgrading infrastructure, government support, a more efficient judiciary, a bankruptcy law, and labor reforms will speed future broadened success. It will be interesting to witness the strength of possible strategic alliances and the competition for the top echelons as the Indian pharmaceutical industry braces itself for the future.

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3. The right to good ideas. Special report: patents and the poor. Economist,
India’s Pharmaceutical Industry: A Growing Influential Force in the World Pharmaceutical Market

Ophthalmic Agents and Managed Care

BY JOHN R. YUEN, PHARM.D., BCNP, RICHARD G. FISCHELLA, R.PH., M.P.H., AND BRUCE I. GAYNES, O.D., PHARM.D.

According to the national report Vision Problems in the U.S., 3.4 million adults are afflicted with vision impairment and blindness in the United States. The number of ophthalmic patients will double in the next 30 years. The report, published by the National Eye Institute in partnership with Prevent Blindness America, further estimates a cost burden to the nation that exceeds $4 billion annually in benefits and lost taxable income. Ocular medications and their managed use are a sizable portion of this total cost.

Ophthalmic agents are among the most commonly self-prescribed medications in today’s pharmaceutical marketplace. Ocular discomfort associated with dry eye may be the most common condition for which nonprescription ophthalmic products are used. Ocular discomfort may affect as many as 4.3 million people in the United States and 20% of all elderly people. In their prescribed forms, ophthalmic medications bring a number of challenges to the managed care organization. For example, this category of medications includes specially compounded products that are storage-sensitive and have certain sterility requirements. In the past decade, an explosion of new glaucoma medications and ocular allergy agents has entered the market. As a result, ocular pharmacology, traditionally one of the least-represented specialty groups in pharmacy, has attracted some attention but still remains one of the least-managed areas of pharmaceutical care by pharmacists.

As a profession, pharmacy will be expected to address these factors and to provide a redefined and proven relevance as a base source of ophthalmic drug experts. The intent of this article is to provide a baseline understanding of the ocular pharmacology specialty, as well as address the intricacies specific to the health professionals who provide ophthalmic pharmaceutical care.

Managed Care

Clinical ocular pharmacology is sometimes poorly addressed in managed care pharmacy services. This is not surprising, since ocular care is a small portion of managed care costs. Nonpharmacist health care professionals in the fields of ophthalmology and optometry have dominated the provisions for pharmaceutical care of the ophthalmic patient.

There is still a shortage of clinically relevant pharmacists specialized in ocular pharmacology. Because specialty areas such as dermatology or ophthalmology often comprise such a small portion of drug formularies, the amount of time that can be spent on reviewing “smaller ticket” items is limited. Often, many ophthalmic policies and procedures rely on ophthalmologists, and sometimes...
optometrists as drug therapy consultants. Although most ophthalmologists have excellent clinical skills, their knowledge of managed care plans, P&T committee formulary reviews, and pharmacoeconomics is often limited.

The challenge set forth to the profession of pharmacy is to create a new generation of ocular pharmacist specialists who can bridge the gap between the expectations of emerging eye care treatments and the expectations of managed care pharmacy in a highly competitive cost-contained market. Pharmacists well versed and involved in the treatment plans of the ophthalmic patient will determine the relevance of the pharmacy profession in treating and managing eye disorders, infections, and cosmetics.

Drug Distribution and Dispensing

Despite the handful of commercially prepared ophthalmic agents that fall within new medication categories, there has been little change over the years in the standard way drugs are delivered to the eye. The medication furnished is either commercially available in its final form or must be compounded through the services of a pharmacist.

The most serious eye conditions still require extemporaneously prepared formulations by a pharmacist. These compounded products have short stability periods and stringent storage requirements. A number of compounding formulas abound in the practice community—much of an institution’s practice standard is determined by the experiences and results taken from the medication prescribers. There is one published text written exclusively on ocular drug compounding.

When one considers some of the few recent advances in ocular pharmacology, technology in drug delivery is showcased. One such advance is seen with the use of carbopol gels. Drugs incorporated into gels have produced ocular products that are easily suspended, well tolerated, and less visually disrupting than previously used suspending agents, namely those using petrolatum or lanolin as a ointment base. Products containing carbopol gels include Pilopine, Vexol, Betoptic S, and Azopt. Newer solvents, such as cyclodextrins, have improved the aqueous solubility, the stability, and the bioavailability of ophthalmic medications while also reducing ocular irritation. Fixed forms of drug delivery such as intraocular implants provide sustained intraocular drug levels of dexamethasone (Surodex) and ganciclovir (Vitrascert). Other intraocular implants are currently under investigation. Other advancements include gel-forming solutions, such as Timoptic-XE, that have the capability of forming gels in the tear film and provide for reduced dosing requirements due to a prolonged contact time to the drug-absorbing cornea. Further use of instrumentation in treating and managing eye disorders, infections, and cosmetics.

Clinical Program Development

The disposition of ophthalmic agents is challenging as well. There are variations in absorption to the intended treatment site due to factors such as tissue integrity, lipophilicity, and chemical characteristics, to name a few examples.

Invariably, most ophthalmic patients present with one or more medical conditions. This brings forth several target populations that require special consideration in managed care, especially hypertensive, diabetic, and AIDS patients. In a popular textbook addressing ocular pharmacology, considerations of special patient populations are addressed.

In order to develop a managed care service in ocular pharmacology, there needs to be a source of expertise within the health care organization. For pharmacy, this requires a pharmacist who is willing and capable of taking on the additional steps necessary to acquire a specialist’s acumen of the subject. Most organizations that have an active pharmaceutical care program in ocular pharmacology still fail to provide hands-on clinical work with the patient.

Clinical program development must begin with access to knowledge. A managed care program in ophthalmic pharmacology should be centered on personnel that are budgeted, trained, and scheduled to provide services in this specialty area. The following information is a starting point to access information in the area of ophthalmology.

In addition to select schools of medicine, optometry, and pharmacy, there are excellent professional organization Web sites pro-
TABLE 1  Eye Organization Web sites

- American Academy of Ophthalmology (www.AAO.org)
- American Optometric Association (www.AAOAPT.org)
- Association for Research and Vision in Ophthalmology (www.ARVO.org)
- National Eye Institute (www.nei.nih.gov)
- Prevent Blindness America® (www.preventblindness.org)

TABLE 2  Essential Texts


TABLE 3  Supplementary Texts


Communications with Patients, Prescribers, and Pharmacists

With the numbers of experts in ocular pharmacology being scarce, program development in ocular pharmacy managed care becomes one of shared communications and unity of effort.

The patient has most access to a pharmacist at the exchange of medications during the drug counseling session. Within the university setting, ocular pharmacology specialists also provide valuable input to the treatment plan through participation in clinics, rounds, and advanced education and training.

If one were to compare the use of extemporaneous compounding formulations used among medical providers, a wide degree of variation would be found. As mentioned earlier, the authors are aware of only one textbook that is written entirely to reference common extemporaneously compounded eye regimens. The more common source material for compounded ophthalmic preparations is transferred by the experience and influence of the attending ophthalmologists and indexed historical files of copied protocols and recipes shared among hospitals in a given region.

