ADHD: Disease or Social Miasma?

On the ninth of February this year, The Canadian Press reported, “Health Canada has ordered a one-day treatment for attention deficit hyperactivity disorder (ADHD) off the market after learning the drug has been ‘linked’ to 20 sudden deaths and 12 strokes, including among children.” The drug was Adderall. On February 11, 2003, Reuters Health stated, “The FDA (U.S. Food and Drug Administration) is aware that children have died after taking the drug, but cannot tell whether the rate is higher among these children than it is in the general population,” said Dr. Robert Temple, director of the FDA’s Office of Medical Policy. Temple was referencing the science of the issue, noting that the deaths occurred over a 10-year span, and that most of the patients involved had significant cardiac disease. He stated that it was not clear if the occurrence of the conditions was higher than the rate without the drug since the data were from anecdotal reports and no formal study of occurrence had been conducted.

The FDA has not, thus far, concluded that there is adequate scientific support to remove the drug from the market. However, the proposal for “drug-induced-injury” has been set in motion. Google already posts several advertisements by attorneys wishing to participate in compensating “victims.” Whether science will confirm a significant relationship between Adderall and heart disease or stroke remains to be seen. Whether litigation is warranted or simply opportunistic remains to be seen. Yet, there are larger issues.

This brouhaha, regardless of its scientific or legal merit, provides an opportunity to inquire about the fundamental benefit of ADHD diagnosis. Does a child who fulfills criteria for ADHD have a disease, or is the child simply “guilty” of failing to fit the behavioral expectations of a technocracy?

So as to settle any immediate pique, let me promptly support the perspective of ADHD as a disease for at least some ADHD-labeled children. There are some children whose behavior is so disordered that it may be argued as dysfunctional in any social context. However, application of ADHD labeling may extend beyond the borders of what one may strictly conclude as disease.

A Look at Attention Deficit Hyperactivity Disorder, a lay publication by the National Institute of Mental Health (NIMH), introduces ADHD consideration with 3 questions: (1) Is it hard for your child to sit still? (2) Does your child act without thinking? (3) Does your child start but not finish things? If taken strictly, is there any child who does not fulfill these criteria at least some of the time? Are these not normal behaviors of childhood? In fairness, the NIMH publication does go on to say, “Most children have trouble sitting still. Many kids don’t finish their schoolwork. Few children sit through meals without tapping, kicking, or drumming. So how do you know what is normal versus what is ADHD?” As regards the initial 3 questions, this is a recurring theme. Regardless of these questions, you may want to read this booklet to learn more about attention deficit hyperactivity disorder, called ADHD for short.

For some time, experts disagreed on how ADHD should be diagnosed—and even on whether it was a real disorder. But in 1998, the National Institute of Mental Health decided that ADHD is a legitimate condition. In addition, most doctors believe that a child shouldn’t receive a diagnosis of ADHD unless the core symptoms of ADHD appear early in life—before age 7—and create significant problems at home and at school on an ongoing basis.

The site goes on to say:

Being different isn’t ADHD. The same is true of hyperactivity. Young children are naturally energetic—they often wear their parents out long before they’re worn-out themselves. And they may become even more active when they’re tired, hungry, anxious or in a new environment. In addition, some children just naturally have a higher activity level than others. Every child is unique, with a distinct personality and temperament. Children should never be classified as having ADHD just because they’re different from their friends or siblings.

So, where do we draw the line? How do we draw the line? What is normal childhood? What is “hyperactivity”? To address these questions, we must enter a very important realm: a realm perhaps not discussed in “polite conversation.” That is, the realm of social structure design. Is ADHD a disease, or are these children simply poorly designed to fit in the neat, tidy, regulated world of a technocracy?

Evolution prepared us to survive a world that, until very recently, was largely an outdoor adventure. Only for the very smallest fraction of evolutionary time have we chosen to live the majority of our lives within the confines of four walls. And, only during the smallest sliver of time have we commanded children to sit most of the day within the neat and tidy rows of a classroom. What loss of perspective leads us to believe that all children are “designed” for this endeavor?

