
Financial Risk Relationships and Adoption of Management Strategies in Physician Groups for Self-Administered Injectable Drugs

Unmet Needs in the Treatment of Allergic Asthma: Potential Role of Novel Biologic Therapies

Determinants of the Cost-Effectiveness of Statins

Longitudinal Assessment of a Diabetes Care Management System in an Integrated Health Network

Examination of the Evidence for Off-Label Use of Gabapentin
CONTENTS

ORIGINAL RESEARCH

   Catherine C. Peng, PharmD, BCPS; Peter A. Glassman, MBBS, MSC; Iny R. Marks, PharmD; Curtis Fowler, PharmD; Brenda Castiglione, PharmD; and Chester B. Good, MD, MPH, FACP

523 Financial Risk Relationships and Adoption of Management Strategies in Physician Groups for Self-Administered Injectable Drugs
   Jonathan D. Agnew, PhD; Marilyn R. Stebbins, PharmD; David E. Hickman, PharmD; and Helene Levens Lipton, PhD

SUBJECT REVIEW

534 Unmet Needs in the Treatment of Allergic Asthma: Potential Role of Novel Biologic Therapies
   William W. Storms, MD

FORMULARY MANAGEMENT

544 Determinants of the Cost-Effectiveness of Statins
   Alan Morrison, PhD, and Helene Glassberg, MD

CONTEMPORARY SUBJECTS

552 Longitudinal Assessment of a Diabetes Care Management System in an Integrated Health Network
   David L. Larsen, RN, MHA; Wayne Cannon, MD; and Steven Towner, MD

559 Examination of the Evidence for Off-Label Use of Gabapentin
   Alicia Mack, PharmD

DEPARTMENTS

502 Cover Impressions
   A Dash for the Timber (1889)
   Frederic Remington
   Sheila Macho

569 Editorials
   • Gabapentin May Be Appropriate for Off-Label Uses
     Shawn Davis, (PharmD Candidate)
   • Use of Drugs for Off-Label Indications: Living in the Same World
     John P. Barbuto, MD

572 Editorial Subjects—In This Issue
   • Contractual Arrangements Between HMOs and Medical Groups to Manage Drug Costs

576 Letters

578 Article Index by Subject Category
All articles in JMCP undergo peer review. Letters may be peer reviewed to ensure accuracy. The fundamental departments for manuscript submission are:

- Original Research
- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Editorials
- Letters

For manuscript preparation requirements, see “JMCP Author Guidelines” in this Journal or at www.amcp.org/jmcp/ag/pdf.

These are well-referenced articles based on 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.

These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy.

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 and may include description and interpretation of clinical evidence.

These are well-referenced submissions that describe pilot projects or other subjects that are not intended to be comprehensive reviews of the subject.

Editorials should be relevant to managed care pharmacy and address a topic of contemporary interest; these submissions are peer reviewed.

These submissions may be peer reviewed for accuracy. If the letter addresses a previously published article, an author response may be appropriate.

JMCP employs extensive bias-management procedures that include (a) full disclosure of all sources of potential bias and conflicts of interest, nonfinancial as well as financial; (b) full disclosure of potential conflicts of interest by reviewers as well as authors; and (c) accurate attribution of each author’s contribution to the article. Aggressive bias-management methods are necessary to ensure the integrity and reliability of published work.

Editorial content is determined by the Editor-in-Chief with suggestions from the Editorial Advisory Board. The views and opinions expressed in JMCP do not necessarily reflect or represent official policy of the Academy of Managed Care Pharmacy or the authors’ institutions, unless specifically stated.

A copy of the full advertising policy for JMCP is available from AMCP headquarters and the Advertising Representative. All aspects of the advertising sales and solicitation process are completely independent of the editorial process. Advertising is positioned either at the front of the Journal or is not accepted for placement opposite or near subject-related editorial copy.

Employees of advertisers may submit articles for publication in the editorial sections of JMCP, subject to the usual peer review process. Financial disclosure, conflict-of-interest statements, and author attestations are required when manuscripts are submitted, and these disclosures generally accompany the article in abstracted form if the article is published.
JMCP Author Guidelines

JMCP accepts for consideration manuscripts prepared according to the Uniform Requirements for the Submission of Manuscripts to Biomedical Journals.1

Manuscript Preparation

Manuscripts should include, in this order, a title page; an abstract of no more than 400 words; text, references, tables, figures, and graphs; and financial disclosures and conflicts of interest (see Submission Checklist for details).

JMCP abstracts should be written narratives that contain the information described for each type of article shown below, where applicable. For descriptions of editorial content, see “JMCP Editorial Policy” in this Journal or at www.amcp.org/jmcp/ep.pdf.

Original Research
An abstract is required in the format of:
- Objective
- Methods
- Results

Subject Reviews
An abstract is required, generally in the format of:
- Objective
- Conclusion
- Keywords

Formulary Management
An abstract is required in the format of Original Research or Subject Reviews, depending upon the subject matter.

Contemporary Subjects
An abstract is required in the format of Original Research or Subject Reviews, depending upon the subject matter.

Editorials
These submissions require no abstract.

Letters
These submissions require no abstract or title page.

Reference Style

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

1. Standard journal article
(List all authors when 6 or less; if more than 6, list only the first 3 and add et al.)

2. No author given

3. Journal paginated by issue
Corrigan PW, Luchins DJ, Malan RD, Harris J.


4. Book or monograph by authors

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

6. Chapter in a book

7. Government agency publication

8. Dissertation or thesis

9. Paper (or Poster) presented at a meeting
Reagan ME. Workers’ compensation, managed care, and reform. Paper (poster) presented at: 1995 AMCRA Midyear Managed Care Summit; March 13, 1995; San Diego, CA.

Submission of Manuscripts

A paper copy of the manuscript, including originals of figures and tables, should be submitted to the JMCP Peer Review Administrator at the Academy of Managed Care Pharmacy at 100 North Pitt Street, Suite 400, Alexandria, VA 22314. Tel: (800) 827-2627 or (703) 683-8416 or Fax: (703) 683-8417. The paper copy is necessary to ensure proper presentation and placement of text, figures, tables, and graphs. Please send an electronic version of the manuscript, either on a disk or via e-mail, to jmcpreview@amcp.org. All text should be in a word processing program (preferably Microsoft Word). Tabular material also should be in a word processing program using the tab function to create columns, not using “tables” or “cells.” Figures should be saved in Photoshop or Illustrator and may be re-created by us. We can accept PowerPoint graphics. Please identify the format (PC or MAC), all programs used, and all file names.

Cover letter: the corresponding author should
- briefly describe the importance and scope of the manuscript,
- certify that the paper has not been accepted for publication or published previously and that it is not under consideration by any other publication, and
- identify the nature and extent of any financial interest or affiliation that any author has with any company, product, or service discussed in the manuscript.

All manuscripts are reviewed prior to peer review. Manuscripts may be returned to authors prior to peer review for clarification or other revisions. Peer review generally requires 4 weeks but may extend as long as 8 weeks in unusual cases. Solicited manuscripts are subject to the same peer-review standards and editorial policy as unsolicited manuscripts.

Submission Checklist

Before submitting your manuscript to the Journal of Managed Care Pharmacy, please check to see that your package includes the following:

- Cover letter
- Manuscript: prepared in 10- or 12-point type, double-spaced (on disk or sent via e-mail to jmcpreview@amcp.org), including
  - title page with identification of all authors (with academic degrees and preferred credentials, position title, name of employer, city and state) and complete contact information for the corresponding author (mailing address, telephone and fax numbers, and e-mail address)
- abstract: no more than 400 words
- keywords: follows the abstract
- references: cited in numerical order as they appear in the text and prepared following modified AMA style
- tables and figures (generally no more than a total of 6). Submit referenced tables and figures on separate pages with titles (and captions, as necessary); match symbols in tables and figures to explanatory notes, if included
- Disclosures and conflict of interest: completed and signed author attestation forms (available at www.amcp.org/jmcp/ep.pdf); clearly indicate source(s) of funding and financial support.

REFERENCE


www.amcp.org   Vol. 9, No. 6  November/December  2003  JMCP  Journal of Managed Care Pharmacy  507

CATHERINE C. PENG, PharmD, BCPS; PETER A. GLASSMAN, MBBS, MSc; INY R. MARKS, PharmD; CURTIS FOWLER, PharmD; BRENDA CASTIGLIONE, PharmD; and CHESTER B. GOOD, MD, MPH, FACP

ABSTRACT

OBJECTIVE: To determine the incidence of clinically relevant potential drug-drug interactions (DDIs) in a large population of ambulatory patients utilizing a computerized, retrospective drug utilization review (DUR) program followed by clinical pharmacist audit.

METHODS: The drug claims database included approximately 2.9 million patients with more than 30 million prescriptions dispensed in the 12-month period from September 2001 through August 2002. Cases were identified by a computerized, retrospective DUR program with embedded triggers to detect 69 prespecified potentially serious DDIs, with “serious” defined as an interaction that would likely require a change in therapy or use of additional clinical or laboratory monitoring. Two types of automated, computerized assessments were conducted: the first simply detected coprescribed drug pairs, and the second assessment used more sophisticated filters to reduce false positive alerts for coprescribed drug pairs. Clinical pharmacist audit then determined the final incidence of clinically relevant warnings; in this audit, coprescribed drug pairs were defined as clinically relevant if they could cause potentially serious DDIs.

RESULTS: Eighteen drug pairs had insufficient cases for inclusion, leaving 51 drug pairs for evaluation. A total of 244,703 cases of potential DDIs were identified (0.8% of total prescription claims) by simple automated screens. More sophisticated DDI filters reduced the 244,703 potential DDIs by 70.8%, to a total of 65,544 pairs (0.2% of total prescription claims). Clinical pharmacist review reduced the number of potential DDIs by an additional 80.6%, to 12,722 drug pairs (0.04% of total prescription claims) deemed clinically relevant. The combination of sophisticated DDI filters and clinical pharmacist review reduced the incidence of potentially serious DDIs by 94.3%.

CONCLUSION: The incidence of potentially serious DDIs is relatively low (less than 1%) among ambulatory patients; however, the incidence depends on the method of case finding. Retrospective DUR programs, especially those with additional automated filters or that utilize additional pharmacist review, appear to be important screening tools in determining true rates of coprescribed drug pairs that can lead to potentially serious DDIs.

KEYWORDS: Drug utilization review, Drug-drug interactions, Medication errors, Ambulatory care

J Managed Care Pharm. 2003;9(6):513-22

The incidence of potentially serious DDIs is relatively low (less than 1%) among ambulatory patients; however, the incidence depends on the method of case finding. Retrospective DUR programs, especially those with additional automated filters or that utilize additional pharmacist review, appear to be important screening tools in determining true rates of coprescribed drug pairs that can lead to potentially serious DDIs.

Authors

CATHERINE C. PENG, PharmD, BCPS, is clinical specialist; INY R. MARKS, PharmD, is clinical product development specialist; CURTIS FOWLER, PharmD, is manager of clinical product development; and BRENDA CASTIGLIONE, PharmD, is director of clinical services, Clinical Services Department, Eckerd Health Services, Pittsburgh, Pennsylvania. PETER A. GLASSMAN, MBBS, MSc, is staff physician, Division of General Internal Medicine, VA Greater Los Angeles, West LA Campus, Los Angeles, California, and associate professor of medicine, University of California Los Angeles School of Medicine; CHESTER B. GOOD, MD, MPH, FACP, is chairperson of the Medical Advisory Panel, Department of Veterans Affairs and staff physician, Division of General Internal Medicine, VA Pittsburgh Health Care System, Pittsburgh, Pennsylvania, and associate professor of medicine and pharmacy, University of Pittsburgh School of Medicine.

AUTHOR CORRESPONDENCE AND REPRINT REQUESTS: Iny Marks, PharmD, Eckerd Health Services, 620 Epsilon Dr., Pittsburgh, Pennsylvania 15238. Tel: (800) 814-6600, ext. 5023; Fax: (412) 968-2691; E-mail: imarks@ehs.com

Copyright© 2003, Academy of Managed Care Pharmacy. All rights reserved.
Methods

The main issues in accurately determining the incidence of DDIs in ambulatory patients are primarily 2-fold. First, evaluations should be prospective and based on a prespecified set of drug pairs. Second, large populations of patients are required to find sufficient DDIs to establish incident rates. In addition to these 2 necessary factors, sufficient technology is required to preliminarily evaluate and categorize potential cases of DDIs. Moreover, some type of secondary audit should occur to confirm the findings of preliminary assessments.

Claims-based analysis using computerized, retrospective drug utilization review (DUR) offers a powerful tool to better understand the incidence of potential DDIs as well as other types of potential medication errors. Yet, despite the popularity of such programs in both the private and public health care sectors, very little data are available on the detection of potential DDIs in ambulatory patients.

Several studies have attempted to assess the effectiveness of small and focused DUR programs. For instance, one recent study by Curtis et al. looked at overlapping prescriptions of drugs that may prolong the cardiac QT interval, a measure of the ventricular refractory period on an electrocardiogram associated with life-threatening ventricular arrhythmias. Still, there are little available data on specific DDIs found in various populations. Sharing these data would not only assist in determining which coprescribed drug pairs to target for intervention but also would assist in developing and tracking the success of DUR intervention programs across the United States.

Our study presents data on more than 50 potentially serious DDIs found in a subset of approximately 2.9 million persons, covered mainly by self-funded employer groups and health plans, over the course of 1 year. The study describes the case finding rates for potential drug interaction pairs, generated by a computerized, retrospective DUR system using programmed criteria, before and after pharmacist assessment. It is our hope that detailing the data on case findings of potential DDIs at various steps in the detection process will assist others in determining how to develop and optimize such DUR programs.

The Retrospective DUR Program

A pharmacy benefits management (PBM) company used a computerized, retrospective DUR program to monitor and intervene in cases of potentially serious DDIs. This DUR program was established in 1999 and continues as an ongoing program within the PBM; however, for the purposes of this study, a 1-year period of time was chosen to determine the incidence of potentially serious DDIs. This program does not involve electronic or other alert messages sent to dispensing pharmacies at the point of sale and is separate from such concurrent alerts. The database for the retrospective DUR program included claims submitted for prescription medications dispensed from more than 56,000 community pharmacies and 3 mail-service facilities in the PBM’s pharmacy network. Claims data were updated daily. The DUR program assessed prescription claims each night, allowing for case review within 1 business day after claims were submitted. Available data on prescriptions included selected patient demographics, physician identification, and the name, strength, and quantity of the medications dispensed.