Establishing liaison with local experts in this area is challenging also. It is estimated by the authors that there are fewer than a dozen practicing clinical ocular pharmacologists in the United States. For the profession of pharmacy, post-doctorate fellowships in ocular pharmacology are a rarity. The majority of specialists distinguished as ocular pharmacologists have a combined M.D./Ph.D. degree and are dispersed within academia. There are also small numbers of specialists found within the professions of pharmacy and optometry, but they, too, are almost exclusively in the university settings or sectors of the pharmaceutical industry. A high degree of success is found in a collaborative effort among the professions of

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<table>
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<th>Source Text</th>
<th>Publisher</th>
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<tr>
<td>Textbook of Ocular Pharmacology</td>
<td>Hagerstown, MD: Lippincott-Raven Publishers</td>
</tr>
<tr>
<td>Ophthalmic Drug Facts</td>
<td>St. Louis, MO: Facts and Comparisons</td>
</tr>
<tr>
<td>Extemporaneous Ophthalmic Preparations</td>
<td>Vancouver, WA: Applied Therapeutics, Inc.</td>
</tr>
<tr>
<td>Ophthalmic Drug Facts</td>
<td>1998</td>
</tr>
<tr>
<td>Ocular Pharmacology and Therapeutics: A Primary and Shared Care Guide</td>
<td>Boston, MA: Butterworth-Heinemann Publishers</td>
</tr>
<tr>
<td>Handbook of Nonprescription Drugs</td>
<td>13th Ed., Chapter 22</td>
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The medical literature has provided a steady but limited supply of ocular pharmacology texts. The field of ophthalmology recognizes the text by Zimmerman, Koonere, Fechtner, and Sharir as the primary reference on ocular pharmacology. In similar fashion, the profession of optometry holds the Bartlett/Jaanus text as its source text. Pharmacy contributions to ocular pharmacology are primarily recognized through work published by the American Pharmaceutical Association. A pharmacy department’s library should provide access to these ocular pharmacology references and others (see Tables 2 and 3).

Quick insight into ocular pharmacology can also be gained through a literature review on the treatment of the ophthalmic patient. Files of pertinent articles can provide timely and sufficient information to a managed care pharmacy program. Of broad ophthalmic interest, the authors provide a short list of review articles and chapters that they have written within the context of their practice experiences (see Table 4, next page).

Medical journals continue to provide the most recent findings shared among ophthalmic medical professionals. A list of the most popular references is in Table 5 (next page).
Ophthalmic Agents and Managed Care

**TABLE 4 Select Review Articles and Chapters by the Authors**


**TABLE 5 Popular Ophthalmic Journals**

- American Journal of Ophthalmology
- Archives of Ophthalmology
- British Journal of Ophthalmology
- Canadian Journal of Ophthalmology
- Clinical and Experimental Ophthalmology
- Clinical Eye and Vision Care
- Cornea
- Current Eye Research
- Current Opinion in Ophthalmology
- Der Ophthalmologe
- Digital Journal of Ophthalmology
- Documenta Ophthalmologica
- Experimental Eye Research
- EyeWorld
- International Contact Lens Clinic
- International Ophthalmology
- International Ophthalmology Clinics
- InterNet Journal of Ophthalmology
- Investigative Ophthalmology and Visual Science
- Journal of the American Optometric Association
- Journal Français d’Ophthalmologie
- Journal of AAPOS
- Journal of Biomedical Optics
- Journal of Cataract and Refractive Surgery
- Journal of Community Eye Health
- Journal of Glaucoma
- Journal of Neuro-Ophthalmology
- Journal of Ocular Pharmacology and Therapeutics
- Journal of Ophthalmic Nursing and Technology
- Journal of Refractive Surgery
- Ocular Immunology and Inflammation
- Ocular Surgery News
- Operative Techniques in Cataract & Refractive Surgery
- Operative Techniques in Oculoplastic, Orbital and Reconstructive Surgery
- Ophthalmologie
- Ophthalmic and Physiological Optics
- Ophthalmic Case Consultations Online
- Ophthalmic Plastic and Reconstructive Surgery
- Ophthalmic Research
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- Ophthalmology Times
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- Primary Care Optometry News
- Progress in Retinal and Eye Research
- Radiation Oncology Investigations
- Retina
- Review of Ophthalmology
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- Seminars In Ophthalmology
- Spektrum der Augenheilkunde
- Survey of Ophthalmology
- The CLAO Journal
- The Wilmer Retina Update
- Vision Research
- Visual Neuroscience
- Vitreous Society Online Journal

ophthalmology, optometry, nursing, research, and pharmacy.

Strides are being made in bringing the profession of pharmacy into the spotlight for ocular pharmacy. Starting in May 2002, the American Pharmaceutical Association is sponsoring training for pharmacists and university educators on ocular pharmacy and self-treatment of ocular conditions. The training is being conducted by some of the authors of this article.

**Clinical and Formulary Considerations**

Many drug regimens use combinations that have questionable efficacy. At times, these “proven” regimens actually have counteractive effects. One such combination therapy is seen in the drug management of glaucoma using adrenergic agents, such as epinephrine, in combination with beta-blocker agents, such as timolol. Though this combination was fairly common at one time, the advent of new glaucoma therapies demonstrated improved efficacy, such as the topical ophthalmic carbonic anhydrase inhibitors first introduced to the market in 1995.

There are a number of commercially prepared combination glaucoma products that are being taken off production due to their limited utility. An example is the category of pilocarpine/epinephrine combination ophthalmic products (i.e., E-Pilo, P1E1, P2E1, etc.). In the past, these combination products were available from Novartis Pharmaceuticals and Alcon Labs. During the year 2001,
Historically, optometry was termed the “drugless” profession. Delivery of vision care by optometrists was originally based on "non-dilated" examinations, without the use of cycloplegic (fixing) and mydriatic (dilating) ophthalmic solutions. The rationale for this approach was that a better subjective refraction could be obtained using retinoscopy without cycloplegic medications. On the other hand, ophthalmologists performed routine ocular exams using medications and indirect ophthalmoscopy. As technology advanced, it became apparent that standard practice of care required the use of dilating agents in the completion of an ophthalmic examination. This led to a broad nationwide push to change optometry practice acts to include the use of mydriatics and cycloplegics as part of the optometric scope of practice. With these legislative changes, optometrists entered into the medical model of eye care, which included advanced examination procedures such as indirect ophthalmoscopy and biomicroscopy.