Is ADHD a disease in the bush of Africa or South America? Do any parents there consider their children to be “hyperactive”? Do any children of rural farm parents in India have ADHD? Or, are the energetic children in such remote areas viewed as gifted, “full of life,” tomorrow’s hunters? Do the children who might be labeled as having ADHD in our community have analogs in rural communities? Or, in the new framework of life within technocracy, are there simply children who don’t fit the seat-clasroom/tidy-home paradigm?

The social structure of a technocracy is a new development
Editorial

on planet Earth. Nowhere in the history of time could we have found a childhood population whose daily average behavior consisted of sedate learning, quiet play, and orderly response. For adults, such endeavors might have been found in a monastery, but only a few are candidates for that life. Most of human history has been founded on extensive daily physical activity.

Perhaps we can even inquire at the next level. Are we creating a society for which some people are obsolete? Do ADHD children have an illness, or simply a genetic structure designed for a different time and place? Clearly, this is a subject that will engender umbrage from those threatened by such questions.

I began with notation of a policy decision in Canada a decision regarding a drug for ADHD. I end with philosophical questions that derive from the ADHD diagnosis itself. I'm wont to do such things. It is not enough to focus on details of individual steps. We must, at least occasionally, look up from our feet to see where we are going. If we are going to expose children to drugs—some argue “dangerous drugs”—then we must inquire about the illness we are treating. As a practical matter, I accept the notion of ADHD—at least in a few children. Yet, where is the boundary beyond which we are treating a child for a genetic variation rather than a disease?

If we are truly sentient, we must look across the world to see if other populations have the same view as we do. We must look at our own course, and ask where we are going. We must look at the design of our society, and ask: “Is society built as our tool, or are we its tools?” If parts of our population no longer fit the social design, what will we do? Shall we define those who do not fit the “social structure do yours” as having a disease? Shall we expose them to “dangerous drugs” to make them fit?

John P. Barbuto, MD
Neurology & Focus
An Outpatient Neurology Clinic at HealthSouth
8074 South 1300 East, Sandy, UT 84094
doctorbarbuto@comcast.net

DISCLAIMERS
The author discloses no potential bias or conflict of interest relating to this editorial.

REFERENCES
Appropriate Econometric Methods for Pharmacoeconomic Studies of Retrospective Claims Data: An Introductory Guide

The Gianfrancesco et al. study in the April 2005 issue of JMCP provides a good opportunity to examine some of the data measurement and analytical issues that should be considered in studies evaluating differences in drug costs or other treatment outcomes using retrospective insurance claims data. Now that large health care claims databases are readily available from government programs (e.g., Medicare, Medicaid, Veterans Affairs), commercial insurers (e.g., WellPoint, Pharmetrics, 13 Magni, Mediact, etc.), and other sources, it is easy to "crunch the numbers" with extremely large national patient data samples and derive conclusions about treatment cost differences, often with very high levels of parameter significance. Whether these conclusions are valid and reliable depends on the robustness of the econometric methods used in the analysis.

Jerry Avorn's recent book *Powerful Medicines* eloquently and engagingly describes the strengths and limitations of retrospective data analysis for pharmacopidemiology and pharmacoeconomics.1 There have been a number of situations where retrospective data analysis have provided invaluable insights into drug treatment outcomes, including studies of phenytoin and phenobarbital,2 troglitazone,3 and rofecoxib.4 There are also situations where retrospective data analyses have failed to detect important confounders and have generated biased assessments of drug effects, most notably with estrogen replacement therapy.5

Data Measurement Issues

Data measurement accuracy is the foundation of appropriate statistical inference. One basic data measurement issue raised by Gianfrancesco et al. concerns the use of billed charges rather than amounts allowed by the third-party payers. Provider-billed charges may exceed amounts allowed by insurance plans by 60% or more.4 Allowed amounts are a much more accurate measure of actual medical costs since they reflect the portion of the bill for which the payer and patient are contractually obligated. For insured patients, billed charges are essentially fictional since the insurance plan decides, based on plan characteristics and provider contracts, what the actual transaction amount will be. While there is a problem with the reliability of allowed amounts when a family has more than one source of insurance coverage, this problem is not resolved by simply using provider charges. Concern about captivated provider benefits or about patients with multiple family insurance plan coverage benefits can be better addressed by isolating such cases from the main patient data and analyzing them separately.