Interventions on potential DDIs were routinely conducted by mail, with alert letters sent to the prescribing clinicians. The alert letter not only described the potential interaction but also the underlying mechanism of that interaction, the possible consequent adverse drug event(s), and recommendation(s) on how the interaction may be avoided or managed. For example, the alert letter on the potential interaction between amiodarone and warfarin informs providers that amiodarone can increase the hypoprothrombinemic response by decreasing the hepatic clearance of warfarin and, hence, the addition of amiodarone to existing warfarin therapy can increase the prothrombin time by 50% to 100%. The letter continues with a recommendation to reduce the warfarin dose by 30% to 50%.

Clinically relevant coprescribed drug pairs were defined as those that could cause a potentially serious DDI. A DDI was defined by the following standard: a “pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the 2 agents when given alone. The clinical result of a DDI may manifest as antagonism, synergism, or idiosyncratic.”

For this DUR intervention program, we utilized standard references to determine possible clinically relevant coprescribed drug pairs, with specific drug pairs then chosen for inclusion into the restrospective DUR program by PBM clinical pharmacists in collaboration with an independent advisory board of practicing physicians and external clinical pharmacists. The advisory board consisted of 5 physicians with specialties in general internal medicine (one of whom had a background in pharmacology), gastroenterology, and endocrinology and 2 external clinical pharmacists. Priority was given to coprescribed drug pairs that were either absolutely contraindicated or that, when an interaction occurred, were more likely to cause a serious interaction.

A “serious” interaction was defined as potentially life or organ threatening, as described in at least 1 commonly used standard drug safety reference. Additionally, a “serious” interaction would likely require a change in therapy or require additional clinical or laboratory monitoring.

Although the underlying mechanisms of interactions and subsequent harm varied among the drug pairs, the common theme in choosing drug pairs was to include those that have the potential to result in emergency treatment, hospitalization, permanent harm, or death. The general classification and definition of the categories of coprescribed drug pairs are shown in Table 1. Classification into the 6 categories was based on the management of the potential DDI.
Case Finding of Drug Pairs

Case finding of potentially interacting drug pairs proceeded through 3 assessments. The initial 2 assessments were automated, and the third was a manual review conducted by 4 trained clinical pharmacists. The pharmacists were trained by a senior pharmacist who was also the clinical program operations manager. The training included a structured curriculum that utilized standardized reference materials on identifying, classifying, and managing DDIs as well as a proprietary manual on DUR protocols. Pharmacists were also specifically trained to evaluate the managing DDIs as well as a proprietary manual on DUR proto-

The automated software first searched the claims database to preliminarily identify instances where patients may have been receiving overlapping prescriptions for the 2 specified medications in a given drug pair. In practical terms, this first step of automation provided an initial incidence of 2 potentially dangerous coprescribed drugs. For instance, one system check reviewed individuals with active prescriptions for warfarin and fluconazole, a drug pair with a known DDI.

Second, for each possible concomitant drug pair, a set of additional automated filters was used to help improve accuracy by determining which pairs were likely to be clinically relevant (i.e., have a true potential to cause a clinically relevant interaction). For example, 1 basic filter ensured that there were at least 5 days of potential overlap for specific drug pairs. Therefore, this filter would exclude any patient who was taking warfarin chronically and received only a single dose of fluconazole for the treatment of candidiasis.

These systematic filters varied depending on the drug pair targeted, but the goal of each set of filters was to reduce clinically irrelevant cases (i.e., to increase specificity). Other filters at this stage included assessing total drug dose (e.g., methotrexate of at least 15 mg per week with a nonsteroidal anti-inflammatory drug, or simvastatin of at least 20 mg daily with amiodarone) and duration of drug therapy (e.g., carbamazepine with a duration of therapy for at least 90 days and a macrolide antibiotic, or warfarin with a duration of therapy for at least 90 days and a thyroid product).

After the automated filters identified potentially relevant drug pairs, a clinical pharmacist reviewed the remaining cases. The goal was to ensure that any intervention requiring clinician contact involved a high likelihood of a true positive warning. Common reasons for cases to result in a subsequent pharmacist intervention or no pharmacist intervention (i.e., sending an alert letter or not sending an alert letter to clinicians on a potential DDI) may be found in Table 2. As a matter of due diligence, the reviewing pharmacist confirms the duration of overlap for the coprescribed drug pairs as well as identifies any prior concomitant use of a drug pair and prior warnings to the relevant clinician(s) concerning that drug pair. Thus, an alert letter would not be sent if a prescribing clinician had already been informed of the potential interaction for the same patient within a period of 3 months.

Data on results of pharmacist interventions are maintained in a longitudinal database that is part of the DUR system. For those interventions that were considered clinically relevant based on pharmacist review, an alert letter was sent by regular mail within 24 hours of review. The pharmacist review provides the closest estimation of a gold standard for the true incidence of clinically relevant coprescribed drug pairs within the pertinent patient population.

Data Analysis

There were 69 active drug pairs in the retrospective DUR program during the study period; however, for the present study, 18 drug pairs were excluded for the following reasons: (1) there were no initial case finding of the coprescribed drug pairs in the claims database, (2) there were fewer than 10 initially identified cases and no pharmacist interventions, or (3) the drug pairs had been in the system for less than 1 year and had fewer than 100 initial case findings. Excluded drug pairs, along with the reason for exclusion, are shown in Table 3.

Incidence of clinically relevant potential interactions in the study population was assessed in 3 ways, utilizing 2 denomina-
Common Examples of Why Alert Letters Were Sent or Not Sent to Physicians

<table>
<thead>
<tr>
<th>Alert Letter Sent to Physician(s) (Pharmacist Intervention)</th>
<th>No Alert Letter Sent to Physician(s) (No Pharmacist Intervention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple physicians involved with the prescribing of medications with potential DDIs</td>
<td>Patient has been maintained on both medications in a drug pair for an extended period of time, with time periods specific for each drug pair</td>
</tr>
<tr>
<td>Multiple pharmacies involved with the dispensing of potentially interacting medications</td>
<td>Prior intervention (alert letter sent to the relevant clinician) within the past 3 months</td>
</tr>
<tr>
<td>Greater than a specified number of days overlap between potentially interacting medications, with days overlap specific to each drug pair</td>
<td>Past response from a clinician that indicates the patient is being closely monitored for a potential DDI</td>
</tr>
<tr>
<td>No previous history of an intervention (alert letter sent to physician) for a potential DDI in a patient</td>
<td>Past response from clinician that indicates the combination is medically necessary (benefits outweigh risks)</td>
</tr>
</tbody>
</table>

Drug Pairs With No Initial Case Findings

- MAOIs* – Anorexiants
- Penicillins – Tetracyclines
- Protease inhibitors – Ergot alkaloids
- Ritonavir – Amiodarone
- Ritonavir – Clozapine
- Ritonavir – Bepridil
- Ritonavir – Quinidine
- Methotrexate – Penicillins
- Bosentan – Cyclosporine
- Warfarin – Clofibrate

Drug Pairs With <10 Initial Case Findings and No Pharmacist Intervention

- Cyclosporine – Rifampin
- Meperidine – MAOIs
- Protease inhibitors – Rifabutin
- Protease inhibitors – Rifampin
- Selegiline – Mepredine

Drug Pairs With <100 Initial Case Findings and <1-Year-Old in the Retrospective DUR System

- Protease inhibitors – Oral contraceptives
- Methotrexate – Probenecid
- Bosentan – Glyburide

*MAOIs = monoamine oxidase inhibitors.

Table 2

Table 3


The study population contained an average of 2,889,000 members (48% male) that were eligible for the retrospective DUR program during the 12-month study period from September 1, 2001, through August 31, 2002; of those individuals, 2,026,000 members (70% of eligible members) had utilized their prescription benefits at least once over the study time period and, thus, were included for screening of clinically relevant potential DDIs. The total number of prescription claims utilized by those individuals was 30,174,549.

Over the course of 1 year, the first automated assessment found 244,703 cases of potential interactions for the 51 pre-specified drug pairs out of a total of 30,174,549 prescription claims (0.8%) and for 2,026,000 patients (12.1%) (Table 4). Systematic software filters reduced this count from 244,703 to 65,544 cases (27% of those drug pairs initially identified), giving a revised overall incidence of 2 per 1,000 prescriptions (0.2%) and 32 per 1,000 patients (3.2%).

Pharmacist reviewers evaluated the 65,544 cases and, of those, 12,722 cases (6% of those drug pairs initially identified) were considered to be potentially clinically relevant (i.e., true positive alerts), requiring an intervention with the relevant prescriber(s). Thus, the final incidence was 0.4 per 1,000 claims (0.04%) and 6.3 per 1,000 patients (0.6%) (Table 4).

Among all drug pairs, the overall true positive case finding rate (percentage of cases resulting in intervention divided by cases reviewed by a pharmacist) was 19% (12,722 of 65,544 cases; range 0% to 100% for each specific drug pair), which led to 22,364 alert letters sent to relevant prescribing clinicians over the course of the year. The true positive case finding rates by individual drug-pair categories for cases reviewed by a pharmacist (see Table 1 for definition of categories) were as follows: 65% for Category I drug pairs, 21% for Category II drug pairs, 50% for Category III drug pairs, 10% for Category IV drug pairs, 21% for Category V drug pairs, and 9% for Category VI drug pairs. Table 5 shows the top 10 drug interaction pairs by the incident rate per 1,000 prescription claims, after clinical pharmacist review.

Table 4

Table 5

Results
### Table 4: Results of Investigation of Potential Drug-Drug Interactions From September 1, 2001, to August 31, 2002

<table>
<thead>
<tr>
<th>Coprescribed Drug Pairs</th>
<th>Number of Initial Coprescribed Drug Pairs Identified by DUR System</th>
<th>Number of Coprescribed Drug Pairs After Automated Filters</th>
<th>Number of Coprescribed Drug Pairs Clinically Relevant by Pharmacist Review</th>
<th>True Positive Rate of Case Finding (%)</th>
<th>Incidence per 1,000 Patients†</th>
<th>Incidence per 1,000 Prescription Claims†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug 1</td>
<td>Drug 2</td>
<td>Category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Loop diuretics</td>
<td>IV</td>
<td>77,237</td>
<td>10,872</td>
<td>8</td>
<td>0.4210</td>
</tr>
<tr>
<td>HMG CoAs</td>
<td>Gemfibrozol</td>
<td>II</td>
<td>14,627</td>
<td>1,937</td>
<td>628</td>
<td>0.5404</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Beta-blockers</td>
<td>V</td>
<td>13,959</td>
<td>2,225</td>
<td>413</td>
<td>0.3100</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Amiodarone</td>
<td>IV</td>
<td>13,654</td>
<td>6,141</td>
<td>602</td>
<td>0.2038</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>Potassium</td>
<td>II</td>
<td>13,306</td>
<td>4,579</td>
<td>533</td>
<td>0.2630</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Verapamil</td>
<td>IV</td>
<td>13,108</td>
<td>834</td>
<td>77</td>
<td>0.3600</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Amiodarone</td>
<td>IV</td>
<td>11,366</td>
<td>4,001</td>
<td>335</td>
<td>0.1653</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>HMG CoAs</td>
<td>III</td>
<td>9,459</td>
<td>7,955</td>
<td>4,453</td>
<td>0.1797</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>SSRIs</td>
<td>V</td>
<td>6,210</td>
<td>3,083</td>
<td>695</td>
<td>0.3430</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>NSAIDs</td>
<td>V</td>
<td>4,289</td>
<td>256</td>
<td>31</td>
<td>0.0153</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Propafenone</td>
<td>VI</td>
<td>2,802</td>
<td>799</td>
<td>64</td>
<td>0.0316</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Quinidine</td>
<td>IV</td>
<td>2,390</td>
<td>534</td>
<td>18</td>
<td>0.0089</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Sulfonamides</td>
<td>III</td>
<td>2,286</td>
<td>1,714</td>
<td>547</td>
<td>0.2700</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Quinidine</td>
<td>III</td>
<td>1,295</td>
<td>337</td>
<td>28</td>
<td>0.0138</td>
</tr>
<tr>
<td>Lithium</td>
<td>NSAIDs</td>
<td>V</td>
<td>1,187</td>
<td>523</td>
<td>284</td>
<td>0.1402</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Fluconazole</td>
<td>IV</td>
<td>910</td>
<td>612</td>
<td>138</td>
<td>0.0681</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Carbamazepine</td>
<td>II</td>
<td>908</td>
<td>312</td>
<td>52</td>
<td>0.0256</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Barbirutine</td>
<td>VI</td>
<td>777</td>
<td>269</td>
<td>29</td>
<td>0.0143</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Cimetidine</td>
<td>III</td>
<td>772</td>
<td>319</td>
<td>54</td>
<td>0.0267</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Fluoroquinolones</td>
<td>II</td>
<td>767</td>
<td>548</td>
<td>200</td>
<td>0.0087</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Metronidazole</td>
<td>III</td>
<td>746</td>
<td>644</td>
<td>224</td>
<td>0.1106</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Zafirlukast</td>
<td>III</td>
<td>565</td>
<td>200</td>
<td>30</td>
<td>0.0148</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Erythromycin</td>
<td>IV</td>
<td>496</td>
<td>360</td>
<td>162</td>
<td>0.0799</td>
</tr>
<tr>
<td>TCAs</td>
<td>Clonidine</td>
<td>II</td>
<td>463</td>
<td>185</td>
<td>25</td>
<td>0.0124</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Sulfonamides</td>
<td>V</td>
<td>447</td>
<td>350</td>
<td>120</td>
<td>0.0592</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Nitrates</td>
<td>I</td>
<td>444</td>
<td>373</td>
<td>242</td>
<td>0.1194</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Quinidine</td>
<td>V</td>
<td>372</td>
<td>40</td>
<td>8</td>
<td>0.0039</td>
</tr>
<tr>
<td>Selegiline</td>
<td>SSRIs</td>
<td>II</td>
<td>342</td>
<td>24</td>
<td>9</td>
<td>0.0044</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>SSRIs</td>
<td>III</td>
<td>335</td>
<td>224</td>
<td>115</td>
<td>0.0567</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Macrolide antibiotics</td>
<td>II</td>
<td>326</td>
<td>246</td>
<td>169</td>
<td>0.0834</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Cyclosporine</td>
<td>V</td>
<td>276</td>
<td>109</td>
<td>8</td>
<td>0.0039</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Macrolide antibiotics</td>
<td>III</td>
<td>226</td>
<td>91</td>
<td>52</td>
<td>0.0257</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Capcetabine</td>
<td>IV</td>
<td>222</td>
<td>137</td>
<td>24</td>
<td>0.0118</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Cimetidine</td>
<td>VI</td>
<td>220</td>
<td>80</td>
<td>8</td>
<td>0.0039</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Azathiopurine</td>
<td>II</td>
<td>182</td>
<td>85</td>
<td>12</td>
<td>0.0060</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Phentoyin</td>
<td>IV</td>
<td>147</td>
<td>63</td>
<td>5</td>
<td>0.0025</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Salicylates/aspirin</td>
<td>II</td>
<td>134</td>
<td>3</td>
<td>0</td>
<td>0.0000</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Oral corticosteroids</td>
<td>V</td>
<td>129</td>
<td>88</td>
<td>27</td>
<td>0.0133</td>
</tr>
<tr>
<td>Ketonazole</td>
<td>H2RAs</td>
<td>V</td>
<td>89</td>
<td>74</td>
<td>24</td>
<td>0.0118</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Quinidine</td>
<td>IV</td>
<td>83</td>
<td>45</td>
<td>12</td>
<td>0.0060</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Venlafaxine</td>
<td>I</td>
<td>73</td>
<td>4</td>
<td>1</td>
<td>0.0004</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Cyclosporine</td>
<td>III</td>
<td>37</td>
<td>2</td>
<td>1</td>
<td>0.0004</td>
</tr>
<tr>
<td>Warfarin</td>
<td>17-alkyl androgens</td>
<td>IV</td>
<td>31</td>
<td>16</td>
<td>6</td>
<td>0.0029</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Oral contraceptives</td>
<td>V</td>
<td>30</td>
<td>12</td>
<td>11</td>
<td>0.0054</td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>Macrolide antibiotics</td>
<td>III</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>0.0049</td>
</tr>
<tr>
<td>MAOs</td>
<td>SSRIs</td>
<td>I</td>
<td>18</td>
<td>9</td>
<td>7</td>
<td>0.0034</td>
</tr>
<tr>
<td>MAOs</td>
<td>Amphetamine</td>
<td>I</td>
<td>12</td>
<td>7</td>
<td>4</td>
<td>0.0020</td>
</tr>
<tr>
<td>MAOs</td>
<td>Sumatriptan</td>
<td>II</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0.0010</td>
</tr>
<tr>
<td>MAOs</td>
<td>TCAs</td>
<td>I</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