Optometry took the next evolutionary step in ocular pharmaceutical care as changes in health care insurance shifted individuals into third-party health care plans. It became apparent that if optometry was to maintain its claim of being "cost-effective" providers of basic "primary" eye care, it would require more than just mydriatics and cycloplegics. The inclusion of all legend drugs became the next goal. With this change in ideology, changes in optometry school curricula were made. The new curricula incorporated courses in general and ocular pharmacology, physical diagnosis, and ocular emergencies. In conjunction with the academic shift, an ongoing legislative effort was initiated to establish broad privileges for optometrists in the use of legend drugs in all 50 states. It took 20 years, but now all states allow the use of topical legend agents for the treatment of ocular allergy, infection, and inflammation, although some states prohibit the use of topical corticosteroids. All but four states allow for the treatment of glaucoma, at least with topical antiglaucoma agents. Twenty-one states allow for the use of controlled analgesic substances as well as the use of injectables if an anaphylactic reaction should arise. In addition, 10 states allow optometrists to use injectables for therapeutic purposes, such as steroid injections for chalazia. The change in the scope of practice of optometry has met continued resistance from organized medicine. Optometrists have encountered difficulties in gaining access to hospital staffs, particularly in large urban areas. In addition, physicians often have significant influence on advising medical plans on the number and type of practitioners that should be included in a particular health plan. Despite the recent marked elevation in the standards of optometric education and mandatory proficiency examinations required for licensure, third-party insurers and major medical plans are still presenting optometrists with resistance in terms of blanket acceptance. Many insurance plans require medical-based requirements that are necessary to gain access to "panel" programs. This includes "board certification" and completion of a residency. While residency programs are available for optometrists to pursue, they are not required for licensure. Moreover, there is no formal "board certification" process available to an optometric clinician. Until insurance companies establish policies to allow access by optometrists in a category that is tailored to the educational standards of the optometry profession, it will be difficult for optometrists to gain access to many traditional physician-dominated health plans. Furthermore, the abundance of ophthalmologic providers, particularly in urban areas, has dampened efforts by optometrists to gain access to already overcrowded health care plans.

Optometrists have addressed this resistance to entry to traditional health care plans by forming their own eye health networks. The Vision Service Plan (VSP), for example, is primarily an optometric-based eye care plan that provides enrollees with eye examinations, contact lenses, and spectacles at reduced costs when they obtain services from participating providers. Companies such as Cole and Davis Vision run similar plans in both commercial retail optical stores and private optometric practices, respectively. Although these plans will pay for a "yearly examination," they often do not provide for medical care, such as the treatment of glaucoma or other eye disorders.

Despite the difficulty optometrists encounter in gaining access and recognition from various insurance providers and hospitals, the accessibility and wide geographic distribution of optometrists allow them to be key triage points into the health care system. Optometrists are now able to diagnose and manage various disorders of the eye independently, thereby alleviating the need for additional patient costs as a result of an ophthalmologic referral. As optometrists garner continued expansion of their scope of practice, insurance providers may view optometric providers as cost-efficient alternatives to ophthalmologic care in select clinical scenarios.

Both companies made the decision to discontinue their entire product line due to a lack of market demand. As noted already, the use of these drugs both individually and in combination has markedly dropped off due to superior agents introduced within the past 10 years.

Combination antibiotic/anti-inflammatory products have also been a source of therapeutic scrutiny. Indiscriminate use of ocular corticosteroid preparations may predispose patients to ocular side effects, including secondary infections, ocular hypertension, glaucoma, and even cataract formation. As an example, prolonged use of a combination product containing a corticosteroid and antibiotic without proper monitoring increases the potential for a secondary fungal or herpetic infection. Corticosteroids are contraindicated in herpetic simplex epithelial keratitis and fungal keratitis since these infections can proliferate in the presence of the drug. In the case of herpes simplex stromal keratitis, specific corticosteroid therapy may be used under close monitoring in order to lessen the permanent scarring of delicate tissues of the cornea.

The American Academy of Ophthalmology states that corticosteroids have no role in the treatment of infectious conjunctivitis.
and that combination eye products containing antibiotics and corticosteroids are seldom, if ever, indicated for the treatment of any ocular inflammation.13 Furthermore, it is generally recommended that primary care clinicians not prescribe or use ophthalmic corticosteroids or their combination products in any ocular condition unless the case is referred to and followed by an ophthalmologist and/or an optometrist. The dangers of indiscriminate corticosteroid use were presented in a case study that documented bilateral cataract formation in a 24-year-old patient who applied 0.12% prednisolone acetate eye drops twice a day for a four-year period.20 Yet there may be exceptions to the practice of not using combination ophthalmics. Patients with low cognitive mental functions who receive short-term treatment following cataract extraction or glaucoma filtering procedures appear to be good candidates for a simplified medication regimen using combination drops.12

It is a known fact that every medication introduced into the eye will have some degree of systemic absorption and possibly systemic side effects.14 Topically applied ocular drugs are primarily absorbed from the conjunctival sac into the systemic circulation through the conjunctival capillaries, from the nasal mucosa after passage through the lacrimal drainage system, or, after swallowing, from the pharynx or the gastrointestinal tract.15 Because topically applied drugs avoid the first-pass metabolic inactivation that normally occurs in the liver, these drugs can exert the same substantial pharmacologic effect as similar doses delivered parenterally. Each 50 microliter drop of a 1.0% solution contains 0.5 milligrams of the drug. This means that solutions applied topically to the eye may provide sufficient systemic absorption to exceed the minimum toxic systemic doses.12

A more recent cause for alarm came from a drug manufacturer who reported several adverse cardiac events associated with excessive systemic absorption of a combination topical ophthalmic product used in routine eye exams.11 In the safety report, three patients were affected by the combination product of 1% hydroxyamphetamine hydrobromide with 0.25% tropicamide (Paremyd, Allergan). One patient died from myocardial infarction, another patient had a nonfatal ventricular fibrillation, and the third case involved syncope and bradycardia. Since then, the product has been withdrawn from the market due to manufacturing problems but will be returning back to production shortly. Systemic absorption of eye drops can be substantially reduced through the targeting of drug administration to the conjunctival cul-de-sac, positioning of the patient’s head, and manual occlusion of the puncta. Detailed instructions on these techniques and the proper administration of ophthalmic medications is covered in textbook references already cited.13,14

Drug therapy is a mainstay in ophthalmic conditions that warrant surgical intervention. Most ophthalmic patients require the use of medicines preoperatively, perioperatively, and postoperatively in corrective and cosmetic ophthalmic surgeries. Even with the evolving use of lasers, seen in corrective visual acuity procedures such as LASIK, glaucoma filtering procedures such as trabeculectomy, and diabetic retinopathy procedures such as panretinal photocoagulation, ophthalmic medications are commonly prescribed to enhance and maintain healthy vision.

**Business Management**

The real issue to drug benefit is one of relevance. Are the services provided to the patient within the scope of one’s given profession and do they provide meaning to successful treatment and reimbursement within the scope of medicine?

In order to challenge the profession of pharmacy to invest in the managed care of ocular pharmacy, one must provide examples of successful insertion within an untapped field.

Of all the professions that treat the ophthalmic patient, optometry has undergone the most significant changes in the past 20 years.22 The story of the optometry profession’s journey into drug therapy is a noteworthy one (see box, previous page).

**Cost Management**

A significant amount of time and effort is devoted to therapeutic application and control of the drug formulary. Ophthalmic agents as a group are not in the top drug classes by expenditure, but ophthalmics can have a high cost per patient. The pharmacy and therapeutics (P&F) committee is responsible for controlling drug access to its respective members. The role of the managed care pharmacist regarding rationale, clinical, and pharmacoeconomic drug analysis is critical to a major part of the success of any pharmacy benefit management (PBM) or health maintenance organization (HMO). Obviously, certain areas of clinical pharmacy, such as infectious disease, cardiology, peptic ulcer disease, etc., have many pharmacist practitioners that are well versed with product selection based on clinical superiority and cost analysis. Medication Utilization Evaluations (MUE) and Cost Containment Reports (CCR) remain vital to the cost management of ophthalmic medications.