Second, adjusting actual drug claims into dose equivalent mg costs is highly misleading. Dose adjustments for age, gender, or other characteristics may not reflect how much medication patients receive should be accomplished with propensity score or instrumental variables estimation methods (see below) not by artificially altering the observed drug costs particularly since this is the key outcome variable in the analysis.

Econometric Methods

Econometric analysis is a highly technical field that is highly relevant to inferring the impact of drugs on health care treatment costs. This presentation is made in a relatively nomenclature fashion, to give the reader a flavor of the motivation behind these technical topics. While most details are skipped over for brevity, references to several relevant technical articles are provided.

Retrospective data analyses using administrative databases such as health insurance claims histories have a number of advantages over prospective randomized controlled trials (RCTs), particularly their larger sample sizes and lower data collection costs. There are many clinical issues that can only be addressed through retrospective data analysis because of time or budget constraints. Retrospective data also have higher external validity since patients and providers do not need to consent to join the study, are not generally aware that their decisions are under study, and thus act in a "real-world" fashion, which is often very hard to replicate in prospective RCTs.

Some clinical trialists pejoratively categorize all retrospective statistical analyses as "exploratory" or "hypothesis-generating" as opposed to RCTs that "reveal causation" and are "hypothesis-testing." However, each study design has its strengths and weaknesses, and both are equally valuable. Many types of patients are excluded from, or will never sign up for, RCTs. For ethical reasons no one is going to conduct an RCT on whether smoking causes cancer, stress causes cardiovascular disease, or on other interventions with significant perceived a priori risks. For financial reasons, innumerable other crucial medical decisions will never be subjected to prospective RCT study. As Avorn aptly points out, retrospective data analysis plays an important counterbalancing "yin" to the RCT "yang.

If a prospective RCT is well-executed, statistical analysis of the results is easy to prespecify and often is no more complex than an independent sample t test. On the other hand, appropriate statistical analysis of retrospective data, particularly for health care claims history, can be exceedingly complicated and can tax the most sophisticated econometric methodologies. The obvious concern with retrospective data is precisely what distinguishes it from RCTs—patients are not randomized to treatment in retrospective claims data analyses; rather, they are assigned to treatment because their physician and/or other provider selected the chosen therapy based on any number of observable and unobservable factors, including (but not limited to) the patients' preferences, medical history, and other characteristics.

Unfortunately, most retrospective claims data are limited in the extent of availability of patient or provider characteristics to use for statistical adjustment. In particular, medical history

344 Journal of Managed Care Pharmacy  JMCP  May 2005  Vol 11, No 4  www.amcp.org
information is generally limited to relatively crude patient disease severity measures such as the Charlson Index, Chronic Disease Score, or comorbidity indicators. Even items that should be straightforward to calculate are often unavailable, such as the provider’s typical prescribing patterns with similar patients. This means that, in most retrospective data analyses, important characteristics that are correlates of treatment choice, patient outcomes, and treatment costs are unobservable confounders. Such confounders will create biased estimates if ignored.

Researchers have understood for decades that such treatment selection bias needs to be accounted for in econometric estimates. James Heckman shared the 2000 Nobel Prize in economics for his pathbreaking 1974 work on econometric methods to detect and correct for treatment selection bias. More recently, sample selection bias estimation methods based on the propensity score and instrumental variables techniques have been further refined and generalized to improve precision and robustness.

Most of these methods start with an equation that estimates treatment choice as a binary (or multinomial) index function of observable explanatory variables, usually using probit (probability unit) or logit regression. This fitted equation generates the “propensity score” for a patient to be assigned to a given treatment. The propensity score is simply an estimated probability, based on observable characteristics in the data, that a specific patient would receive the treatment in question. Propensity score methods are often used to match patients receiving one treatment with others at the same level of propensity controlling for all observable explanatory factors, and to determine whether treatment costs are similar or different in these propensity-matched cohorts. Alternatively, the estimated propensity score, \( p \), itself can be included as an explanatory variable in a regression, with treatment costs or other patient outcomes as the dependent variable, and treatment assignment, \( w \), as another explanatory factor. Extensions of this approach include adding additional explanatory variables consisting of various low-order polynomial and power terms of \( p \) recentered at the sample mean of \( p \) and interacted with \( w \). Woodruff outlines conditions under which such propensity score estimators are consistent and asymptotically efficient.