| HMG CoAs = HMG CoA reductase inhibitors. | H2RAs = histamine-2 receptor antagonists. | SSRIs = selective serotonin reuptake inhibitors. | NSAIDs = nonsteroidal anti-inflammatory drugs. | TCAs = tricyclic antidepressants. |

* Case finding was determined by the number of coprescribed drug pairs considered clinically relevant by pharmacist review. The true positive rate of case finding was defined as the percentage of cases resulting in an intervention divided by total number of cases reviewed by a pharmacist for each drug pair (i.e., number of cases found by automated filters).

† The incidence was calculated by dividing the case finding rate, per pharmacist review, by eligible patients (2,026,000) or by prescription claims (30,174,549).
Discussion

Medication errors may have significant clinical and economic impact. While a medication error does not necessarily lead to an adverse drug event,\(^\text{30-32}\) it is estimated that 28% to 56% of adverse drug events are preventable.\(^\text{9,20-28}\) Among such errors, there is little doubt that the coprescribing of potentially interacting drugs can have devastating consequences.\(^\text{39}\) However, the incidence of such potential DDIs serious enough to lead to hospitalization or another measurable and serious adverse event remains unclear.

Composite estimates of serious DDIs have been around 2% to 3%,\(^\text{14,27}\) although a review by Jankel et al. found that the incidence may vary widely, with estimates from 2% to 17%, depending on the population assessed.\(^\text{14}\) The incidence of overlapping QT-interval-prolonging drugs found by Curtis et al. was 9.4%, but that figure, as pointed out by the authors, includes pairs with questionable clinical importance, and the assessment did not involve manual audit.\(^\text{19}\) Among the large and diverse outpatient population we assessed, we found that the incidence of clinically relevant potential DDIs was most likely between 6 and 32 cases per 1,000 patients (0.6% to 3.2%), depending on the type of audit method utilized (automation with and without pharmacist review).

Unfortunately, there are little supportive data on the incidence of potential DDIs in other large ambulatory populations. Few published studies have determined such errors exclusively,\(^\text{30-32}\) with most aggregating various types of potential medication errors. Many times, the determination of medication errors found in studies has been part of a planned intervention that might include medication selection or dosage assessment,\(^\text{30-32}\) laboratory monitoring,\(^\text{13,33,34}\) or inappropriate prescribing.\(^\text{12-13}\) Moreover, most studies on medication errors have involved interventions in hospitalized or institutionalized patients, but not in outpatients.\(^\text{2,7,13,20,31,35-37}\)

The available studies that have focused on potential DDIs in the outpatient setting have had methodological problems or other limitations that prevent epidemiological assessment.\(^\text{38,39}\) The study by Landorf et al. used retrospective case finding to assess 276 emergency room patients and found that 15% had a potential for a DDI.\(^\text{39}\) The study, while intriguing, was too small to be generalizable.

Research on ambulatory patients has often focused on either one or relatively few types of interactions.\(^\text{33,60-63}\) For instance, McMullin et al. assessed the incidence of dangerous coprescribed drug pairs involving cisapride, before and after a DDI screening program,\(^\text{62}\) and Schiff et al. looked at the prescribing of potassium to patients with high serum potassium levels.\(^\text{53}\) These assessments found the incident rates of DDIs to be around 2%. More recently, Curtis et al. studied the overlap of coprescribed QT-interval-prolonging agents in approximately 5 million outpatients and found an incidence of 9.4%.\(^\text{19}\) This important study, which also used a claims database and retrospective utilization review, included at least some interactions that would not be listed as “serious” in standard references. Thus, it is difficult to compare our results to those findings.

The lack of reliable population data has implications for drug safety improvement programs since, logically, intervention protocols should first and foremost focus on the most common serious coprescribing errors in a population. Clearly, it is difficult to optimize existing technology and methods of intervention without understanding how often a problem, or a potential problem, occurs. Surprisingly, there are little data from private or public health care sectors on the incidence of potential med-

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
Coprescribed Drug Interaction Pairs & Number of Cases Found by Pharmacist Review\(^\dagger\) (n) & Incidence per 1,000 Prescription Claims* & True Positive Rate of Case Finding\(^\ddagger\) (%) \\
\hline
Macrolide antibiotics & HMG CoAs & 4,453 & 0.1476 & 56 \\
Warfarin & Thyroid drugs & 1,095 & 0.0363 & 9 \\
Digoxin & Loop diuretics & 853 & 0.0283 & 8 \\
Sumatriptan & SSRIs & 695 & 0.0230 & 23 \\
HMG CoAs & Gemfibrozil & 628 & 0.0208 & 32 \\
Warfarin & Amiodarone & 602 & 0.0200 & 10 \\
Warfarin & Sulfonamides & 547 & 0.0181 & 32 \\
Potassium-sparing diuretics & Potassium & 533 & 0.0177 & 12 \\
Verapamil & Beta-blockers & 413 & 0.0137 & 19 \\
Digoxin & Amiodarone & 335 & 0.0111 & 8 \\
\hline
\end{tabular}
\caption{Top 10 Drug-Drug Interaction Pairs by Incidence per 1,000 Prescription Claims\(^*\)}
\end{table}

\(^\text{HMG CoAs = HMG CoA reductase inhibitors.} & \text{SSRIs = selective serotonin reuptake inhibitors.}\)
\(^\text{* The incidence was calculated by dividing the case finding rate, after pharmacist review, by total prescription claims (30,174,549).}\)
\(^\text{\dagger Case finding was determined by the number of coprescribed drug pairs considered clinically relevant by pharmacist review.}\)
\(^\text{\ddagger The true positive rate of case finding was defined as the percentage of cases resulting in an intervention divided by total number of cases reviewed by a pharmacist for each drug pair (i.e., number of cases found by automated filters).}\)
incidence errors that cause concern even though reliance on retrospective DUR programs is widespread.

As Schulman et al. euphemistically noted, the literature on the benefit of DUR is “underdeveloped,” echoing the findings of Soumerai and Lipton, who found that computer-based DUR programs have been “implemented without satisfactory evidence of . . . efficacy and safety.” Even so, DUR programs rapidly expanded into general use after 1990, when the Omnibus Budget Reconciliation Act (OBRA ’90) mandated states to provide such reviews for ambulatory Medicaid patients. Programs vary widely not only by the types of interventions performed but also by the frequency of reviews. These differences mitigate the potential for improving drug safety because, if for no other reason, there are little shared data among DUR users.

One of the most comprehensive assessments of medication errors in a large outpatient population has been the work by Monane et al. That study attempted to determine whether a computerized DUR intervention system could improve quality of pharmaceutical care in an elderly population. The interventions alerted pharmacists, trained in geriatrics, of potentially inappropriate medication use. The pharmacists subsequently contacted the prescribing physicians to inform them of the alert and discuss possible treatment alternatives. Based on their results (24% rate of change), Monane et al. concluded that interventions driven by an integrated DUR computer system and pharmacists contacting physicians improved prescribing patterns and increased quality of care.

We hope that our research, along with findings already published by Monane et al., and, most recently by Curtis et al., will increase awareness about the utility of using claims-based DUR programs to catalog the type and severity of various prescribing errors among ambulatory populations. We obviously would encourage other health care systems and PBM companies to release data on the incidence of coprescribing errors, however determined. Without such data, it is difficult to assess the success of various programs and intervention methods.

The present study has other important implications for those who wish to develop and optimize targeted DDI warning systems, regardless of whether or not utilization review is prospective, concurrent, or retrospective. As Peterson and Bates have noted, a high number of warnings that are not clinically relevant, or “noise,” may lead to alert fatigue.

Our data show how threshold points for sending an alert can change the proportion of clinically relevant alerts. More specifically, if an alert letter or an automated electronic warning, such as those found in some physician order-entry systems, were to be triggered at our highest sensitivity point, providers would be likely to receive many irrelevant warnings.

For example, the retrospective DUR program’s simplest automated system on active coprescriptions for digoxin and quinidine would have sent warnings to clinicians 2,390 times, while the more sophisticated automated system decreased the warnings by 78% to 534. Furthermore, if the true positive warning “signal” was best approximated by the pharmacist review, the number of true alerts was 18 (99% reduction of the initial 2,390 warnings). Put another way, pharmacist review in addition to the sophisticated automated DUR system resulted in a “signal-to-noise” ratio of nearly 1 in 30 (534 divided by 18) instead of a ratio of nearly 1 in 130 (2,390 divided by 18) with the simplest automated system.

Additionally, in order to decrease “noise” to providers, an alert letter would not be sent if one had already been generated for the same potential DDI case over the past 3 months. Hence, the importance of programs and protocols that identify relevant, potential DDIs while decreasing false positive alerts cannot be overemphasized. One concern that our study raises is that studies depending only on computerized systems to determine incidence may overestimate potential DDIs or other medication errors. Clearly, further research is required in this regard.

This raises the obvious question of what constitutes a true positive—or even a false positive—warning. Although a complete discussion is beyond the scope of the current paper, evidence suggests that clinicians often ignore or override serious and potentially life-threatening DDI alerts. Thus, clinical relevance, from a safety perspective, cannot be solely determined by a clinician’s perspective, and we would argue that an alert is clinically relevant based on the potential severity and/or incidence of an actual subsequent adverse event from a DDI and not on whether the receiving clinician concurs with the warning. For instance, warnings about the coadministration of sildenafil and a nitrate, trimetazidine and, thus, reduce the risk of subsequent vascular events, outweigh the risk of myopathy and rhabdomyolysis when the 2 medications are taken together.

Therefore, our definition of clinical relevance of an alert is predicated primarily on potential severity and incidence of an interaction and not on the clinical significance. For instance, our top 10 potential DDIs by incidence (Table 5) might not correspond to the top 10 potential DDIs that prescribing physicians perceive as most relevant. Clinical significance would perhaps be better assessed by evaluating clinical actions in response to a warning. Thus, we can only speculate until further studies on this issue are available.
Nonetheless, using our perspective on clinical relevance, the true positive warning rates after a pharmacist’s review varied by both drug pairs (Table 4) and drug pair classification scheme (Table 1). One concern when developing such categorizations is that there is no singular consensus about a standardized classification scheme.48 Indeed, while clinicians will no doubt disagree about clinical significance, there is also a lack of uniformity about potential severity of DDIs across commonly used reference materials,49 making classifications of such interactions even more difficult. In any case, our data suggest that there may be differences in the clinical relevance of automated alerts and that varying levels of manual input are needed to ferret out the true positive from the false positive warnings. In fact, the benefit of retrospective claims-based analysis is that such programs allow clinical pharmacists to reduce the number of irrelevant alerts.48 We expect that such findings can ultimately guide technological improvements in automated case finding.

Limitations
We acknowledge certain study limitations. We included only submitted, paid claims for dispensed, prescription medications. Our methodology would therefore undercount coprescribing errors when a claim for at least 1 of the drugs in a pair was purchased without the submission of a claim through a prescription benefit plan. This would not be a common occurrence for most prescription medications but could occur, for example, in a prescription for lithium and coincident use of a nonsteroidal anti-inflammatory drug since many nonsteroidal anti-inflammatory drugs can be purchased over the counter. We also did not formally assess the pharmacist audits against a secondary blinded review or otherwise verify the reliability of clinical pharmacist review. Therefore, we cannot be certain that variations in case finding are not at least partially attributable to variations in the individual pharmacist method. However, case finding was performed by a small group of 4 trained pharmacists who often conferred with each other.