**Conclusion**

Many changes in ocular therapy within the last decade have begun to hit the “radar screen” of managed care plans. New, more effective, therapies with perceived higher costs and new prescribers have definitely changed the face of ophthalmic pharmacotherapy. Especially with the advent of more expensive glaucoma therapy, managed care plans have begun to implement cost containment strategies within their perspective plans. Ocular allergy medication has also raised the level of interest due to expensive ocular allergy medications and direct-to-consumer advertising. However, pharmacoeconomic studies are underway to demonstrate the cost-effectiveness of such therapies, especially in the treatment of potentially blinding conditions like the glaucomas.

The finest efforts in managed care ocular pharmacy are attributed to members in the practice fields of ophthalmology, optometry, research, and industry. Until now, pharmacy impact has been present but rarely acknowledged.

Pharmacy as a profession is summoned to prove its relevance...
in the area of ocular pharmacology as it applies to the managed care of our ophthalmic patients.

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Constructing Mail Survey Questionnaires to Maximize Rates of Return and Assure the Validity and Reliability of Responses

OBJECTIVES: Because the results generated from mail survey questionnaires can be a rich source of information for practitioners, administrators, marketers, and policy-makers, the researcher must have confidence in the validity and reliability of the estimates obtained. Following simple tenets of survey questionnaire construction can help prevent spurious results. After completing this continuing education program, participants will be able to:

• Identify methods of increasing the likelihood of a higher rate of return for mail surveys.
• Discuss the importance of a properly written cover letter.
• Describe the components of a properly written cover letter.
• Design survey questions to collect demographic, personal, and practice-related data.
• Identify some potential pitfalls when constructing attitude scales.
• Construct items comprising a summated ratings scale.

KEYWORDS: Survey, Questionnaires, Validity, Response Rate

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The Academy of Managed Care Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. Individuals may obtain up to 1 contact hour of credit or 0.10 Continuing Education Unit (CEU). The ACPE number is 233-000-02-003-H04. Certificates will be mailed within eight weeks to participants who successfully complete the CE exam and achieve a score of 70% or more and submit the exam to AMCP prior to June 30, 2003. Learning objectives and test questions follow on pages 230-231.

In general, the investigator seeks to maximize the number of responses obtained from the sampled population. A higher response rate affords the investigator greater confidence that the results obtained reflect those that would be obtained from the entire population; or, more correctly, it reduces the possibility that the responses obtained are biased. A sound sampling procedure and a high response rate minimize the likelihood that responses will come disproportionately from certain segments of the sampled population or from persons with predisposed attitudes or behaviors that might not reflect those of the population as a whole.

For example, if an investigator mailed out a survey to determine how satisfied plan members were with their health plans, a low response rate might raise concern that a disproportionately greater number of people extremely dissatisfied with their plan...
had responded. A low response rate to a survey asking phar- 
sists about their propensity to provide cognitive services would 
raise concern that pharmacists who already do this or have posi-
tive attitudes about such behaviors were more likely to have 
returned the survey, thus overestimating pharmacists’ propensity 
to provide such services. A low rate of return may also preclude 
the use of certain statistical procedures, particularly if the initial 
sample was itself small.

Although there is no way to guarantee high rates of return, 
investigators can do several things to minimize the likelihood of 
their being especially low. They must first familiarize themselves 
with the pool of potential respondents to the survey. Losing sight 
of who comprises the sample population could lead to mistakes 
that jeopardize a good response rate. Investigators should make 
certain that questions make sense to the respondents, employ con-
tventional language at an appropriate reading level, avoid using 
technical jargon that may be unfamiliar to respondents, avoid 
using abbreviations or acronyms, and avoid terminology or infer-
ences that respondents might find offensive.

The Cover Letter

Secondly, investigators should construct a cover letter to accom-
pany the survey instrument. The cover letter should be relatively 
brief yet explain the purpose of the research project in language 
that the respondent can understand. The purpose should be stat-
ed in a way that reflects the potential benefits that may accrue as a 
result of the research. For example, if an investigator were con-
ducting a project to determine health literacy, the cover letter 
might state that the knowledge gained from the project will be 
used to tailor educational materials that will improve members’ 
understanding of how to maximize the benefits they gain from 
their health insurance coverage.

The cover letter should also declare how the recipient was 
selected, the anonymity and confidentiality of responses, and what 
will be done with the data after the project is completed. The cover 
letter should also inform recipients that they are in no way bound 
to complete the survey, yet assure them that completion should not 
cause them any undue stress (should that indeed be the case). 
Finally, the cover letter should express the importance of attaining 
as many responses as possible, thank the recipient genuinely for 
responding, provide contact information for the principal investi-
gator, and notify the recipient of any reward associated with being 
selected to receive the survey often attempt on some level to 
understand the purpose of the questions comprising the survey. 
We may need that information some time in the future." Persons 
selected to receive the survey often attempt on some level to 
understand the purpose of the questions comprising the survey. 
Potential respondents might become disengaged or even offended 
if questions appear frivolous.

A survey can become lengthy even if only the necessary ques-
tions are asked. Even some information that was deemed nec-

Essential consideration is the survey’s length. A survey that 
is too long creates a burden on respondents to complete it. The 
researcher should have a clear picture of what data are needed in 
order to test the research hypotheses. It is often tempting to tack 
additional questions onto the survey because, “Well, we’re going 
through the trouble of conducting this survey. Why not ask them? 
We may need that information some time in the future.” Persons 
selected to receive the survey often attempt on some level to 
understand the purpose of the questions comprising the survey. 
Potential respondents might become disengaged or even offended 
if questions appear frivolous.

A survey can become lengthy even if only the necessary ques-
tions are asked. Even some information that was deemed neces-
sary may have to be forfeited if the survey becomes too long. 
Understanding the population will allow the investigator to 
adequately estimate how long filling in the survey can take; 
typically, respondents should not be asked to spend more than 
15 to 20 minutes to complete the questionnaire.

Constructing the Survey

Demographic, Personal, and Practice-Related Questions

There are typically several components to any survey. Aside from 
the item questions that focus on the attitude or behavior of inter-
est, there are questions soliciting personal information about the 
respondents, such as age, gender, racial/ethnic background, level 
of education, and level of household income. The investigator may 
also be interested in obtaining other types of information, depend-
Crafting these questions might be regarded as the “easy” or unscientific part of constructing the survey, but if it is done poorly, problems may develop, such as ambiguous responses and poor rates of return. The first issue confronting the investigator is whether to employ open-ended or closed-ended question formats to solicit the information. Open-ended questions are easier to write but the answers are much harder to interpret and code for analysis. Open-ended questions are useful when: (1) respondents’ own words are essential to answering the research question, (2) respondents are willing and able to provide these answers, (3) the research is exploratory and the range of possible answers is unknown, (4) one of the investigators or someone else involved with the project has the ability to interpret, code, and analyze the responses, and (5) there is a preference for reporting the data as grouped responses rather than using statistical procedures.