The main problem with propensity score methods is that they are based on the assumption of “strong ignorability,” which requires that, given the observable explanatory variable \( s \), the estimated treatment effect is unbiased. As an example, in looking at treatment costs for lower back pain in a Michigan managed care plan, I found the drug-specific cost estimates to be very different, depending on whether or not one adjusted for the impact of pain severity on medication choice. If back pain severity truly impacts drug choice and one ignores this by leaving that important characteristic out of the estimation equation, the key assumption of the propensity score method would fail, and one would get a biased estimate of the drug treatment costs. If, on the other hand, one could be confident that back pain and other observed variables (e.g., age, gender, ethnicity, medical history), adequately explained drug choice, then the propensity score method would eliminate drug treatment selection bias from the cost estimates.

Because of the ignorability assumption, propensity score methods preclude the possibility that there are important unobservable characteristics (error components) that affect both treatment choice and treatment costs or outcomes after adjusting for all available explanatory factors. Since such an ignorability assumption is often untenable with retrospective claims data, it is usually preferable to use instrumental variables methods to adjust for treatment selection bias in this context. Instrumental variables methods often also start with the estimated propensity score, \( p \), but they explicitly allow for unobservables that are correlated with treatment choice as well as with treatment costs or other outcomes.

An instrumental variable is any exogenous variable that is correlated with the choice of treatment but not correlated with the unobservables that impact treatment outcomes and treatment costs. Certainly, the estimated propensity score, \( p \), fits such criteria since it is a function (e.g., a logit or probit regression function) only of observable exogenous factors that predict treatment choice. Low-order polynomial and power transformations of \( p \), are also valid instrumental variables. It is perfectly acceptable to have a larger number of instruments than potentially biased treatment effects in the estimation equation. Such cases are referred to as “over-identified.” However, problems can arise if the instruments are highly collinear with each other or with other explanatory variables in the treatment cost equation. Multicollinearity statistics and diagnostic tests should be examined to ensure that this is not a serious issue in each specific situation.

Ideally, one would like to find an instrumental variable that only explains treatment choice and has no impact on treatment outcomes or treatment costs. A classic health care services research example of this was demonstrated in the McClellan et al. evaluation of cardiovascular surgical outcomes in which they used patients’ residential proximity to certain types of hospital as an instrument. Certain hospitals are more likely to utilize specific cardiovascular surgical techniques, so patients living closer to those hospitals are more likely to receive those treatments. But people don’t choose their residences based on local hospital surgery preferences. Thus, while patient residential location is correlated with surgical treatment, it is clearly not correlated with the outcomes of surgery.

Heckman’s original (1979) selection bias regression correction method, which uses the inverse Mills ratio transformation of the propensity score as an additional regressor in the treatment cost regression, can be thought of as a propensity score method if one assumes that the inverse Mills ratio is the precise additional explanatory variable that preserves the propensity score.
framework. This is precisely the case when all the unobservables in the propensity equation and unobservables in treatment costs are joint-normally distributed. The Heckman method can be relabeled as an instrumental variables method if the inverse Mills ratio is used as an instrument for the selection-based treatment effect rather than directly including it as a regressor in the treatment cost equation. The question of whether propensity score methods are better than instrumental variables methods or vice versa is still unsettled and probably varies from case to case. Any valid instrumental variable should be included in the propensity score estimation equation and also could be included as an additional regressor in the treatment cost equation. But adding such an instrumental variable to the treatment cost equation will only eliminate selection bias if the strong ignorability assumption holds.

Instrumental variables methods may be preferable in the context of retrospective claims data analyses since they explicitly allow for unobservable correlates of treatment choice and treatment costs. Also, any time one can estimate a propensity score, one also can use it (and/or its transformations) as a valid instrument. Moreover, because of their properties in estimating simultaneous equations as 2-stage least squares estimators, instrumental variables estimators create valid estimates of the natural (policy-relevant) parameters, unlike reduced-form parameters that confine the higher-order impacts of exogenous variables amplified through all relevant equations. Propensity score estimators are better thought of as reduced-form parameter estimators. There are empirical examples where propensity score methods do better than instrumental variables methods and vice versa.15,16 This debate directly parallels an earlier debate as to whether sample selection models are better than 2-part models in estimating health care cost functions since the econometric issues are very similar.12,13