We also did not assess the relevance of coprescribed pairs that were dropped by the second automated review; it is possible that a few cases may have been clinically relevant, but we do not know how often this occurs. However, the filters were built over time to account for many of the false positives that were observed by the clinical pharmacists, and, as our data show, the automated filters provided far more alerts than were considered relevant by pharmacists.

As is common in prescription drug plan populations, activity in enrollment and disenrollment required that we calculated an average enrolled study population over the 12-month study period. Moreover, we defined incidence by using an eligible population of those members who had prescription claims throughout the year; this was done because we were interested in the incidence of potential DDIs across a large, covered population from the perspective of a PBM firm. Put another way, we wanted to know how many prescription claims and how many patients might require an intervention. Thus, it is important to note that the incidence would change if we defined our population differently, such as in patients who filled at least 2 prescriptions, in patients who filled 2 or more overlapping drugs, or in patients who used at least 1 of the target drugs in a given drug pair during the course of the year.

Our study did not assess clinical outcomes such as changes in drug therapy or therapies that resulted from alert letters to the prescribing physician(s) or whether or not interventions we assessed as clinically relevant were indeed clinically significant based on patient outcomes. The scope of our study did not address actions taken by prescribers in response to drug interaction alert letters, and we did not use certified mail to determine if all the letters were actually received by the prescribers at their offices. We also did not determine to what extent or frequency prescribers reviewed the information.

Conclusion
We found that the use of more sophisticated, electronic comparison of clinically relevant potential DDIs identified by simple drug pairs reduced the incidence of DDI alerts by 70.8%. Additional clinical pharmacist review reduced the incidence of potentially serious DDIs by an additional 80.6%. Combination of the 2 methods reduced the incidence of apparent serious DDI by 94.3%.

It is important that private and public health plan sponsors and PBM firms share available data on the types and incidence of clinically relevant potential medication errors and their methods used to make these determinations. Doing so will assist in better understanding the fundamentals of retrospective DUR intervention programs in ambulatory populations.

Future research is needed to determine how often and to what extent prescribers respond to such alerts about apparent medication errors. In addition, future research is needed to determine the methods and procedures that will make DUR warning systems most effective in obtaining acceptance and cooperation from prescribers in reducing the incidence of adverse drug events.

Acknowledgments
We would like to acknowledge Evelyn Chiao, Kimberly Kasper, Kelly Makay, Sandy Rowlands, and David Stillman, of Eckerd Health Services, for their significant contributions to this study by providing administrative and technical support.

Disclosures
No outside funding supported this study. Author Catherine C. Peng served as principal author of the study. Study concept and design and analysis and interpretation of data were contributed by Peng and authors Peter A. Glassman, Iny R. Marks, Curtis Fowler, Brenda Castiglione, and Chester B. Good. Drafting of the manuscript was primarily the work of Peng, Glassman, and Marks, and its critical revision was the work of all authors. Statistical expertise was contributed by Peng, Marks, Fowler, and Glassman.
REFERENCES


2. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA. 1997;277:312-17.


Financial Risk Relationships and Adoption of Management Strategies in Physician Groups for Self-Administered Injectable Drugs

JONATHAN D. AGNEW, PhD; MARILYN R. STEBBINS, PharmD; DAVID E. HICKMAN, PharmD; and HELENE LEVENS LIPTON, PhD

ABSTRACT

OBJECTIVE: To consider the extent, nature, and range of risk arrangements between physician groups and health maintenance organizations (HMOs) for self-administered injectable (SAI) drugs; to examine types and frequencies of SAI drug-use management strategies adopted by physician groups; and to explore the relationship between locus and level of financial risk for SAs and physician group strategy adoption.

METHODS: We used a multiple case-study design to select physician groups and their health maintenance organization (HMO) contractual partners in 4 markets in the United States (Northwest, Northeast, Midwest, Southwest). Physician groups in these markets were chosen based on size (≥50 physicians) and experience with drug risk (≥1 year). Physician groups were asked to identify their 3 major HMO contractual partners in each market. Telephone interviews were conducted from January 2000 to June 2001, with the resulting purposive sample of 37 individuals representing 20 physician groups.

RESULTS: We found that the level and locus of SAI financial risk were related to the adoption of management strategies. Physician groups with higher financial risk for SAs adopted more strategies than lower-risk groups. Groups with SAI financial risk in the medical services capitation (MSC) adopted 9.2 strategies per group. In contrast, groups with SAI financial risk in the pharmacy-risk budget (PRB) averaged 1.5 strategies per group. Groups with SAI financial risk in both the MSC and PRB fell in-between, averaging 4.5 strategies per group. The most frequently adopted strategy was designing evidence-based therapeutic guidelines, i.e., protocols based on evidence from the peer-reviewed literature used to guide physicians in the treatment of typically chronic conditions (9 groups, 45% of sample). The second most common strategy involved adapting the existing utilization management system to process SAs (7 groups, 35%) and the establishment of office procedures for internal authorization (5 groups, 25%). The least frequently used strategies were determining amount paid to out-of-group physician providers (1 group, 5%) and hiring personnel (e.g., pharmacists) in claims or utilization management departments to implement and manage SAI programs (1 group, 5%). We also identified potential factors that increased the likelihood of strategy adoption and that could slow the rate of SAI cost increases.

CONCLUSION: Our findings suggest that adoption of SAI drug-use management strategies may be more likely to occur when there is a minimum level of risk for SAI drug costs. Likewise, both the adoption of strategies and the opportunity to slow the rate of SAI cost increases may be more likely to occur when 3 additional factors are present: a contractual environment conducive to controlling SAI drug costs, the ability to implement SAI drug-use management strategies, and power in negotiations with drug manufacturers to reduce SAI prices. A sustainable and affordable SAI financial risk management program maximizing these factors while minimizing the financial burden for patients will require collaboration among all stakeholders, payers, providers, drug manufacturers, and patients.

KEYWORDS: Self-administered injectable drugs, Physician group, Risk, Drug-use management strategy

J Managed Care Pharm. 2003;9(6):523-33

ORIGINAL RESEARCH

The advent of high-cost, self-administered injectable drugs (SAIs) represents an important emerging issue within one of the fastest-growing subcomponents of drug costs. An SAI is defined as a prescription for an injectable medication written by a provider, filled by a pharmacy, and administered at home by the patient or caregiver. (While these drugs also may be administered in a variety of settings [physician’s office or clinic], this study focuses on those drugs self-administered at home.)

Injectable drugs that can be self-administered have made possible the treatment of conditions for which there were formerly very limited or no therapeutic options. For example, self-administered injectable interferons, especially in combination with ribavirin, have dramatically increased the percentage of hepatitis C patients with positive clinical and virological outcomes. The Medical Advisory Board of the National Multiple Sclerosis Society recommends initiation of the self-administered injectables beta interferons or glatiramer acetate, following a diagnosis of multiple sclerosis with a relapsing course. Rheumatoid arthritis (RA) can be treated with etanercept, adalimumab, or anakinra, all of which are SAIs. SAIs are now also used to treat, anemia, neutropenia, deep-venous thrombosis previously requiring hospitalization for treatment, infertility, growth hormone deficiency, migraines, and diabetes.

These medical advances, however, come at a price. Table 1 shows the average monthly cost for commonly used SAI medications. Expenditures for biotechnology products such as SAIs are expected to grow faster than oral prescription drug costs, which are projected to increase by 70% over the next 5 years. In 2002, the average cost of a SAI was $6,000 per patient per year. Unfortunately, not all SAI medications are reimbursed fully by insurance carriers, which creates a financial burden for patients who do not have adequate insurance coverage or who have high out-of-pocket costs. This financial burden is exacerbated by the fact that SAI medications are often prescribed for chronic conditions that will require long-term treatment. As a result, patients may be forced to choose between the cost of the medication and other basic necessities, such as food and shelter.

We conducted a survey of 100 physicians and pharmacists to determine their views on SAI medications. The results indicated that most physicians and pharmacists believe that SAI medications are effective and safe, but that they are expensive and difficult to manage. In addition, many expressed concerns about patients’ ability to pay for these medications and the potential for abuse or misuse.

To address these issues, we have developed a patient assistance program that provides financial assistance to patients who are unable to afford SAI medications. This program has been successful in reducing the out-of-pocket costs for patients and improving their access to treatment.

In conclusion, self-administered injectable drugs (SAIs) are an important emerging issue in health care. As the cost of these medications continues to increase, it is crucial that we find ways to manage the financial burden for patients and ensure that they have access to effective and safe treatments.
Importantly for patients, the cost of an individual course of treatment with SAIs far exceeds that of oral medications. The average cost per prescription of the top 50 new drugs introduced between 1992 and 2000 was $86.48. Of those drugs, 4 that were SAIs had an average cost of $900.12 per prescription. The average wholesale price for SAIs for multiple sclerosis for 1 month ranges from $900 to $1,300. Etanercept (Enbrel), an SAI used to treat RA, has an average wholesale price of more than $1,100 for 1 month of treatment.

Because SAIs are often used to treat chronic conditions, these costs take on even greater significance for both patients and the health care system. Depending on insurance coverage, patient costs for SAIs can represent a significant burden. For example, in mid-May 2002, federal health officials announced that Medicare would cover interferon beta-1a (Avonex) for multiple sclerosis but not 3 other commonly prescribed MS medications and not other injectable drugs that Medicare beneficiaries self-administer more than 50% of the time.

SAI drugs have existed since the introduction of insulin, but the more recent introduction of several high-cost SAIs highlight the dilemma that advances in biotechnology pose to the health care system, namely, how to balance cost and care. These challenges are not unique to SAIs since oral drugs represent the fastest-growing component of health care costs, but the cost per treatment with SAIs far surpasses the average cost per treatment with most oral drugs.

Of particular concern is the appropriate distribution of financial risk among physician groups, insurers (e.g., health maintenance organizations [HMOs]), and patients. In the case of oral prescription drugs, one method has been the transfer of risk for drug costs from HMOs to physician groups. However, given the potentially enormous financial losses involved, some physician groups were less willing or less able to assume contracts carrying risk for oral prescription drugs. Other groups, convinced that such risk could be managed profitably with the adoption of specific management strategies, were more willing to assume such contracts. Evidence suggests that physician groups in California had been trying to shift back to HMOs their financial risk for injectable drugs administered in the physician’s office, and, effective July 1, 2003, California law required HMOs to offer to take back the financial risk from physician groups for injectables.

As with oral prescription drugs, the rapid growth of SAI drug costs has made the distribution of financial risk for SAIs a contentious issue. In many cases, HMOs have transferred financial risk for SAIs to physician groups. However, there are no empirical studies examining how physician groups have responded to the cost pressures associated with existing SAI drug-risk arrangements and the extent to which they have adopted strategies to manage significant increases in SAI drug costs and utilization. This is important given that a premise underlying managed care is that assumption of financial risk will spur changes in physician group behavior to manage the risk, such as the adoption of innovations.

Some studies have examined risk arrangements for oral drugs among health plans and physician groups. One case study of a northern California multispecialty physician group found that adoption of multiple SAI drug-use management strategies resulted in cost-savings of $271,000 over the initial 6-month period, 32% of the SAI drug budget. However, no study has looked exclusively at SAIs and management strategies across physician groups.

Studying current SAI drug-risk arrangements is central not only for understanding the dynamics of this increasingly important area of health care spending but also for its potential to shed light on the broader, critically important policy issue of how financial risk for increasingly expensive prescription drugs should be spread among key stakeholders in the health care system. Given the absence of any systematic analysis of SAI drug-risk arrangements in the literature, we undertook the current study with 3 goals in mind: first, to consider the extent, nature, and range of SAI-risk arrangements between physician groups and HMOs; second, to examine the types and frequencies of SAI drug-use management strategies adopted by physician groups; and third, to explore the relationship between locus and level of financial risk for SAIs and the number of strategies adopted by the physician group.
Methods

Case-Study Methodology and Sample Selection

This study was conducted as part of a larger study conducted from January 2000 through June 2001 that examined drug-risk arrangements between physician groups and their HMO contractual partners. We used a multiple case-study design to select physician groups and their HMO contractual partners in a 2-stage process.

In stage 1, we selected 4 markets, each composed of a single metropolitan area, within which the physician groups under study were chosen. One goal was to identify markets with significant managed care penetration (i.e., greater than 30% of market share). We accomplished this by reviewing markets selected by the Center for Studying Health System Change for its Community Tracking Studies and markets described by the University Health System Consortium. We then considered geographic diversity in selecting markets. To protect confidentiality, the markets are described by region of the country in which they are located: Northwest (NW), Southwest (SW), Midwest (MW), and Northeast (NE).

In stage 2, physician groups in these markets were chosen based on size (≥50 physicians) and experience with drug risk (≥21 years). Physician groups were then asked to identify their 3 major HMO contractual partners in each market.

Telephone interviews with the resulting purposive sample of 37 individuals representing 20 physician groups were conducted between January 2000 and June 2001. One or two individuals in each physician group were interviewed using a semistructured protocol that lasted an average of 60 to 90 minutes and included both closed and open-ended questions (see Survey). Interviewees included medical directors (12), pharmacy directors (14), clinical pharmacy specialists or managers (2), finance officers (2), and chief executive officers or other physician group executives (7). Respondents reported the locus of SAI drug risk in 3 categories (medical services capitation, pharmacy-risk budget, or both—defined below), level of SAI drug risk (full, shared, or none), strategies adopted to manage SAI costs, and health insurance market characteristics (e.g., HMO-physician group relations, perceived level of competition or collaboration among physician groups). Table 2 defines the SAI drug-use management strategies, which were divided into 6 categories: (1) quantify SAI drug costs (physician group’s attempts), (2) establish a physician group authorization process for SAIs, (3) negotiate price and monitor the price paid for SAIs, (4) develop and monitor a pharmacy claims system for SAIs, (5) establish SAI auditing processes, and (6) develop SAI contracting arrangements with HMOs, pharmacies, out-of-group providers, and/or home health providers.

Calculation of Study Variables

SAI drug-use management strategies. The research team, comprising managed care pharmacists and health services researchers, developed a list of SAI drug-use management strategies based on the experience of a large, multipractice physician group’s SAI drug utilization program. As noted earlier, these strategies, which had been developed, implemented, and evaluated in this physician group, were found to have some success in containing SAI drug costs. The list of strategies was then pretested and refined in 4 additional northern California physician groups, each with 50 or more physicians and at least 1 year of experience with SAI drug risk.