Investigators will usually use closed-end questions to solicit personal and demographic information. Two very important standards for writing these types of questions are the exhaustiveness and mutual exclusivity of the response choices. Exhaustiveness implies that the response choices adequately cover the possible range of answers. For example, an investigator surveying a population of pharmacists who is interested in their primary work setting would offer response choices that include “community-independent,” “community-chain,” “supermarket,” “hospital-distributive,” “hospital-clinical,” “long-term care,” “managed care,” and “pharmaceutical industry” at the very least. While it is appropriate and even advisable to include an “other” response category to cover the entire range of choices, if too many respondents feel they have to select “other,” the investigator loses valuable data.

Mutual exclusivity implies that the response choices are distinct; they do not overlap. Should the choices not be mutually exclusive, the respondent will not know which to choose as the answer to the question. Consider the following example:

**Q. Which of the following best describes your favorite activity?**

- a. Outdoor
- b. Hunting/fishing
- c. Hiking
- d. Reading
- e. Sports

Outdoor, hunting/fishing, hiking, and sports are not mutually exclusive so a respondent may have difficulty selecting the most appropriate choice.

Investigators may want to consider using open-ended questions to solicit exact age or a length of time; when a specific figure is entered, the data are richer and may allow the researcher to conduct more powerful statistical tests. For example, if age is categorized into groups such as 30–39 years, 40–49 years, etc., a respondent who is 39 years old chooses the same answer as someone who is 30 years old, and likewise for the 40– and the 49–year-old. Even though the 39- and the 40-year-old are separated by only one year, they will be grouped in analyses similarly with others who are farther from their age.

It is best to take care, though, when soliciting data that may be sensitive in open-ended questions. For example, respondents may be more comfortable reporting a range for household income rather than a specific figure. In fact, respondents may not be aware of the exact figure. In general, the investigator should consider looking at how previous researchers have framed demographic questions as well as how the U.S. Census Bureau frames its census questions.

**Developing Items for a Summated Ratings Scale**

Most researchers use summated ratings scales rather than interval-level or multidimensional scales. Summated ratings scales are a list of item statements to which respondents indicate some level of agreement or other affective response on a numeric scale. The items comprising an attitude scale should represent the universe of existing stimuli to that referent object. In other words, researchers need to consider all aspects of a phenomenon that may constitute a person’s attitude towards it.

For example, an investigator interested in gathering customers’ attitudes about a community pharmacy should query respondents on everything about the pharmacy that evokes an affective response. This would include, but not necessarily be limited to, aspects of the pharmacy layout/design, the selection of available products, arrangement of the products, prices of product lines, the courtesy and competence of the employees, the aesthetic appearance of the pharmacy, its location, hours of operation, the professionalism of the pharmacy/prescription department staff, the speed and accuracy of prescription dispensing, counseling services offered by the pharmacy, and the ability of pharmacy staff to solve both medication- and insurance-related problems. Most of the time, because the various aspects of the referent object under study are not as obvious as the ones in the hunting/fishing example, drafting the items requires a considerable investment of time and energy.

There are at least three sources to be considered when identifying domains of the referent object under study. First and most important is the available literature, particularly primary sources. A thorough literature review will give an investigator considerable insight and inevitably bring to light certain approaches to the topic not previously considered. The review might also make it clear that the investigators’ goals are too ambitious or that the topic does
not lend itself well to investigation. On the other hand, the investigator may find a previously validated tool that measures the referent object more reliably and thus avoid the burden of creating an entirely new survey instrument.

The literature search must be comprehensive. For example, if an investigator is interested in identifying health beliefs, the literature review cannot be confined to merely plugging the terms “health” and “beliefs” into a search engine and seeing what comes up. A thorough literature review should take days or even weeks to complete. The initial queries should search for a comprehensive set of terms in a variety of databases; the investigator should read the initial abstracts and articles discovered and then reiterate the process with additional terms generated from the initial search. Novice researchers may confuse their search to one database such as International Pharmaceutical Abstracts, Medline, or Micro-Medex but, depending upon the nature of the topic, other databases from the areas of psychology, business, law, education, nursing, and medicine, along with the Internet, should be utilized and may prove to be invaluable.

A second source of information is colleagues and experts in the field. The ideas that can be generated from a few discussions with colleagues (whether they are fellow practitioners, administrators, or academics) can be pleasantly surprising. Not only will their insights offer a different perspective, but the actual process of discussing the matter with peers will also be quite stimulating, helping to “grease the wheels” of the project. The literature review may have identified experts on the same or a similar subject with whom the investigator is not personally acquainted; more often than not, these experts are more than happy to share their insights and experiences. While experts are likely to have published extensively on the subject, discussions with them may reveal information not yet in print or provide the same sort of stimulation as is derived from talking with colleagues.

A third source, one that is often overlooked, is persons who meet the sampling criteria. In referring to the previous example concerning customers’ attitudes toward a community pharmacy, gathering information from actual customers can be valuable in identifying pharmacy attributes that matter to them. An investigator interested in measuring pharmacists’ attitudes and experiences with communications generated by direct-to-consumer advertising of prescription drugs should consult with practitioners when creating the survey. Gathering this type of information may simply involve interviewing a small number of persons chosen on the basis of convenience. A more formal and potentially rich data source for soliciting domains of the referent object is to use focus groups or nominal group techniques.4,5

Once all of the relevant domains have been identified, the next step is to construct the actual item stimuli. It is usually necessary to construct several stimuli for each domain. For example, in the example on attitudes toward a pharmacy, several stimuli will be required to get at the “aesthetic appearance” domain. Consumers judge a pharmacy’s appearance by its colors, lighting, merchandising, and signage, at the very least. Generating more than one item for each domain also allows the investigator to test the validity and reliability of the stimuli comprising each domain and the domain itself (discussed further in the next section).

Cautions investigators should heed when constructing items for a scale are summarized in Table 1. An example of a vague item question would be “How are things coming along at your job?” “Coming along” is ambiguous. The respondents do not know whether this refers to a general level of satisfaction, progress on certain projects, or how well their most recent performance evaluations went.

Some common words have multiple interpretations, such as the word fair, which can mean “just,” “equitable,” “impartial,” or “not very good.” In surveys related to managed care pharmacy, words like “quality” and “access” should be avoided in items unless they are further clarified.

Basing words and phrases are those that elicit emotional responses that have little to do with the referent object. The investigator has to be careful when using terms like “abortion rights,” “socialism,” or even “capitalist” when designing survey items. The objective investigator will resist the temptation to charge up respondents, who may otherwise end up responding more to the survey itself than to the referent object. Similarly, investigators must be careful not to elicit socially desirable answers from respondents. For example, in inquiries about a pharmacist’s medication counseling behavior, “I counsel as often as other pharmacists,” or “I follow the procedures dictated by OBRA 1990” almost forces the responding pharmacist to provide an affirmative response. In cases like this, it would be better to present one or more scenarios and ask respondents how often they engage in specific behaviors.