Furthermore, Guanfrancesco et al. ignore issues that lead to bias in their reported regression t-statistics. If drug treatment selection bias exists, then correcting for it by using an estimated propensity score (widely-propensity score transformation) rather than the “true” propensity score will create biased t-statistics, just as using the estimated mean rather than the true mean biases the estimates of the standard deviation in the simple univariate case. Regardless of which estimation method is used, one should adjust the estimated model coefficient standard errors for this “heteroskedasticity” induced by including a fitted propensity score (and/or its transformations) in the treatment cost regression. The simplest and most accurate way to accomplish this is to bootstrap the entire estimation step sequence, using resampling with replacement to obtain a sufficient number of sample replicates (using the original sample size) to generate robust parameter confidence intervals.17 Split-sample model validation (estimating the model on a random half of the data and validating on the other half) is a very useful way to compare alternative estimation models, particularly when sample sizes are large, as is usually the case with retrospective claims data.

Another major item of concern in any estimation of treatment effects on health care costs relates to the fact that nearly all health care cost samples are highly skewed, with a small percentage of patients accounting for a large proportion of total costs. Logarithmic transformation, or some other power transformation of the cost variable(s) is often an appropriate correction, but this adjustment creates a number of additional complexities that are often inappropriately ignored. First, when one transforms costs to the log-scale, one cannot simply take the exponent of the estimated treatment coefficient to predict the treatment effect on the raw cost scale. As Dun & others have pointed out, log-transformations (or other power transformations) create a “retransformation bias” that must be accounted for in calculating treatment effects in the cost scale.18,19 Guanfrancesco et al. do not use this retransformation bias into account in generating their estimates of the cost differences between drug treatment groups.

Second, as described in Dieter et al., in situations where a subset of patients exhibit zero-levels of cost or spending and are therefore not measurable after a log-transformation, a common “trick” is to treat their spending as if it were a very small positive number (e.g., $1), and then include their observation with a dependent value of log($1) = 0. This trick actually creates a potentially arbitrary and serious bias in estimating all model coefficients. For example, if adding $1 to a zero-cost individual’s spending is inconsequential, why not add 5.01 instead or, even better, $0.000001? It is easy to demonstrate that all model coefficient estimates are highly sensitive to the choice of these arbitrary small spending amounts. Since none of the amounts are truly justified, the analyst will be inducing an arbitrary artificial bias into the estimation process. A more robust solution is to estimate a 2-part model or a sample selection model, splitting the patients sample into the subgroup with zero expenditures and the subgroup with positive expenditures and estimating a person’s predicted costs in 2 parts—the probability that they have positive expenditures times the expected value of expenditures, given that they’re positive.20

There are a number of additional important issues in estimating drug treatment effects on patient health care costs in retrospective claims database analyses. These include the fact that disease dates of diagnosis are often unknown, and diagnostic episodes are often either left-censored, right-censored, or both in retrospective claims data. For example, in looking at mental health patients, one seldom is interested in only the subset of cases that are initially diagnosed during the retrospective data observation period. Even if one were, the lack of health care utilization prior to the first observed diagnosis-related claim or service could reflect either a new diagnosis, the fact that the condition was in remission, or that the patient was transferred to the observed insurance plan. All nonincident
cases in the sample are termed “left-censored.” Similarly all sample patients who are not “cured” or dead by the last date in the observation period are considered “right-censored.” Statistical methods for dealing with these episode-censoring concerns include hazard functions, survival models, Cox proportional hazards models, and other multivariate extensions of the Kaplan-Meier survival curve.2,34,35

Also, the fact that one often has repeated observations on (a subset of) the same patients over time in retrospective claims data, allows the use of fixed-effect or random-effects variance components models to adjust for patient-specific unobservables.132 GIanfrancesco et al. did not take advantage of the additional precision that these repeated episodes per patient adds to the estimation process. Moreover, they treat each episode as an independent event, ignoring issues of treatment switching and censoring of episode events.