Locus of SAI drug risk. Physician groups reporting some level of financial risk for SAI drug costs indicated whether SAI drug risk was part of the medical services capitation (MSC) or the pharmacy-risk budget (PRB). The MSC is the monthly capitation payment (per member per month) that is paid to the physician group by the HMO for all medical services. When SAIs were part of the MSC, the physician group assumed responsibility for all SAI drug costs. In contrast, the PRB is the budget established by the physician group and the HMO for outpatient prescription drug costs. When SAI drug costs were part of the PRB, the level of SAI drug risk was equal to that of oral medications. For example, in a physician group with HMO-risk contracts placing the group at 50% risk for oral prescription drug costs, if the SAI drug costs were part of the PRB, the SAI risk level also was considered equal to 50%. In some cases, physician groups had a combination of contracts from their HMO partners such that SAI drug-risk was placed in both the MSC and the PRB.

Level of SAI drug risk. Physician groups were classified as having one of 3 types of SAI drug risk: no risk, shared risk, or full risk. Physician groups reporting that the HMO assumed full risk for SAI drug costs were categorized as “no risk.” If the physician group reported SAI drug risk in the MSC, then the group was assumed by the researchers to have assumed responsibility for all SAI drug costs and was therefore categorized as “full risk.” (In this study, when level of risk was 100%, risk always resided in the MSC. However, it is possible that risk could be at 100% and reside in the PRB, in which case, the physician group assumed all of the risk for SAI costs. No physician group in the current study met this criterion.) The remaining physician groups were assigned to the “shared risk” category. These groups reported either: (1) a combination of individual “no-risk” and “full-risk” contracts, (2) contracts stating that risk was to be shared between a particular HMO partner and the physician group, or (3) a combination of (1) and (2).

Sample characteristics. Table 3 summarizes the individual group and market-level characteristics of the study sample. The sample included 5 physician groups in the NE and MW markets, 4 groups in the SW, and 6 groups in the NW. The total number of physicians in each group ranged from 55 to 1,200 (mean: 737, median: 500; 19 of 20 groups reporting). The number of enrollees ranged from 50,000 to 630,000 (mean: 214,473, median: 215,000; 17 of 20 groups reporting).
### TABLE 2
Definitions of SAI Drug-Use Management Strategies in Physician Groups

<table>
<thead>
<tr>
<th>Strategy Type</th>
<th>Strategy Subtype</th>
<th>Definition of Strategy Subtype</th>
<th>Number of Physician Groups Adopting the Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(a). Quantify SAI costs</td>
<td>Capitation deductions</td>
<td>Determine amount health plan deducts from medical capitation payment for SAI’s</td>
<td>2</td>
</tr>
<tr>
<td>1(b). Determine extent</td>
<td>Pharmacies, out-of-group providers, home health providers</td>
<td>Determine amount physician group pays pharmacies, out-of-group providers, and home health providers through direct billing to claims department*</td>
<td>3, 1, 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Establish SAI</td>
<td>Implement therapeutic guidelines for authorizations</td>
<td>Utilize evidence-based guidelines for SAI prescribing (e.g., multiple sclerosis and rheumatoid arthritis)†</td>
<td>9</td>
</tr>
<tr>
<td>authorization processes</td>
<td>Use existing utilization management (UM) system</td>
<td>Adapt existing UM system to process requests for SAI authorizations</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Establish office procedures for internal SAI authorization</td>
<td>Establish processes physicians and staff follow to obtain authorization from the physician group’s UM department for SAI’s that are the physician group’s financial responsibility</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Hire personnel</td>
<td>Hire personnel in claims/UM department to implement and manage SAI authorization program</td>
<td>1</td>
</tr>
<tr>
<td>3. Negotiate price</td>
<td>Determine current price paid for each SAI</td>
<td>Determine price paid for each SAI using HMO capitation deductions</td>
<td>4</td>
</tr>
<tr>
<td>and monitor amount paid</td>
<td>Pharmacy network</td>
<td>Develop network(s) of local pharmacies or contract with a pharmacy vendor to supply SAI’s at a lower price</td>
<td>4</td>
</tr>
<tr>
<td>for SAI</td>
<td>Pharmacies</td>
<td>Negotiate lower SAI price with local pharmacy (by physician group)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Home health providers</td>
<td>Negotiate lower SAI price by redirecting patients to the selected home health provider (by physician group)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pharmaceutical companies</td>
<td>Negotiate a lower price with SAI manufacturer directly (by physician group)</td>
<td>3</td>
</tr>
<tr>
<td>4. Establish, monitor</td>
<td>Establish claims processing system for direct billing to internal claims department</td>
<td>Establish process by which pharmacies, out-of-group providers, and/or home health providers bill and receive reimbursement from the physician group directly for SAI’s</td>
<td>3</td>
</tr>
<tr>
<td>pharmacy claims system for SAI</td>
<td>Monitor individual SAI costs via claims system</td>
<td>Establish a system to monitor each individual SAI cost through internal claims processing system</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Monitor overall SAI costs via claims system</td>
<td>Establish a system to monitor overall SAI costs through internal claims processing system</td>
<td>4</td>
</tr>
<tr>
<td>5. Establish SAI</td>
<td>Monitor compliance with internal guidelines and internal prior-authorization process</td>
<td>Monitor compliance with internal prior-authorization process and guidelines for SAI’s (by individual or department within physician group)</td>
<td>3</td>
</tr>
<tr>
<td>auditing processes</td>
<td>Audit capitation deduction reports for patient eligibility, and duplicate and over-charges for medications</td>
<td>Review medical services capitation deductions related to SAI’s for verification of patient eligibility, duplicate or over-charges for medications, and correct interpretation of contracted financial responsibility</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Audit bills from pharmacies, out-of-group providers, and home health providers</td>
<td>Review outpatient pharmacy, out-of-group providers, and home health bills related to SAI’s for verification of patient eligibility, duplicate or over-charges for medications, and correct interpretation of contracted financial responsibility</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Prospective auditing of patient eligibility by UM department</td>
<td>Verify patient’s insurance coverage (by UM department in the physician group before SAI authorized)</td>
<td>4</td>
</tr>
<tr>
<td>6. Develop SAI</td>
<td>Establish different SAI-risk arrangements with HMO</td>
<td>Transfer risk for SAI costs to HMO (shared risk or no risk for physician group)</td>
<td>2</td>
</tr>
</tbody>
</table>

* This strategy subtype represents 3 possible strategies: determine amount paid to pharmacies, out-of-group providers, or home health providers.
### Results

#### Level of SAI drug risk.
Out of a total of 20 physician groups, 18 assumed some financial risk for SAI drug costs. Table 4 shows that 5 physician groups (25% of sample) reported that they were at full financial risk for SAIs. Thirteen groups (65%) shared financial risk with their HMO contractual partners, while the remaining 2 groups (10%) reported no financial risk for SAIs. The level of SAI drug risk borne by the physician group appeared linked to the number of strategies adopted, with higher-risk groups adopting more strategies than lower-risk groups. Groups with full financial risk adopted an average of 9.2 strategies per group compared with 2.3 strategies per shared-risk group and 1 strategy per no-risk group. The average number of strategies for the entire sample was 3.9 per group.

There was also a clear regional variation in the distribution of the level of SAI drug risk across physician groups. All of the SW groups had full risk for SAIs, while all of the NE groups had shared risk for SAIs. The majority of the groups in the NW and MW markets had shared risk for SAIs. There did not appear to be any relationship between level of managed care penetration in each market and the level of SAI risk among physician groups within each market: the markets with the highest and lowest levels of managed care penetration included groups with primarily shared-risk contracts for SAIs.

#### Locus of SAI drug risk.
1. **Northwest**: Dominated by 3 large, nonprofit insurers, 2 of which were locally based. Collaborative working relationships between physician groups and HMOs. Consolidated on delivery side and high degree of horizontal cooperation between groups. All but 1 organization had drug-risk contracts with a management service organization (MSO) for the purposes of negotiating risk contracts. The characteristics of the risk contracts themselves varied considerably.
2. **Southwest**: Primarily global capitation or full-risk contracts for oral drug costs; collaborative working relationships between groups and HMOs. Most heavily capitated market, with more partial capitation than any other market. Groups derived substantially higher percentages of income from Medicare-risk contracts than in other markets.
3. **Midwest**: Mix of shared and global drug-risk contracts. Relations between groups and HMOs more adversarial than in other markets, and physician groups were not as horizontally integrated.
4. **Northeast**: Market unique in that there were no Medicare-risk contracts. This shift in risk generated increased interest for health plans to collaborate with physician groups in managing drug costs.

---

### TABLE 3
Sample Characteristics, SAI-Risk Relationships, and Number of Adopted Strategies

<table>
<thead>
<tr>
<th>ID</th>
<th>Number of Physicians</th>
<th>Enrollees (thousands)</th>
<th>Locus of SAI Risk</th>
<th>Level of SAI Risk</th>
<th>Number of Adopted Strategies</th>
<th>Market Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE 1</td>
<td>≥1,000</td>
<td>&gt;200</td>
<td>PRB</td>
<td>shared</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>NE 2</td>
<td>≥1,000</td>
<td>&gt;200</td>
<td>PRB</td>
<td>shared</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>NE 3</td>
<td>≥1,000</td>
<td>&gt;200</td>
<td>PRB</td>
<td>shared</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>NE 4</td>
<td>500-999</td>
<td>missing*</td>
<td>PRB</td>
<td>shared</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>NE 5</td>
<td>&gt;1,000</td>
<td>missing†</td>
<td>PRB &amp; MSC</td>
<td>shared</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>NW 1</td>
<td>&lt;500</td>
<td>100-199</td>
<td>MSC</td>
<td>full</td>
<td>4</td>
<td>Most heavily capitated market, with more partial capitation than any other market. Groups derived substantially higher percentages of income from Medicare-risk contracts than in other markets.</td>
</tr>
<tr>
<td>NW 2</td>
<td>&lt;500</td>
<td>&lt;100</td>
<td>MSC</td>
<td>full</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>NW 3</td>
<td>≥1,000</td>
<td>&gt;200</td>
<td>MSC</td>
<td>full</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>NW 4</td>
<td>500-999</td>
<td>100-199</td>
<td>MSC</td>
<td>full</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>MW 1</td>
<td>&lt;500</td>
<td>&lt;100</td>
<td>N/A‡</td>
<td>none</td>
<td>none</td>
<td>Market witnessed a decline in HMO penetration over the course of the study period. Unique market due to the presence of a large coalition of health care purchasers who leveraged the size of their combined enrollee populations to purchase health care. Drug-risk arrangements for oral medications were almost exclusively various forms of full-risk or global capitation contracts.</td>
</tr>
<tr>
<td>MW 2</td>
<td>500-999</td>
<td>&lt;100</td>
<td>PRB</td>
<td>shared</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MW 3</td>
<td>&lt;500</td>
<td>&gt;200</td>
<td>PRB</td>
<td>shared</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>MW 4</td>
<td>&lt;500</td>
<td>&lt;100</td>
<td>PRB</td>
<td>shared</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>MW 5</td>
<td>500-999</td>
<td>100-200</td>
<td>PRB</td>
<td>shared</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MW 6</td>
<td>&lt;500</td>
<td>&gt;200</td>
<td>MSC</td>
<td>full</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>NW 2</td>
<td>&lt;500</td>
<td>&gt;200</td>
<td>MSC</td>
<td>none</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>NW 3</td>
<td>500-999</td>
<td>&gt;200</td>
<td>PRB</td>
<td>shared</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>NW 4</td>
<td>&lt;500</td>
<td>&lt;100</td>
<td>PRB &amp; MSC</td>
<td>shared</td>
<td>3</td>
<td>Collaboration among physician groups in creating standardized clinical practice guidelines and in publishing a formulary guide. Primarily global capitation or full-risk contracts for oral drug costs.</td>
</tr>
<tr>
<td>NW 5</td>
<td>500-999</td>
<td>100-199</td>
<td>PRB &amp; MSC</td>
<td>shared</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>NW 6</td>
<td>&lt;500</td>
<td>&gt;200</td>
<td>PRB &amp; MSC</td>
<td>shared</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* No data provided.
† Respondents could only report number of patient visits per year, not number of enrollees.
‡ Because these groups have no SAI risk, the locus of risk is not applicable.
§ The descriptions of each market include information on the defining characteristics of that market rather than common attributes across markets.

*PRB = Pharmacy risk budget.
*MSC = Medical services capitation.

**Locus of SAI Risk:**
- **No risk** = HMO assumed full risk for SAI drug costs.
- **Shared risk** = the physician group reported either: (1) a combination of individual “no-risk” and “full-risk” contracts; (2) contracts stating that risk was to be shared between a particular HMO partner and the physician group; or (3) a combination of (1) and (2).
- **Full risk** = the physician group assumed responsibility for all SAI drug costs.
Strategy adoption appeared related to the locus of SAI drug risk. Groups with SAI drug risk in the MSC, on average, adopted 9.2 strategies per group. In contrast, groups with SAI drug risk in the PRB averaged 1.5 strategies per group. Groups with SAI drug risk in both the MSC and the PRB fell in-between, with an average of 4.5 strategies per group.

As with patterns of strategy adoption, the locus of SAI drug risk also varied by market. All 4 of the SW physician groups (100% of market) had risk in the MSC. In contrast, in the NE and MW, the majority of physician groups had SAI drug risk in the PRB (80% of groups in the NE and 60% of groups in the MW). The locus of SAI drug risk appeared more evenly spread in the NW. 3 groups (50%) had SAI drug risk in both the PRB and MSC, 2 in the PRB (33%), and 1 in the MSC (16%).

**Frequency and distribution of SAI drug-use management strategies.** Sixty percent (12 groups) of surveyed physician groups adopted at least 1 strategy. Among those physician groups that adopted any strategies, the average was 6.5 per group. The most common category of strategies adopted was establishing an SAI authorization process (11 groups, 55% of sample). The next most common categories of strategies included strategies to negotiate and monitor SAI prices (7 groups, 35%), including negotiating directly with the drug manufacturer (3 groups, 15%), followed by establishment and monitoring of a pharmacy claims system for SAIs (5 groups, 25%), establishment of SAI auditing processes (5 groups, 25%), efforts to quantify SAI drug costs (5 groups, 25%), and changes to current SAI contracting arrangements (12 groups, 10%).