It may be appropriate on rare occasions to lead respondents,
particularly if there is a concern that they may provide socially desirable answers. For example, in assessing medication compliance, one might consider informing potential respondents that “many people often forget to take their medication as directed,” before asking them how often they forget to take their own medications. This technique should be used judiciously, however, as the results of leading questions may be suspect.

A very common mistake, even among experienced researchers, is to construct compound or double-barreled items. For instance, if you were asked to indicate on a scale how much you like pizza and hot dogs, you might not know how to respond. What if you love pizza, but have no appetite for hot dogs? A double-barreled question puts the respondents in a quandary, resulting in their either leaving the question blank, responding to only one of the two stimuli, or even averaging their response to the two stimuli. The remedy is simply to divide the item into two separate stimuli.

Another common error is the use of superlatives. If a respondent is asked to evaluate something like “This is the best pharmacy plan I have ever had,” it creates problems on several fronts. For one, words like “best” and “worst” are ambiguous. Secondly, the respondents may have too little experience with other pharmacy plans to make a comparison. Finally, some respondents may be relatively satisfied with the current plan but perhaps at one time had a plan that they were even more satisfied with. These respondents would have little choice but to disagree or strongly disagree with the statement despite being satisfied. Similar problems result when descriptors such as “very” and “quite” are added to items.

Investigators should consider reversing the effect of some item statements. For example, if most of the stimuli represent something positive about the referent object, inject a few items that point to something negative about it. An example of a negatively worded item on a scale designed to measure a pharmacist’s job satisfaction would read, “I do not feel as though I have an opportunity for advancement in my current job.” A respondent who is agreeing or disagreeing with all of the statements, good and bad, may not really be paying attention to the stimuli, perhaps warranting that the responses be discarded. If this is happening frequently, the investigator must question the validity of the scale, the directions provided to respondents on how to complete the survey, and perhaps the sampling procedures.

Suggestions #10 and #11 in Table I go hand in hand. They will help ensure the validity of the responses obtained. For example, where an investigator is concerned with attitudes and behaviors resulting from direct-to-consumer (DTC) prescription drug advertising, an item such as “Because of DTC ads, more people request specific prescription medications by name” induces speculation by the respondent on the habits of other individuals. The item should be written in a manner that solicits information about a personal consequence and reflects a potential resultant behavior on the part of the respondent. Rewritten, “Because of certain DTC ads, I am more inclined to request a specific medication by name,” the item requires the respondents to be knowledgeable only about their own intentions.

Similarly, asking someone to rank the “convenience” of a pharmacy is less effective than asking them to respond to an item stimulus such as, “Pharmacy X’s hours of operation are convenient for me.” The latter is not only more clear but can provide more specific information to discern preferences among different types of persons (by gender, occupation, age, or other variable).

Investigators may want to elicit from respondents information about a frequency of behavior or give them a timeframe for which answers to certain questions apply, for example, a general state of health or level of stress. A period that is too short, such as “yesterday,” is transient and does not necessarily indicate general health or stress if the respondent simply felt under the weather. On the other hand, asking respondents to provide information for too long a period, such as “the past year,” results in their having to engage in significant recall and make a judgment about what were probably varying degrees of health or stress. Given that sampling frame and research objectives differ from one study to the next, there is no universally accepted timeframe but periods such as “the past 30 days,” “the past four weeks,” or “the past two months” are often appropriate and may yield more reliable responses.

Conclusion

Data obtained from mail survey questionnaires can be very helpful to administrators as they make decisions. Decisions based upon a poorly constructed survey questionnaire, however, can be more deleterious than those based upon no information at all. Although survey research can be quite complicated, avoiding a few common pitfalls will enable the investigator to have more confidence in the results obtained. This continuing education article should help administrators and researchers to construct survey questionnaires that maximize rates of return and produce valid and reliable results.

REFERENCES

Upon completion of the continuing education module, pharmacists will be able to:

1. Identify situations for which surveys may be utilized to collect data.
2. Identify important research design and sampling considerations in survey research.
3. Design an appropriate cover letter to accompany a mail survey that maximizes its rate of return.
4. Select an appropriate scaling procedure.
5. Describe methods used to assess the validity and reliability of a summated ratings scale.
6. Describe procedures used to determine the potential for nonresponse bias in mail surveys.

**SELF-ASSESSMENT QUESTIONS**

1. A higher rate of return to a mail survey questionnaire is important because:
   a. It gives the investigator more confidence that the results typify the entire population.
   b. It reduces the likelihood that respondents differ in some way from nonrespondents.
   c. It may allow the investigator to use more powerful statistical procedures.
   d. All of the above.

2. Which of the following is the most effective way to improve a mail survey’s rate of return?
   a. Using small font size to keep the questionnaire from becoming too lengthy.
   b. A nominal reward.
   c. Multiple mailings and reminders.
   d. Enhancing the questionnaire with graphics and illustrations.

3. Which of the following is NOT appropriate for inclusion in a cover letter accompanying a mail survey?
   a. Assure survey recipients that their responses are anonymous and will remain confidential.
   b. Warn survey recipients that the project will fail if they do not provide a response.
   c. Inform survey recipients of the benefit that will be derived from the research.
   d. Inform survey recipients of how their responses will be used and what will be done with them when the project is completed.

4. Which of the following statements is true?
   a. It is never appropriate to elicit personal or demographic information with an open-ended question format.
   b. Survey respondents typically enjoy the use of catch phrases and jargon in survey questions.
   c. Response choices to multiple-choice questions should be mutually exclusive and exhaustive.
   d. The use of open-ended questions is ideal for research that involves sophisticated statistical procedures.

5. Mutual exclusivity among response choices implies that:
   a. The response choices are distinct and do not overlap.
   b. The response choices cover the entire range of possibilities.
   c. The response choices do not offend any particular group of persons.
   d. The response choices are somewhat difficult to comprehend.

6. Which of the following is true?
   a. Items in a scale eliciting attitudes toward a referent object should be representative of the universal set of attributes possessed by that object.
   b. With enough practice, a through review of the literature should take only a few hours.
   c. A literature review should typically be confined to one database in order to ensure efficiency and accuracy.
   d. All of the above.

7. Which of the following are appropriate as resources for deriving item stimuli comprising a summated rating scale?
   a. The opinions of colleagues.
   b. Focus groups of persons meeting the sampling criteria.
   c. The primary literature.
   d. All of the above.

8. Which of the following would be good advice to an investigator constructing item statements to comprise a summated ratings scale?
   a. Avoid the use of double-barreled statements.
   b. Avoid the use of superlatives.
   c. Carefully intersperse items that require reverse coding.
   d. All of the above.

9. Suppose as a pharmacy manager you were designing a questionnaire to gauge the level of job satisfaction of pharmacy technicians. Which of the following item stimuli would be most appropriate?
   a. “My job is arduous.”
   b. “I have the best job of anyone I know.”
   c. “My job stimulates me to think and pays me well.”
   d. “My job provides me with an opportunity to use my own judgment.”