Finally, it is often suggested that statistical test adjustments such as the Bonferroni correction for multiple comparisons should be undertaken when evaluating the coefficients in multivariate regression analyses and with multiple patient subgroups.31 Such statistical corrections are often much too drastic and substantially increase the risk of type II errors (failing to detect an effect that is truly there). As Ken Rothman, the editor of Epidemiology, stated:

The theoretical basis for advocating a routine adjustment for multiple comparisons is the “universal null hypothesis” that “chance” serves as the first-order explanation for observed phenomena. This hypothesis undermines the basic premises of empirical research, which holds that nature follows regular laws that may be studied through observations. A policy of not making adjustments for multiple comparisons is preferable because it will lead to fewer errors of interpretation when the data under evaluation are not random numbers but actual observations on nature. Furthermore, scientists should not be so reluctant to explore leads that may turn out to be wrong that they penalize themselves by missing possibly important findings.31

All of these econometric issues increase the complexity of statistical inference dramatically when using retrospective claims data, particularly in comparison to statistical analysis of RCTs. The variety and complexity of statistical tools and alternatives that can plausibly be brought to bear on any given estimation problem create the additional concern that if one has many different estimation procedures at hand, it is easy and tempting to find some sequence of estimation methods that achieves the “predetermined” answer, while ignoring other estimation methods. Any retrospective database provides the overly enthusiastic analyst with ample opportunity to “torture the data until it reveals the truth.”2

However, bootstrapping and split-sample validation of model results provide a more balanced and robust assessment of model parameter precision and safeguard the estimates against such inappropriate “overfitting.” In any case, with all of the recent econometric advances in health care cost analysis, it is unacceptable to simply ignore retrospective data analysis issues such as (1) treatment selection bias, (2) log-cost or other power transformation bias, (3) variance components models with repeated observations, or (4) data censoring issues. When application of alternative reasonable estimation approaches give similar answers, one can conclude that the results are robust. When different plausible estimators give very different answers, it is difficult to draw any conclusions from the estimates. Given all of these issues, it is never acceptable to present a single econometric model estimate, just as in cost-effectiveness analysis it would not be acceptable to present model point estimates without running appropriate model sensitivity analysis. The value of any statistical analysis is not to generate the “correct” answer but to show what range of parameters are plausible, given the available information.

Joel W. Hay, PhD
Associate Professor
Department of Pharmaceutical Economics and Policy
University of Southern California School of Pharmacy
1960 East Al материалов St., CHP 140
Los Angeles, CA 90033
jhay@usc.edu

DISCLOSURES
The author discloses no potential bias or conflicts of interest relating to this editorial.

REFERENCES
Prior Authorization and the Formulary Exception Process—Examples From the Real World

Managed care organizations (MCOs) are constantly faced with the challenge of balancing cost savings generated by prior authorization (PA) programs and formulary decisions with member disruption, physician disruption, employer group concerns, and the administrative costs of running the program itself, while complying with all pertinent legal and regulatory requirements. The goals of these programs are fairly straightforward—to encourage and provide coverage for the best quality care at the lowest overall price. In this issue of JMCP, the Professional Practice Committee of the Academy of Managed Care Pharmacy describes prior authorization as applied to pharmacy benefits management and the formulary exception process.

The tools MCOs have available to attain the same or better clinical or service outcomes at lower cost comprise more than PA and formulary management. Other tools include quantity limits, step-care protocols, copay tiers, coinurance, deductibles, provider network access, concurrent and retrospective drug utilization review (DUR) programs, physician profiling, case management, disease state management, and various strategies that promote the effective use of generic drugs. Each of these programs alone can have an impact, but maximum value is realized when careful coordination of all these programs is woven together to create a comprehensive management plan that benefits the members, providers, employer groups, and the health plan.

Examination of the medical literature reveals articles that illustrate the clear cost benefit of these aforementioned programs, while other articles question their effectiveness and value. MCOs implement these utilization management principles for one primary reason—they work. Unlike in academia, the locus of many MCOs is not to publish but to provide value to employer groups and individual members while generating a financial return on investment for the MCO. Thus, much of the cost-savings data associated with managed care interventions are not available in the published literature. An increased interest is now emerging in the managed care community to publish the benefits of these programs so that others may take advantage of successful programs or avoid investing in interventions that are found to be inefficient or insufficient.