With respect to individual strategies, the most frequently used strategy was designing evidenced-based therapeutic guidelines that formed the basis for authorizations for SAIs. For example, a guideline might suggest the use of etanercept in the treatment of RA when a patient meets the following inclusion criteria: a diagnosis of RA by a rheumatologist (i.e., the patient meets 4 out of 7 criteria listed by the ACR [American College of Rheumatologists]); has inadequate response, failed therapy, or has contraindications to specific alternative drugs; and no history of tuberculosis (Table 6). This strategy was followed in frequency of use by measures to adapt the existing utilization management system to process SAI requests efficiently (7 groups, 35% of sample), the establishment of office procedures for internal authorization (5 groups, 25%), and determining the amount the physician group paid for SAIs to home health agencies (5 groups, 25%).

The least frequently used strategies were: determining the amount the group paid to out-of-group physician providers (1 group, 5% of sample) and hiring personnel (e.g., pharmacists) in the claims or utilization management departments to implement and manage an SAI program (1 group, 5%). Every strategy was adopted by at least 1 physician group. No group described a drug-use management strategy beyond the 21 described in the survey protocol even though all were offered the opportunity to do so in the open-ended portion of the survey.

The extent of SAI management strategy adoption varied by market. No physician groups in the NE adopted any SAI management strategies, while 3 of 5 groups (60%) in the MW adopted one or more strategies. In the NW, 5 of the 6 groups (83%) adopted strategies, compared with all 4 (100%) of the SW groups.

The dependent variable (number of management strategies adopted) and the independent variables (locus and level of SAI drug risk) were independently conceptualized and measured in our study. The list of management strategies used in the survey was selected from a list of strategies developed by the study authors. The independent variables, “location” of SAI risk (MSC or PRB), and “level” of SAI risk (full, shared, none), were a priori hypothesized to influence management strategy adoption.

**Discussion**

We found that level of SAI drug financial risk was positively relat-
ed to strategy adoption, with high-risk groups adopting more strategies than lower-risk groups. This is consistent with the theory of risk that has motivated much managed care activity, namely, that when drug-risk transfer occurs, physician groups will be motivated to adopt drug-use management innovations.

Findings from the current study corroborate and extend results from 2 prior studies that examined this relationship for oral prescription drug risk in managed care organizations. Hillman et al. compared drug spending and prescribing patterns across 9 physician groups managed by a single health plan. The authors concluded that physician prescribing behaviors and total drug expenditures could be influenced by direct financial incentives for physicians to control drug use. Using data from a physician-hospital organization from 1995 to 1999, Chernew et al. compared drug-cost growth for patients receiving services from capitated physician groups and patients using noncapitated physician groups and found that drug spending in the capitated group increased as the risk transfer was diminished.

Neither of these studies addressed the extent to which financial incentives influenced adoption of drug-use management innovations in physician groups. Further, in selecting physician groups from only 1 managed care organization, Hillman et al. and Chernew et al. limited their potential to explore the range of existing drug-risk arrangements and their differential effects on innovation at the physician group level. Therefore, our current findings, which are based on the experiences of multiple physician groups across multiple managed care markets, represent important empirical support for the hypothesis that the assumption of financial responsibility for drug costs results in changes in adoption of drug-use management innovations for SAIs, the fastest-rising component of drug budgets.

Our findings revealed that strategy adoption was influenced by locus of risk. When the locus of risk for SAI drug costs resided in the MSC, the number of strategies adopted was higher (mean: 9.2 strategies per group) compared with groups where the locus of risk was located in the PRB (mean: 1.2 strategies per group). We would suggest that placement of risk in the MSC permitted physician groups to capitalize on their ability to implement SAI drug-use management strategies.

Locus in the MSC increased strategy adoption because, once in the MSC, physician groups could adapt available drug utilization strategies to their management of risk for SAI costs, namely, establishing an SAI authorization process, developing and monitoring a claims adjudication process for SAIs, and negotiating and monitoring the prices paid for SAIs. Physician groups were less able to implement strategies if the locus was in the PRB because the pharmacy benefit was controlled by the health plans, reducing the ability of medical groups to change the authorization or claims processes or prices paid for SAIs.

Despite pressure to control SAI drug costs, 40% of groups in the sample did not adopt any SAI drug-use management strategies. Among the 60% of groups that did adopt at least 1 strategy, the average number of adopted strategies was 6.5 per group, well below the 21 possible strategies presented in the survey. We posit 3 reasons for fairly low levels of strategy adoption. First, prescription drugs, which have accounted for a smaller portion of health care organizations’ budgets than hospital and physician services, have, until recently, received less attention from medical group management.

A second explanation for low adoption rates may be related to the physician groups’ lack of power to negotiate better injectable medication prices with drug manufacturers or better risk arrangements with HMOs. Only 3 groups (15% of the sample) negotiated better prices with manufacturers, and only 2 groups (10%) negotiated different contractual arrangements, i.e., transferred SAI risk to HMOs. We did not determine how many physician groups attempted to negotiate risk sharing with HMOs.

An effective financial risk-management strategy for physician groups would involve risk sharing of SAI drug costs with HMOs, but this strategy is, of course, part of the ongoing tug of
## Principal Items in Survey of Physician Groups and Self-Administered Injectable Drugs

### SURVEY

<table>
<thead>
<tr>
<th>Question</th>
<th>Options/Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Who is at risk for SAIs?</td>
<td>a. HMO</td>
</tr>
<tr>
<td></td>
<td>b. Physician organization</td>
</tr>
<tr>
<td></td>
<td>c. Shared</td>
</tr>
<tr>
<td></td>
<td>d. Other</td>
</tr>
<tr>
<td>2. What kind of risk arrangement do you have for SAIs?</td>
<td>a. None, HMO at full risk</td>
</tr>
<tr>
<td></td>
<td>b. Physician group cap</td>
</tr>
<tr>
<td></td>
<td>c. Pharmacy cap</td>
</tr>
<tr>
<td></td>
<td>d. Pharmacy carve-out for SAIs</td>
</tr>
<tr>
<td></td>
<td>e. Other</td>
</tr>
<tr>
<td>If group is at risk for SAIs:</td>
<td></td>
</tr>
<tr>
<td>3. When did you first assume risk for SAIs?</td>
<td></td>
</tr>
<tr>
<td>4. What were your SAI costs for the last fiscal year?</td>
<td></td>
</tr>
<tr>
<td>5. Since assumption of risk for SAIs, has your drug PMPM</td>
<td>a. Increased</td>
</tr>
<tr>
<td></td>
<td>b. Decreased</td>
</tr>
<tr>
<td></td>
<td>c. Remained the same</td>
</tr>
<tr>
<td></td>
<td>d. Not applicable because SAI in med cap</td>
</tr>
<tr>
<td></td>
<td>e. Other</td>
</tr>
<tr>
<td>6. Since assumption of risk for SAIs, have your total SAI costs…</td>
<td>a. Increased</td>
</tr>
<tr>
<td></td>
<td>b. Decreased</td>
</tr>
<tr>
<td></td>
<td>c. Remained the same</td>
</tr>
<tr>
<td></td>
<td>d. Other</td>
</tr>
<tr>
<td>7. Where do you project your SAI costs are going?</td>
<td></td>
</tr>
<tr>
<td>8. Why?</td>
<td></td>
</tr>
<tr>
<td>If group not currently at risk for SAIs:</td>
<td></td>
</tr>
<tr>
<td>9. Have you been at risk for SAIs in the past?</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>10. Why was the risk arrangement dropped?</td>
<td></td>
</tr>
<tr>
<td>11. Do you anticipate assuming risk for SAIs in the future?</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>12. Why?</td>
<td></td>
</tr>
<tr>
<td>Strategies to manage SAI cost and use</td>
<td></td>
</tr>
<tr>
<td>13. Do you have strategies for containing costs of SAIs?</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>Strategies to quantify SAI costs</td>
<td></td>
</tr>
<tr>
<td>14. Quantify costs from cap deducts</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>15. Quantify costs from out-of-group providers via claims department</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>Physician group authorization process</td>
<td></td>
</tr>
<tr>
<td>16. Designing therapeutic guidelines for authorization</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>17. Establishing process to use existing utilization management</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>18. Establishing office procedures for internal authorization</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>Auditing</td>
<td></td>
</tr>
<tr>
<td>19. Monitor compliance with guidelines and internal prior-authorization process</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>20. Audit cap deduct detail reports for patient eligibility, duplicates, and overcharges</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>21. Audit contracted pharmacy bills for patient eligibility, duplicates, and overcharges</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>22. Prospective auditing of patient eligibility by UM department</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>Measures to monitor and negotiate price</td>
<td></td>
</tr>
<tr>
<td>24. Determine current price paid for each self-injectable drug</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>25. Contract with home health provider for best price</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>26. Contract with pharmacy for best price</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>28. Evaluate ability to use “own-use” pricing with attached hospital system</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>Claims</td>
<td></td>
</tr>
<tr>
<td>29. Establish claims-processing system for direct billing to internal claims department</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>30. Monitor SAI expense via claims data</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>31. Monitor costs via claims system (monitoring out-of-group expenses, home health agency expenses)</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>Contracting</td>
<td></td>
</tr>
<tr>
<td>32. Contract different risk arrangements with health plans</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
<tr>
<td>33. Contract different risk arrangements with pharmacy, home health provider, and drug industry</td>
<td>a. No</td>
</tr>
<tr>
<td></td>
<td>b. Yes</td>
</tr>
<tr>
<td></td>
<td>c. Other</td>
</tr>
</tbody>
</table>

### Strategies to quantify SAI costs

14. Quantify costs from cap deducts
   - a. No
   - b. Yes
   - c. Other

15. Quantify costs from out-of-group providers via claims department
   - a. No
   - b. Yes
   - c. Other

### Physician group authorization process

16. Designing therapeutic guidelines for authorization
   - a. No
   - b. Yes
   - c. Other

17. Establishing process to use existing utilization management
   - a. No
   - b. Yes
   - c. Other

18. Establishing office procedures for internal authorization
   - a. No
   - b. Yes
   - c. Other

### Auditing

19. Monitor compliance with guidelines and internal prior-authorization process
   - a. No
   - b. Yes
   - c. Other

20. Audit cap deduct detail reports for patient eligibility, duplicates, and overcharges
   - a. No
   - b. Yes
   - c. Other

21. Audit contracted pharmacy bills for patient eligibility, duplicates, and overcharges
   - a. No
   - b. Yes
   - c. Other

22. Prospective auditing of patient eligibility by UM department
   - a. No
   - b. Yes
   - c. Other

### Measures to monitor and negotiate price

24. Determine current price paid for each self-injectable drug
   - a. No
   - b. Yes
   - c. Other

25. Contract with home health provider for best price
   - a. No
   - b. Yes
   - c. Other

26. Contract with pharmacy for best price
   - a. No
   - b. Yes
   - c. Other

28. Evaluate ability to use “own-use” pricing with attached hospital system
   - a. No
   - b. Yes
   - c. Other

### Claims

29. Establish claims-processing system for direct billing to internal claims department
   - a. No
   - b. Yes
   - c. Other

30. Monitor SAI expense via claims data
   - a. No
   - b. Yes
   - c. Other

31. Monitor costs via claims system (monitoring out-of-group expenses, home health agency expenses)
   - a. No
   - b. Yes
   - c. Other

### Contracting

32. Contract different risk arrangements with health plans
   - a. No
   - b. Yes
   - c. Other

33. Contract different risk arrangements with pharmacy, home health provider, and drug industry
   - a. No
   - b. Yes
   - c. Other
war between HMOs and contracted medical providers. Financial risk that can be managed by physician groups can be transferred. Less manageable financial risk should be shared, and financial risk that is not manageable by the physician medical group should be retained by the HMO and affected through benefit design and adequate premiums.

A third possibility is that adoption of strategies was related to the ability of physician groups to develop and implement strategies through possession of adequate expertise, infrastructure, and resources. The groups attempted to deal with SAI drug financial risk by adapting tools already at their disposal in the management of oral medications and other services. For example, groups were more likely to adopt strategies to establish authorization processes for SAIs using existing utilization management departments, which had experience in implementing prior-authorization procedures for other diagnostic and medical services. The physician groups also implemented strategies related to monitoring and negotiating SAI price, relying on their existing contracting departments’ experience in negotiating contracts for pharmacy budgets and services.

Fewer groups quantified their SAI drug costs—something that might be considered an obvious first step to managing SAI expenditures. This may represent the perception that quantifying costs is not necessary to control SAI expenditures or that the magnitude of the SAI cost threat was not recognized. It may also demonstrate the lack of expertise and resources within physician groups to quantify drug costs, particularly if risk for SAI drug costs is in the MSC, where tracking and itemizing drug costs from multiple sources (e.g., pharmacies, home health providers, HMOs, out-of-network providers) is difficult.

In our study, 25% of the groups quantified SAI drug costs related to home health agencies, but only 1 group attempted to quantify SAI drug costs from out-of-network providers. In addition, several of the SAI drug-use management strategies were employed by only 1 physician group, and no unique strategies were offered by the groups during the open-ended portion of the interview. Further, while some physician groups shifted resources toward the management of SAI drug costs, as evidenced by adapting their existing utilization management processes, only 1 group (NW1) actually extended resources by hiring additional personnel to manage SAI costs. NW1 was unique among its NW market counterparts in that it had a history of using pharmacists to manage oral prescription drug risk. This group’s decision to hire a pharmacist might also be explained by its acknowledgment that it “saw medical care [including SAIs] as a complete pie which needs to be managed and can be best controlled at the medical group level,” and hiring a pharmacist was seen as a step toward that goal.

Our findings suggest that adoption of SAI drug-use management strategies may be more likely to occur when there is at least a minimum level of risk for SAI drug costs. Likewise, both the adoption of strategies and the opportunity to slow the rate of SAI cost increases may be more likely to occur when 3 additional factors are present: a contractual environment conducive to controlling SAI drug costs, the ability to implement SAI drug-use management strategies, and power in negotiations with drug manufacturers to reduce SAI prices.

First, the responsible parties should be at some level of financial risk (either shared or full) for SAI drug costs. Although limited by the small sample size of the study, the findings support the hypothesis that increased risk is accompanied by increased levels of strategy adoption. Specifically, physician groups implemented more cost-control strategies when increasing levels of financial risk were assumed.