10. Suppose you are interested in assessing consumers’ attitudes toward switching from prescription to OTC antibiotics. Which of the following item stimuli is best? (Assume each item stimulus begins with “Allowing antibiotics to be sold over the counter . . . ”)
    a. “… is a very bad idea.”
    b. “… will help me to afford to buy antibiotics for my family when needed.”
    c. “… will increase the susceptibility of high-risk individuals to drug-resistant microbial strains.”
    d. “… will increase access to antibiotics for certain people.”

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This test affords 1 hour (0.10 CEU) of continuing pharmaceutical education in all states that recognize the American Council on Pharmaceutical Education. To receive credit, you must score at least 70% of your test answers correctly. To record an answer, darken the appropriate block below. Mail your completed answer sheet to: Academy of Managed Care Pharmacy, 100 N. Pitt Street, Suite 400, Alexandria, VA 22314. If you score 70% or more, a certificate of achievement will be mailed to you within eight weeks. If you fail to achieve 70% on your first try, you will be allowed only one retake. The ACPE Provider Number for this lesson is 233-000-02-003-H04. This offer of continuing education credit expires June 30, 2003.

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Available in May 2002

The highly anticipated portfolio known as Pharmacy’s Framework was presented to Academy members at the 14th Annual Meeting in Salt Lake City on April 4, 2002. The portfolio consisted of two commissioned white papers, a self-assessment tool (a grid of component tasks), and a user’s guide. The CD-ROM disk containing the presentation at the Annual Meeting and the portfolio of materials is now available. The Academy encourages its members to be early adopters of the Framework, applying the Framework self-assessment tool to real-life experience. The tool can be used to help improve the quality of drug therapy management. Short term, the Framework will reduce the burden of re-inventing the wheel each time there is a drug therapy program to be evaluated. Longer term, the Framework will be a platform for the establishment of best practices and create a library of data at the Academy. The intention is to share the results with professionals who are interested in achieving similar results for their own health care programs.

Final copies of Pharmacy’s Framework for Drug Therapy Management in the 21st Century may be ordered from the AMCP and FMCP websites, www.amcp.org and www.fmcpnet.org. The first copy is free; additional copies are $25.00 each.

AMCP’s Format for Formulary Submissions Moves Ahead

The Format is being adopted at a rapid pace. Current estimates are that organizations that have adopted the Format cover over 100 million lives, approaching 30% of the U.S. population.

2002 Outlook on Health Care Issues: Much Debate, Not Much Action Anticipated

While Congress will seriously debate numerous health policy issues during the remainder of 2002, prospects for final action on most proposals are either remote or at best unlikely. Prescription drug coverage for the Medicare program is the most visible and most controversial health care issue before Congress. Public support for a drug benefit remains high, and both Republicans and Democrats have placed it near the top of their legislative agendas. Nevertheless, there are numerous areas of policy disagreement to be overcome before prospects for enactment improve.

Major differences between the parties are in the scope of coverage, the choice of entities to administer the benefit, funding levels and sources, and whether the benefit would be enacted by itself or as part of a more comprehensive Medicare reform package. The disappearance of the federal budget surplus and the 2002 Congressional elections will certainly affect the debate. Two legislative proposals AMCP is watching are the reauthorization of the Prescription Drug User Fee Act (PDUFA) and a change in the payment methodology for Medicare Part B drugs.

Republican and Democratic leaders in both Houses of Congress and the Bush Administration all agree that the user fee program has improved the ability of the FDA to process new drug approvals and support its continuation. The only issue is whether Congress will simply reauthorize the program or use the PDUFA bill to address other issues, such as patent extensions, post-market surveillance, incentives for increased use of generics, and direct-to-consumer advertising.

Congress has been presented with evidence that Medicare is wasting billions of dollars per year overpaying for drugs and that change is necessary to better align reimbursement with the actual costs of acquiring drugs. Whatever happens here will be an indication of things to come in the debate over the Medicare pharmacy benefit.

AMCP Joins Pharmacist Provider Coalition Seeking Medicare Funding for Pharmacists’ Patient-Care Services

AMCP, the American Society of Consultant Pharmacists (ASCP), and the American Pharmaceutical Association (APhA) have all joined the Pharmacist Provider Coalition (PPC). PPC was founded by the American Society of Health-System Pharmacists (ASHP) and the American College of Clinical Pharmacy (ACCP) to secure passage of the Medicare Pharmacist Services Coverage Act of 2001 (S. 974 and H.R. 2799). The coalition is working to get Medicare patients access to pharmacists’ medication therapy management services.

The Medicare Pharmacist Services Coverage Act of 2001 would amend the Social Security Act to include pharmacists among the health care professionals classified as health care providers, which would allow pharmacists to bill Medicare for providing high-level patient care services. Among the other health care professionals the Social Security Act currently recognizes as providers are registered dieticians, nurse practitioners, physician assistants, certified nurse midwives, and clinical social workers.

AMCP has supported this stance since 1999 when the Academy first published its position statement on Medicare Prescription Drug Coverage (in the "Where We Stand" series). The statement is available at http://www.amcp.org/professional_res/position/medicare/medposition.asp.

Modification of HIPAA Privacy “Prior Consent” Requirement Applauded

The Confidentiality Coalition, of which AMCP is a member, recently sent a letter to members of Congress applauding the Bush Administration’s notice of proposed rulemaking on Health Insurance Portability and Accountability Act (HIPAA) privacy regulations. The HIPAA privacy rules proposed in November 1999, which become effective April 14, 2003, the Confidentiality Coalition believes, are onerous, inconvenient, and costly and could possibly endanger patient health. The Bush Administration, in its review of the rule, expressed concern about the pragmatic implications and unintended consequences of the regulation. (The Coalition, an offshoot of the Health Care Leadership Council, consists of over 100 organizations; its primary purpose is to lobby for privacy rules that are practical, consistent, and clear.)

The letter the Coalition sent to Congress describes how, without the proposed modifications, patients could experience signifi-
cant delays in obtaining medications if pharmacists could not fill prescriptions until patients were present to sign a consent form. Friends and family would not have legal authority to sign consents, and thus could not pick up prescriptions for individuals too ill to come themselves.

AMCP Board of Directors Approves Position Statement on Regulation of PBM Companies

The Academy’s Board of Directors approved a position statement on government regulation of pharmacy benefit management companies (PBMs) during its regular meeting at the Annual Meeting in Salt Lake City. The statement asserts that government should encourage an environment in which pharmacists and other health care professionals working within managed care organizations, including PBMs, can continue to develop innovative and integrated strategies and programs to manage prescription drug benefits for covered patient populations.

Further, the Academy opposes proposals that would unduly restrict the use of these strategies and programs because such restrictions would undermine the ability of Academy members to deliver patient-oriented pharmaceutical care and contain continuing increases in the costs of pharmaceuticals. Economic realities, medication safety, patient noncompliance with drug regimens, and other pragmatic considerations require flexibility so that benefit programs can be designed to assure that drug benefits remain affordable and are delivered in a way that maximizes the opportunity to achieve the therapeutic outcomes desired by patients and the health care professionals responsible for their care.