MCOs are searching for new and innovative ways to continue these management programs while keeping the administrative costs to a minimum. Many MCOs’ efforts have turned to automation of PA and nonformulary criteria when feasible. The automation process for pharmacy benefits involves the application of coverage criteria as the pharmacy claim is submitted electronically (online) by the pharmacy provider at the point of service. Automation is particularly efficient when used for programs where the diagnosis can be inferred by surrogate drug markers or in situations where other medications need to be used first. Beta-blockers are not a good surrogate marker for identifying members with congestive heart failure because of the numerous other potential indications for their use, ranging from hypertension to migraine headache prophylaxis, but insulin is a good surrogate marker for a diagnosis of diabetes because of its very low potential for off-label use.

Two common classes of medications that present good opportunities for automating approval criteria include the cyclooxygenase 2 (COX-2) inhibitors and the leukotriene receptor antagonists (LRAs). Given the recent attention to the COX-2 inhibitors, including the market withdrawal of Vioxx on September 30, 2004, and Bextra on April 7, 2005, drug use management of this class becomes more important for patient safety reasons. Although there is no evidence to show that the COX-2 inhibitors are more clinically effective than nonsteroidal anti-inflammatory drugs (NSAIDs), they may be safer in patients who are at a high risk for developing a gastrointestinal (GI) bleed. Many MCOs provide coverage for the COX-2 inhibitors when the member is at higher risk of a GI bleed, e.g., older than 65 years, receiving concomitant therapy with an anticoagulant, or having previously tried generic prescription NSAIDs.

Automation is particularly useful in this situation because the requisite information is readily available in the drug claims processing system. The date of birth is required for all pharmacy claims, permitting instant identification of persons potentially at greater risk for a GI adverse event because of advanced age. The claims processing system can be programmed to recognize a list of NSAIDs and anticoagulants and determine if there are previous or concurrent pharmacy claims for those medications within a predetermined time frame. If there are claims for those targeted medications in the member’s profile, the system will automatically allow payment for the COX-2 inhibitor pharmacy claim, requiring no paperwork or other intervention.

The standard request process—via paper or phone call—would remain necessary for those members with other medical conditions (e.g., previous ulcers) that would normally be eligible for coverage but the relevant information is not captured in the pharmacy claims data. Still, the use of pharmacy claims history significantly reduces the administrative burden (hassle factor) associated with PA for pharmacists, members, and prescribers.

Similarly, the LRA class of drugs presents a great opportunity for criteria automation. If the MCOs’ drug benefit plan covers LRAs for asthma or allergic rhinitis, surrogate drug markers can be used to identify those members in each category. If the MCOs criteria allow for coverage of the LRAs as a first- or second-line option for the treatment of asthma, the computer system can screen prior pharmacy claims for medications such as albuterol or inhaled corticosteroids. Since it is unlikely that these products are being used to treat a condition other than asthma, the system can be programmed to automatically
approve coverage and pay an electronic claim for an LRA when there are concurrent or prior pharmacy claims for these products.13

Published data suggest that LRAs are equal to or less effective than nasal steroids or oral antihistamines when used to treat allergic rhinitis.14 If the MCO covers the LRA as a second- or third-line treatment for allergic rhinitis, the system can be programmed to scan for prior claims for oral antihistamines or intranasal corticosteroids. Despite the differences in indications and the use of various alternatives that may be required first, the automatic approval process that evaluates previous claims remains the same. The authorization occurs without any intervention from the pharmacist, physician, or MCO as long as the necessary member information is in the pharmacy claims database.

The benefits and implications of automation are significant, and many MCOs continue to look for opportunities to add more of these programs while transitioning existing manual PAs to an automated platform. The most prominent advantage of automation of approval criteria is that it allows for continued management of high-cost, highly utilized medications at the point of service and eliminates the unnecessary rejection of claims, which results in decreased member disruption and dissatisfaction with the benefits. All automatic approvals are invisible to the member, physician, and dispensing pharmacist. Automation decreases the time involved by the dispensing pharmacist and the physician because it removes paperwork and phone calls from the appeals process, thus allowing pharmacists and physicians more time to take care of patients. Automation also decreases the administrative burden on MCOs, permitting reallocation of resources to effectively manage other medications and disease states.

It is important to remember that the goal is to focus resources and management strategies on the areas where the most impact can be obtained with the least amount of hassle and incursion on providers of care. Automation allows the MCO to continue to effectively manage a variety of medications and conditions but with less time and effort for all parties involved. The ultimate goal of any PA, nonformulary, quantity limit, and other pharmacy benefit management tool is to promote appropriate utilization while keeping prescription drug benefits affordable.