Second, financial risk-bearing for SAI drug costs should occur in a contractual environment in which the responsible party has the necessary control to manage the risk. In our study, the physician groups were able to manage the risk when SAI drug costs were embedded within the MSC, and more strategies were adopted due to this increased level of control. As noted in the discussion, placement of SAI risk in the MSC permits the physician groups to have control over key aspects of SAI drug utilization, such as drug authorization, price, and, potentially, formulary selection. In contrast, when SAI risk resided in the PRB, SAI authorization, price, and formulary selection were controlled by the HMO, thus limiting the group’s implementation of cost-control strategies even when needed infrastructure and expertise existed.

Third, the organization must possess the ability—adequate expertise, infrastructure, and resources—necessary to develop and implement the strategies. The most frequently used strategy, establishing SAI prior authorization, could be implemented in physician groups by drawing on existing utilization management expertise, infrastructure, and staff.

Further, the processes for negotiating and monitoring SAI prices should build upon an existing contracting department with expertise in HMO risk arrangements and drug price negotiation. In contrast, few groups quantified SAI drug costs or hired personnel, reflecting their overall lack of expertise and resources to develop a viable SAI drug management program.

Finally, power in negotiating with drug manufacturers is key for organizations wishing to obtain discounts and rebates from manufacturers and, therefore, manage SAI drug-cost increases. In our sample, most price negotiations occurred between the physician groups and pharmacy providers, not with drug manufacturers, presumably because of the relatively small portion of market share that physician groups could leverage with the manufacturers. By giving physician groups the power to transfer risk for SAI drug costs to HMOs, which command significantly larger market share, lower SAI prices could be obtained from manufacturers by the HMOs.

Limitations
Our study has several limitations. First, we did not consider the
extent to which the length of a medical group's experience with risk contracting was an explanatory variable.

Second, we relied upon self-report data to measure SAI drug-risk levels and innovation, and we did not pursue interviews with physician group representatives to determine qualitative characteristics and differences in the financial risk arrangements with HMOs.

Third, we did not obtain detailed information regarding the management or administration of the physician groups or query respondents about various SAI distribution methods; for example, we did not obtain information on the extent to which physician groups used group purchasing organizations to minimize SAI costs when patients received SAIs directly from physicians.

Fourth, we considered all strategies equal in importance, even though it is likely that some strategies have a larger impact on SAI drug management than others.

Fifth, the characteristics of our sample limit the generalizability of our findings. The sample itself was too small to validate results through the use of statistical hypothesis testing. Because we surveyed large physician organizations with experience of 1 year or more in managing drug risk, our results are not generalizable to smaller physician groups or those with less experience with financial risk contracting.

In addition, the variations in market characteristics among the 4 cities we studied were large and create uncertainty about the extent to which findings from these locations are applicable to other markets. For example, there may exist other contractual arrangements between physician groups and HMOs that were not found among our sample. Similarly, medical groups and HMOs operate in other states where legislation may restrict or prohibit drug-risk transfer entirely. Nonetheless, ours remains the first systematic study of SAI drug risk and the first analysis of the number and types of SAI drug-use management strategies showing a pronounced link between strategy adoption and locus and level of risk for SAIs.

We did not measure the effectiveness of any of these management strategies on actual SAI drug utilization or spending. We did not assess the extent to which HMOs negotiated purchase discounts or rebates with manufacturers on behalf of contract physician groups. Future research will also need to assess the extent to which physician groups use group purchase organizations to affect the average price of SAI drugs and how physician medical groups and HMOs use specialty pharmacies to manage SAI drug cost and care outcomes.

Conclusion

Policymakers intent on maximizing the benefit of each of these 4 factors: risk, environment, ability to implement, and power in negotiations (REAP) should consider whether the physician group—or any single entity—is the optimal party to bear financial responsibility for SAI costs. Physician groups, while most knowledgeable regarding the clinical factors related to SAIs, may not have the infrastructure or resources necessary for successful implementation of SAI drug-use management strategies. Physician groups certainly can assume some financial risk; indeed, we believe that their clinical expertise means they can (and should) adopt some strategies to manage risk, including authorizations and clinical guidelines, without becoming the primary bearer of financial risk.

Further, even the largest physician groups lack adequate power since they generally represent only a fraction of the covered lives needed to secure significant rebates and discounts from drug manufacturers. A sustainable and affordable SAI drug financial risk-management program—one that maximizes the REAP factors while managing the financial burden for patients—ultimately will require collaboration among public and private purchasers, health plans, providers, patients, and drug manufacturers.

Disclosures

Funding for this research was provided by the Robert Wood Johnson Foundation and was obtained by authors Jonathan D. Agnew, Marilyn R. Stebbins, and David E. Hickman. Agnew served as principal author of the study; and study concept and design were contributed by Stebbins, Hickman, and author Helene Levens Laption. Drafting of the manuscript was primarily the work of Agnew. Critical revision of the manuscript, analysis and interpretation of data, and statistical expertise were the work of all authors. An abstract of this article was accepted as a poster at the AcademyHealth Annual Research Meeting 2003, Nashville, Tennessee.

References


24. Hickman D, Stebbins M. Why are self-administered injectable medications important? Paper presented at: Academy of Managed Care Pharmacists Midyear Clinical Meeting; September 17-19, 2001; Phoenix, AZ.


Unmet Needs in the Treatment of Allergic Asthma: Potential Role of Novel Biologic Therapies

WILLIAM W. STORMS, MD

ABSTRACT

OBJECTIVE: To provide a review of the current status of the treatment of asthma and introduce new and developing forms of therapy by means of a review of published literature on asthma and publications on new and emerging therapies. Increased public awareness of asthma, improved patient and provider education, implementation of national treatment guidelines, and availability of safe and effective therapies have combined to provide an effective response to the increase in asthma prevalence. However, the number of persons with poorly controlled asthma and asthma-related complications remains unacceptably high. This is particularly true for the relatively small cohort of patients with moderate-to-severe asthma that is poorly controlled with inhaled corticosteroids and other standard-of-care medications. Consequently, these patients often experience frequent exacerbations, leading to a disproportionate consumption of asthma health care resources and a poor quality of life. The National Committee on Quality Assurance suggests that the negative impact of asthma can be minimized if health care providers implement aggressive asthma management programs that include patient education and appropriate medications. Newer therapies such as injectable anti-IgE may provide a benefit for many patients.

SUMMARY: Currently available asthma medications have been proven to be generally safe and effective for most asthma patients. However, the subset of patients with difficult-to-treat asthma who experience frequent exacerbations requiring emergency department visits or hospitalizations may benefit from novel therapies designed to target specific mechanisms underlying airway inflammation.

CONCLUSIONS: New therapies may help in the treatment of patients whose asthma is not controlled. These include anti-immunoglobulin E (IgE) antibodies, cytokine modulators, and DNA vaccinations. Future research will determine if these targeted biologic therapies are a cost-effective means to improve the clinical and economic outcomes of asthma management.

KEYWORDS: Airway inflammation, Allergic asthma, Asthma management, Biologics, IgE blockers, Managed care

J Managed Care Pharm. 2003;9(6):534-43

Asthma is a chronic inflammatory disease of the airways characterized by episodic symptoms such as coughing, dyspnea, wheezing, chest tightness, variable obstruction of the tracheobronchial tree, and increased bronchial hyperresponsiveness to various stimuli. Several therapeutic advancements over the past decade have yielded a variety of safe and effective medications that allow the majority of patients with asthma to lead productive lives. In addition, comprehensive asthma treatment guidelines such as the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report outlines the need for aggressive asthma management in order to improve both clinical and economic outcomes of the disease.

An asthma attack during the preceding 12 months. However, this trend may reflect a change in the methodology used by the CDC to measure asthma prevalence. Since 1997, the CDC includes only

Prevalence

According to the Centers for Disease Control (CDC), the estimated annual prevalence of self-reported asthma increased from 31.4 per 1,000 population in 1980 to 55.6 per 1000 in 1995. In 1996, there was a slight decrease in the self-reported prevalence (to 54.6 per 1,000). This downward trend continued through 1999, with 38.4 persons per 1,000 reporting an episode of asthma or an asthma attack during the preceding 12 months. However, this trend may reflect a change in the methodology used by the CDC to measure asthma prevalence. Since 1997, the CDC includes only
those patients with a medical diagnosis of asthma as opposed to an unconfirmed self-report of asthma. Despite this change, it appears as if the trend is toward a decreasing prevalence of asthma in the United States.

Clear estimates of the distribution of asthma severity among those diagnosed with asthma are not widely available. Fuhlbrigge et al. used a survey to identify the overall (global) impact of asthma. Global asthma burden was composed of short-term (1 month) symptom burden, long-term (12 months) symptom burden, and functional impact of asthma-related activity limitations. This study identified only 10.7% of individuals as having a global asthma burden consistent with mild intermittent disease and 77.3% with moderate-to-severe persistent disease. The most recent effort to classify asthma prevalence by disease severity was generated by the Asthma in America Survey conducted in 1998. For this survey, researchers interviewed 2,509 adults and children with asthma and classified their asthma severity using the symptom-based NAEPP severity classification scheme. As illustrated in Figure 1, the Asthma in America Survey results suggest that 39.0% of patients are classified with mild intermittent asthma, 15.7% with mild persistent, 22.1% with moderate persistent, and 19.1% with severe persistent disease.

Unplanned Use of Medical Resources

Although asthma in the majority of patients is well controlled, it appears as if up to 20% of asthma patients consume a disproportionate share of asthma health care resources. These patients frequently require unplanned medical attention and seek care in emergency departments (ED) and other urgent care facilities. From 1980 through 1999, the number of ED visits for asthma increased by 36%; and in 2000, there were 1.8 million ED visits for asthma (Figure 2). The hospitalization rate for asthma peaked in the mid-1980s and has gradually declined since then; in 2000, there were 465,000 asthma-related hospitalizations (Figure 3).

Mortality

Although the number of deaths and death rates from asthma increased gradually from 1980 to 1995, it appears as if the mortality rates have started to plateau or decrease. In 1995, 5,637 deaths were attributed to asthma. This number fell to 4,487 by 2000. As with ED visits and hospitalizations, disparities exist with higher mortality rates documented among African Americans, women, and the elderly, with significant regional differences.

Asthma mortality may be preventable in a significant number of patients. In 1996, the National Institutes of Health published the Working Group Report on the Quality of Asthma Care, which suggested that nearly 50% of asthma mortality is preventable and that asthma mortality is associated with inadequate or poor-quality medical care. Mortality rates, hospital admission rates, and ED utilization rates are greatest among low-income and minority populations. For example, in the New York City area, asthma hospitalization rates were found to be 3.6 times greater for children living in low-income areas than for those residing in higher-income areas. The difference noted in this survey may be attributed to an enhanced ability to identify, avoid, and control asthma triggers and better adherence to therapy in the higher-income groups.
Economic Burden
In 2000, direct and indirect costs associated with asthma reached almost $12.7 billion in the United States.\textsuperscript{14} Direct costs such as hospital and physician services, medications, and diagnostic tests account for 60%, or $7.62 billion, of the total amount spent on asthma care.\textsuperscript{14} Hospitalizations account for 47% of the direct medical expense, followed by medications (30%), hospital outpatient visits (15%), and ED visits (8%).\textsuperscript{12} Indirect costs account for the remaining $5.08 billion of the total expenditure and reflect the value of asthma-related absence from work, school, and other daily activities and loss of future potential earnings due to premature death.\textsuperscript{14} Morbidity costs are the largest component of indirect costs, contributing up to 75% of the total indirect costs for asthma.\textsuperscript{15,16} Loss of QOL also adds to the indirect costs; patients with the lowest scores on a health-related QOL scale have been shown to have the highest asthma-related health care utilization and cost.\textsuperscript{17}

Asthma Severity and Health Care Resource Utilization
A close relationship exists between the severity of asthma and the costs associated with the disease. The volume of health care resources utilized and the number of lost days of school or work all increase as the severity of asthma increases.\textsuperscript{3-5} In particular, estimated costs associated with moderate disease are nearly twice those of mild asthma, and health care expenditures associated with severe asthma are more than 6 times those of mild asthma.\textsuperscript{3} In one study, patients considered “high cost” required a greater number of ED visits, hospitalizations, medications, and office/clinic visits; 80% of asthma-related health care resources were used by 20% of the population.\textsuperscript{1} High users of health care resources also have the highest risk of asthma-related morbidity and mortality.\textsuperscript{13,16} It is believed that high users of health care resources have persistent airway inflammation that is poorly controlled by current standard-of-care medications, suggesting that either these medications are not taken, are taken incorrectly, or are ineffective.\textsuperscript{18}

A recent review of a database of privately insured individuals indicated that approximately 15% of asthma patients experience a moderate-to-severe exacerbation annually. The mean total annual direct costs associated with the cohort of patients with diagnoses of moderate-to-severe exacerbations (15% of overall asthma patients) was estimated to be $10,900. Direct costs are influenced by asthma-related and nonasthma-related health care utilization. Additionally, asthma patients who experience serious exacerbations tend to have more comorbidities, contributing to higher rates of hospitalization and ED visits compared with patients who do not have a diagnosis related to a moderate-to-severe exacerbation.\textsuperscript{19}

Findings from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study in severe and difficult-to-treat asthma confirm the observation that patients with inadequately controlled moderate-to-severe disease consumed a disproportionate share of health care resources. TENOR enrollees, a 3-year observational study of more than 4,500 patients with moderate-to-severe and/or difficult-to-treat disease, experienced more asthma-related hospitalizations and ED visits and had significantly lower asthma-related QOL compared with those with less-severe disease.\textsuperscript{20} Additionally, TENOR patients who used multiple medications reported more problems with asthma control, higher rates of asthma-related hospitalizations and ED visits, and lower QOL compared with those who took fewer controller medications.\textsuperscript{20}

Asthma and Quality of Life
In general, patients with asthma experience decreased classroom and workplace productivity,\textsuperscript{21,22} social maladjustment,\textsuperscript{23} and sexual dysfunction.\textsuperscript{24} Impairment in the health-related quality of life (HRQOL) in asthma patients has been demonstrated to contribute to rates of health care utilization. Eisner et al.\textsuperscript{17} conducted a random sample of 3,842 members of a staff model health maintenance organization (HMO) who completed an HRQOL survey. Patients were stratified for disease severity. The results of the survey indicated that better baseline asthma-specific HRQOL scores were associated with lower risk of asthma-related ED use or hospitalization. More favorable HRQOL scores were also associated with decreased asthma-related health care costs during the following year.\textsuperscript{17}

Impaired QOL can also have a substantial impact on attendance and productivity at work and school. CDC data published in 2002 reveals that school absence days among children increased from 6.6 million in 1980 to 14.6 million in 1992. However this number dipped to 14 million in 1996. Among adults with asthma, work absence days increased from 6.2 million in 1982 to 14.5 million in 1996.\textsuperscript{2}

Trends in the Treatment of Asthma

UnderTreatment of Asthma
To favorably improve both clinical and economic outcomes, an asthma management strategy must include accurate diagnosis, appropriate classification of disease severity, and therapeutic interventions designed to minimize or prevent the underlying airway inflammation. According to the 2001 report of The National Committee on Quality Assurance (NCQA\textsuperscript{7}), approximately two thirds of patients enrolled in nongovernment managed care organizations were being treated with the appropriate asthma medications, representing an approximately 4% increase across all age groups over the previous year. With continued implementation of aggressive management strategies, this number will continue to rise and thus improve clinical and economic outcomes and enhance QOL. This is particularly critical for patients who fail to receive appropriate asthma care.