The Board’s action, based on a recommendation from the Academy’s Legislative Committee, responds to regulatory and legislative proposals that would limit the ability of pharmacists working within a managed care organization to use tools and services such as formularies, pharmacy networks, or mail delivery of prescription drugs.

The position statement can be accessed via the Academy Web site at the following page: http://www.amcp.org/professional_res/position/index_position.asp

State House Review Reveals Potential Impact of Pending Legislation

The states have been busy, too. With the continuing increase in prescription drug costs and the issues of prescription drug assistance for seniors, health coverage for the uninsured, and patient confidentiality looming, it is more important than ever for AMCP to keep a keen eye on the states as their legislators examine proposals to both encourage and in some cases prohibit the use of managed care tools to reduce state health care woes.

Legislative trends that bear watching in the states are proposals on mandated benefits, anti-mail-order legislation, formulary management, standardized ID cards, drug pricing, confidentiality, prescription drug assistance for seniors, and the regulation of PBMs.

Mandated benefit proposals are especially prevalent. Over 20 states have introduced legislation requiring coverage for specific products or services, infertility treatment, hormone replacement therapy, and contraceptives among them. Meanwhile, some states are trying to curb the proliferation of mandated benefits by forming advisory committees to study the impact of current and proposed mandates.

Regulation of PBMs is emerging as a possible trend. In six states—Alabama, Maryland, Iowa, Illinois, Missouri, and Georgia—legislation on the subject has been introduced. The Georgia legislation proposes to regulate PBMs as in-state pharmacies. Proposals in the other five states have the potential to prohibit PBMs from maintaining a select pharmacy network; they stipulate that state pharmacy boards would regulate the market conduct of PBMs, while state insurance commissions would monitor their financial status.
AMCP Members receive many benefits, including:

▲ AMCP Publications . . .
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▲ Registration Discounts . . .
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▲ Career Information Services . . .
A service that provides AMCP members with the opportunity to advertise their availability for employment, and employers the opportunity to advertise their positions that are available within their organizations.

▲ Fax-on-Demand . . .
A popular service that offers quick answers to questions about AMCP and managed care pharmacy.

▲ Member-Only Access to Information on the AMCP Web Site . . .
An important link to the latest updates on clinical, market, legislative and regulatory, and administrative issues shaping the practice of managed care pharmacy.

▲ Weekly News . . .
An e-mail service that reviews the week’s events of importance to the pharmacy profession.

▲ Legislative and Regulatory Updates . . .
An essential information service that provides our members with key information on issues that affect managed care on a national and a state-by-state basis.

▲ Meetings With Congressional Leaders . . .
Each year, AMCP coordinates and assists our members to meet directly with policy makers to discuss concerns and issues affecting managed care.

▲ AMCP Committee Involvement . . .
Opportunities exist through AMCP’s leadership to become involved, network with peers, and influence the direction of managed care pharmacy.

Join AMCP today.
No other organization offers you the same depth of information and influence in managed care pharmacy.

A membership application is on the next page side for your convenience. After completing, please mail or fax to AMCP.
## Membership Application

### Member Information

- Mr.  
- Ms.  
- Mrs.  
- Dr.

**FIRST NAME** 

**LAST NAME**

**TITLE**

**ORGANIZATION NAME**

**ORGANIZATION ADDRESS**

**CITY**

**STATE**

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**HOME ADDRESS**

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**WORK TELEPHONE**

**FAX**

**HOME TELEPHONE**

**E-MAIL ADDRESS**

**REFERRED BY**

### Demographic Information

**Please tell us:**

I. Are you a pharmacist?  
- yes  
- no

II. What degrees/designations do you hold?  
- B.S. Pharmacy  
- Pharm.D.  
- M.P.A.  
- M.P.H.  
- Ph.D.  
- J.D.  
- M.B.A.  
- R.Ph.  
- Other

III. Which of the following best describes your employer? (check one)  
- Health Plan  
- Medical Group  
- Integrated System  
- Hospital  
- College or University  
- PBM/Mail Service  
- Home Care  
- Long-term Care  
- Retail Pharmacy  
- Consulting Firm  
- Pharmaceutical Manufacturer  
- Government (VA, PHS, Military, State)  
- Not Currently Employed  
- Other

IV. Which of the following best describes your job function(s)?  
- Director/President  
- Assistant Director/Vice President  
- Staff Pharmacist  
- Clinical Pharmacist  
- Clinical Coordinator  
- School/College Faculty  
- Student  
- Resident/Fellow/Graduate  
- Contract/Purchasing  
- Network Management  
- Professional Relations  
- Formulary Management  
- Distribution/Supply Chain  
- Customer Service  
- Consultant  
- Marketing/Sales  
- Other (specify)

V. How many years have you been in your current role?  
____ year(s)

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Every year dozens of managed care pharmacy professionals contribute their expertise and time to review articles for JMCP. Their critical comments are instructive to authors and serve to improve the quality of the papers published. JMCP is grateful to all who helped in 2001 and 2002, and here we acknowledge them, with special thanks.

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These articles are based upon original research that has not been published elsewhere and reflects use of the scientific method. The research is guided by explicit hypotheses that are stated clearly by the authors. An abstract is required, generally in the format of Background, Objective, Methods, Results, Conclusion.

Subject Reviews

These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy. These articles do not require an abstract.

Formulary Management

These are well-referenced, comprehensive reviews of subjects relevant to formulary management methods or procedures in the conduct of pharmacy and therapeutics (P & T) committees. These articles may not include an abstract but should begin with an overview of the background of the subject and objective of the article.

Contemporary Subjects

These submissions describe pilot projects or other subjects that are not intended to be comprehensive reviews of the subject. These manuscripts should be well-referenced but not necessarily comprehensive. If original research, then include an abstract that follows the format of Original Research (Background, Objective, Methods, Results, Conclusion).

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These submissions are peer-reviewed but require no abstract.

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### Manuscript Preparation

Manuscripts should include, in this order, a title page, a separate page identifying all authors (including degrees, employers, contact information, and financial disclosure and conflicts of interest), an abstract of no more than 300 words, text, references, figure captions, tables, and figures.

**JMCP** abstracts should be written narratives that contain the information described for each type of article shown below, where applicable:

- **Original Research**
  - Background
  - Objective
  - Methods
  - Results
  - Conclusion

- **Subject Reviews**
  These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy. These articles do not require an abstract.

- **Formulary Management**
  These are well-referenced, comprehensive reviews of subjects relevant to formulary management methods or procedures in the conduct of pharmacy and therapeutics (P & T) committees. These articles may not include an abstract but should begin with an overview of the background of the subject and objective of the article.

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- **Editorials**
  These submissions are peer-reviewed but require no abstract.

- **Letters**
  These submissions may be peer-reviewed for accuracy but require no abstract or title page.

### Reference Style

References should be prepared following AMA style. Shown below are examples of common types of references.

1. **Standard journal article**
   (list all authors when four or less, when five or more, list only the first three and add et al.)

2. **No author given**

3. **Journal paginated by issue**

4. **Book or monograph by authors**

5. **Book or monograph with editor, compiler, or chairman as author**

6. **Chapter in a book**

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