It is important to be selective in the choice of programs to automate. The potential benefits of automation in PA criteria, nonformulary criteria, step-care, and other pharmacy benefit management strategies are only partially realized because there are limitations. For example, new members to a health plan have no administrative claims history from which to apply prior-use criteria. Furthermore, existing members may experience significant changes in their pharmacy benefits. Members may change group enrollment, potentially removing the claims history in some claims processing systems if the primary member number changes as a result of a change in group enrollment. A manual process remains necessary for these situations.

Pharmacy Benefits Management

and the Medicare Modernization Act

The Medicare Modernization Act provides a new set of challenges for physicians, pharmacists, and MCOs. The Centers for Medicare and Medicaid Services (CMS) states that health plans may implement various utilization management techniques (PA, quantity limits, etc.) and various formulary designs, which represent the cornerstone of any pharmacy benefits management program.15 CMS recognizes that these management techniques exist and provide for good clinical and financial management of the pharmacy benefit. The criteria that are used to evaluate the exception requests must be supported by evidence-based literature and sound clinical rationale.

CMS supports multiple formulary benefit designs as long as the base requirements for the formulary are met. For example, a complaint formulary will have at least 2 drugs per therapeutic category and class (when applicable), and the prescription drug plan (PDP) or Medicare Advantage Prescription Drug Plan (MA-PD) will have an established formulary coverage exceptions process to allow for a “medical necessity” review for nonformulary medications. “Medically necessary” is a somewhat ambiguous term that must be clearly defined by the plan’s policies for individual exception requests. The plan must be careful in its policy writing because those policies must address as many different clinical scenarios as possible.

The Medicare rule for exception requests has many implications for PDPs and the physician community. The PDPs criteria for copayment tier exceptions must take into consideration whether there is a therapeutically equivalent drug covered on the formulary and also must consider the number of drugs on the formulary that are in the same category as the requested drug. The requirements placed on physician requests are also outlined. A physician may request a copayment tier coverage exception by providing a supporting statement to the plan. This statement will need to explain why the formulary alternatives would not be as effective as the requested product and/or that the formulary products would result in an adverse event for the member. It is difficult to predict with certainty what the outcomes of any therapy will be in advance. Plans will have to be as specific as possible in their coverage exceptions criteria in order to clarify this grey area. The exceptions review process must remain consistent to ensure that the pharmacy benefit is administered uniformly to all members, while providing flexibility to accommodate providers and members in unique clinical situations. Plans and providers will be challenged to meet CMS’s regulatory requirements while continuing to do what is best for the individual member without incurring avoidable costs.
The copayment tier exceptions themselves pose some interesting questions. CMS states that tiering exceptions must be made when the higher-tier drugs are determined to be medically necessary. This will allow coverage for a higher-copayment-tier drug at a lower cost-sharing level when approved as medically necessary. Yet, PDPs and MA-PDVs have been granted authority to designate copayment tier(s) for certain high-cost or unique otherwise drugs that are exempt from the copayment tier exceptions process. Overland on the medical exceptions process are the complexities of financial coverage in Medicare Part D, including the $250 annual deductible and the “doughnut hole” area of its benefits (i.e., no coverage for drug costs between $2,250 and $5,100).

The Academy of Managed Care Pharmacy (AMCP) has published a summary of the CMS regulations in order to help clarify some of these issues. This information can be found in the members’ area of AMCP’s Web site: http://www.amcp.org. Updates on these regulations and additional information can be found at CMS’s Web site: http://www.cms.hhs.gov.

As Medicare Part D unfolds, beginning on January 1, 2006, there will be a great influx of members who are new to pharmacy benefits, and all Medicare members will be “new” to the complex Medicare Part D benefit. PDPs and MA-PDVs will be challenged unlike never before in managing these pharmacy benefits, including the large volume of claims and exception requests that will occur. Developing and maintaining solid clinical utilization management programs and using tools like automation will be paramount to delivering quality customer service and positive clinical outcomes.

Eric J. Calley
PharmD
DUR Clinical Pharmacy Specialist
Highmark BlueShield
120 Fifth Ave., Suite 1122
Pittsburgh, PA 15222
eric.calley@highmark.com

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

REFERENCES