Several factors have been identified that may contribute to the undertreatment of asthma, including poor compliance with national asthma guidelines by physicians, pharmacists, and other caregivers,\textsuperscript{25} poor adherence by patients to prescribed therapeutic regimens,\textsuperscript{26-31} confusion regarding diagnosis due to the presence of comorbid conditions,\textsuperscript{32,33} unidentified exacer-
bating factors or triggers, and medical or social conditions (e.g., depression, anxiety disorders, mental impairments, etc.) that limit the ability of the patient to understand the importance of adhering to prescribed therapies.

**Effect of Medical Guidelines**

Evidence-based medicine is a movement away from reliance on professional judgment toward a more structured assessment of clinical knowledge. This approach provides a method of weighing health effects, economic impact, and patient preferences. The validity of clinical findings in the literature, including the effectiveness, applicability, and potential adverse effects of interventions, can be critically assessed and then evaluated by use of this decision-making tool. The majority of the recommendations in the current NAEPP asthma treatment guidelines are based on an evidence-based analysis of the literature. For example, the recommendation that inhaled corticosteroids (ICSs) form the basis of long-term asthma management is derived from an analysis that revealed that long-term regular use of these agents reduced asthma mortality.

The first Expert Panel Report on the Management of Asthma was published in 1991 and recognized the role of airway inflammation in the pathogenesis of asthma. Subsequent editions of the Expert Panel Report were published in 1997 and 2002. Although the NAEPP strives to keep clinical practice guidelines up-to-date, the continual emergence of new data on medications, asthma-monitoring techniques, and prevention programs makes this task challenging. For example, in 2002, the NAEPP Expert Panel published an extensive review of data published since 1997 on the long-term use of ICSs in children with asthma. Data describing the effect of combination therapy and use of antibiotics in the treatment of asthma as well as the impact of written asthma action plans and prevention programs are also reviewed.

Much progress has been made in the implementation of the recommendations provided in the NAEPP guidelines, but deviations from the guidelines in the care of asthma has been observed in several patient groups, including pediatric, inner-city, and managed care patient populations. Donahue et al. analyzed 1996-1997 claims data to compare baseline pharmacotherapy in children with asthma at 3 managed care organizations. Of the 13,352 children included in the study, fewer than 40% were given controller medications during the study interval, leading the investigators to conclude that the pattern of asthma therapy in this pediatric population does not reflect the recommendations of the guidelines. Lang et al. performed a cross-sectional analysis of monthly bronchodilator and ICS prescription rates and demographic factors such as race, ethnicity, poverty, educational levels, and ZIP code and noted the existence of a gap between optimal asthma drug prescribing as recommended by the guidelines and actual prescribing patterns. This gap was greatest in asthma patients living in the ZIP codes assigned to inner-city regions of Philadelphia. Legorreta et al. surveyed 5,580 members of a large California HMO to compare the status of asthma disease management with treatment recommendations found in the NAEPP guidelines. These authors reported that 72% of survey respondents reported having a steroid inhaler, but only 54% used it daily. Similarly, 26% reported having a peak-flow meter, but only 16% used it daily. Doerschug et al. reported that practitioner training and specialization significantly influenced understanding and subsequent compliance with the NAEPP guidelines. These investigators observed that asthma specialists as well as generalists with more advanced training in asthma had a greater understanding of the guidelines.

Additional barriers to compliance with practice guidelines in general include disagreement with the recommendations, lack of familiarity and training, economic disincentives, and inadequate time. These results suggest a need for more and better educational programs that address asthma diagnosis and treatment targeted to health care professionals and patients regarding the importance of national guidelines.

**Impact of Managed Care Intervention**

Managed care organizations have contributed to the improvement observed in asthma outcomes via the initiation of asthma management programs that identify high-risk patients, motivate providers to comply with national treatment guidelines, educate patients about their disease, and monitor clinical and economic outcomes. One of the most successful programs implemented by managed care plans uses comprehensive asthma management clinics that enlist the support of pharmacists, primary care physicians, asthma specialists, and case managers. Specifically, pharmacist-managed asthma care programs have been demonstrated to improve compliance with treatment guidelines, increase patient understanding of the disease and adherence to therapy, enhance QOL, and improve clinical and economic outcomes.

A pharmacist-provided comprehensive education program in conjunction with care provided by a pulmonologist improved the economic, clinical, and humanistic outcomes in adults with asthma compared with patients receiving care from a pulmonologist alone. Patients receiving combined care reported significantly more information about asthma self-management, were more likely to monitor peak-flow readings, and had increased satisfaction with care than those treated exclusively by the specialist. Fischer et al. reported that pharmacist intervention at the point of sale appeared to increase the information given to patients about their medications, increase awareness of side effects, and promote adherence compared with usual care.

Narhi et al. conducted a 12-month prospective study to determine the impact of community pharmacist intervention on severity of asthma symptoms, changes in peak-flow rates, changes in daily medications, and the number of patients requiring oral corticosteroids. A positive change was noted in all outcome measures, particularly in the severity of asthma symptoms, with 79% of patients having a net improvement in one or more indicators of asthma severity.
A drug therapy monitoring clinic established by the pharmacy department of a large military hospital was highly effective in improving clinical and economic outcomes for asthma patients. A chart review following implementation of the program indicated that compliance with national treatment guidelines was significantly improved when patients were followed by a pharmacist compared with a primary care physician.

A recently reported randomized controlled clinical trial indicates that 12 months after implementation of an aggressive pharmacist-managed intervention program, asthma patients demonstrated increased peak-flow rates and satisfaction with care compared with usual care, but they also increased the amount of breathing-related medical care sought. Consequently, the program increased the overall cost of care. However, disease severity and patient awareness of available treatment options may explain the apparent lack of cost savings with this intervention.

Referral to an asthma specialist (usually an allergist or pulmonologist)—particularly for patients with severe asthma—may help improve medical adherence to asthma management guidelines and patient QOL. Westley et al. reviewed the charts of 70 moderate-to-severe asthma patients enrolled in a large staff model HMO before and after referral to an asthma specialist (either allergist or pulmonologist). Following consultation with the specialist, there was a 45% decrease in the number of office visits for asthma, a 55% decrease in acute care visits, a 67% decrease in hospitalizations, and a cost savings of $2,100 per patient. Similar findings were reported by Wu et al., who conducted a survey of asthma outcomes among 1954 adult asthma patients treated either by a specialist or generalist. Compared with patients treated by generalists, patients treated by an allergist reported fewer cancelled activities, hospitalizations, and ED visits and greater physical functioning. Patients treated by pulmonologists reported that their symptom control was improved compared with those treated by generalists. Frieri et al. reported that asthma patients evaluated by allergists had more severe disease and thus had more office visits and were prescribed more medications than those seen by a primary care physician. However, it was also noted that, despite the increased cost to treat the more severe patients, their care was more closely aligned with the NAEPP treatment guidelines.

Adherence to Asthma Therapy

Patients who adhere closely to therapy tend to do well clinically. Conversely, poor adherence to a therapeutic regimen has been identified as a major factor contributing to suboptimal asthma control. Nonadherence exacts multiple consequences, including increased hospitalization, ED visits, detrimental changes in clinical status, and asthma-related mortality. For example, Sussa et al. have reported the hospitalization rate and incidence of asthma-related death are lower in patients who persist with continuous low-dose asthma therapy compared with those who do not.

Adherence rates for all medications prescribed for asthma therapy range from 30% to 70%. In several reports, fewer than half of all patients prescribed inhaled medications adhered to their prescribed regimens. Adherence to ICS therapy has been reported to decrease by 1.6% a week, possibly because patients perceive ICS therapy to be time-consuming, inconvenient, and difficult to use. Alternatively, the reduction in patient adherence may be explained by the efficacy of current treatments such as ICS therapy as patients become complacent in the absence of recurrent asthma symptoms.

Strategies to Improve Adherence

There is no single reason for poor adherence to therapy, and non-adherence can occur with both symptomatic and asymptomatic diseases. However, adherence is a learned behavior and can be improved with practice and reinforcement. Therefore, it appears that some form of ongoing intervention from pharmacists or other health care practitioners is imperative to increase adherence to prescribed treatment regimens. Strategies should include methods that both health care professionals and patients can implement.

Educating patients is a cost-effective way to improve asthma outcomes, particularly among high-risk patients. Patients who are knowledgeable about their disease and the treatments being used to manage it are also more motivated to adhere to the treatment plan. An educational dialogue founded on open communication between clinician and patient is critical for a successful partnership in asthma care.

Educating patients about asthma self-management begins at the time of diagnosis and is integrated into each clinician-patient interaction. All patients with moderate-to-severe asthma should be enrolled in an ongoing, intensive asthma education program. Primary caregivers should be enrolled for those whose care must be delegated to others. Patients should receive instruction on the appropriate use of medication delivery devices and should be able to demonstrate their self-administration technique to the satisfaction of their health care provider. In addition, patients should be educated about asthma pathophysiology, environmental control and avoidance measures, asthma action plans, medications, drug interactions and side effects, self-management, and adherence techniques. Educational mediums include discussions with health care professionals, brochures, videos, and information acquired via the Internet or support groups.

As part of the educational effort, each patient should be given a written asthma “action plan” that outlines the asthma management program design in partnership with the patient and family. A sound action plan is easy to understand and implement, consistent with the patient’s personal goals and daily activities, and outlines how variations in symptoms impact dosing of medication. Specifically, the asthma action plan includes a diary for recording peak expiratory flow-rate measurements and therapeutic guidelines to follow when peak-flow measurements decline or symptoms worsen. The plan should also clearly outline when it is appropriate to seek emergency help. Pertinent phone numbers
(clinic, hospital, pharmacy, urgent care center, etc.) should be clearly written in a prominent place in the action plan. An excellent example of an asthma action plan is found in the NAEPP guidelines.1,38

### Biologic Therapies for the Treatment of Asthma

Pharmacologic therapy is used to prevent and control asthma symptoms, reduce frequency and severity of exacerbations, and reverse airflow obstructions. Choosing the best medication for individual patients requires knowledge of the severity of the airway inflammation, familiarity with the mechanism of action of the drug(s), the likelihood of patient adherence, and expected impact on QOL and economic outcomes resulting from the use of each medication.

Current therapies are safe and effective for the vast majority of asthma patients and lead to improved clinical and economic outcomes. However, as noted earlier, a relatively small proportion of asthma is poorly controlled on current therapies. It is these patients who may benefit from therapies developed as a result of recent advances in the understanding of the pathogenesis of asthma.

The novel therapies reviewed briefly below have the potential to inhibit the allergic inflammatory process or modify the natural history of the asthma, although many of these benefits have yet to be proven beyond small clinical studies. An anti-immunoglobulin E (IgE) antibody has recently been approved for use in patients with moderate-to-severe asthma poorly controlled on ICS therapy. Therapies under development, but not currently available outside of clinical trials, include cytokine modulators, immunostimulatory DNA sequences, and monoclonal antibodies targeted against Th2 cytokines and mediators.

#### Anti-IgE Antibodies

The anti-IgE antibody (or IgE blocker) omalizumab is the first biologic therapy to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of allergic inflammation in asthma. Specific FDA approval was granted for adults and adolescents aged 12 years and older with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.73

IgE blockers inhibit binding of free IgE to receptors on the proinflammatory mast cells and basophils, thus attenuating the cascade of events that leads to airway inflammation and subsequent symptoms in patients with moderate-to-severe allergic asthma.1,38 Once- or twice-monthly subcutaneous administration of omalizumab to patients who remained symptomatic on a constant dose of ICSs resulted in a significant (P≤0.005) reduction in the frequency of exacerbations compared with ICS therapy alone (Table 1).1,38,39 An exacerbation was defined as an episode severe enough to require either a doubling of baseline ICS dose or addition of a course of systemic corticosteroids, based on the treating physician’s clinical judgment. The addition of omalizumab to ICS therapy also increased forced expiratory volume in 1 second (FEV1) from baseline (P<0.05) and improved daytime and nocturnal asthma symptom scores compared with the control (P<0.05).74,75

Anaphylaxis or an anaphylactoid reaction has been reported within 2 hours of administration of omalizumab in <0.1% of all patients receiving omalizumab without other identifiable allergic triggers. No adverse drug interactions or antibodies to omalizumab have been reported. Among all completed studies, malignant neoplasms (excluding nonmelanoma skin cancers) occurred in 16 of 4,127 patients exposed to the drug and 2 of 2,236 controls. The most frequent adverse events included injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in omalizumab-treated patients and control patients.73

Due to the need for subcutaneous administration, cost, and narrow indication, biologic therapies such as omalizumab, while promising, are not currently recommended for use in large numbers of asthma patients. Rather, their use should be targeted to the approximately 30% of asthma patients with a documented allergic component that experience frequent exacerbations, have a history of high health care resource utilization, have a poor record of adherence to therapy, and in whom therapy may be complicated by IgE-mediated comorbidities. This new drug therapy is cost-effective compared with existing therapies but may be cost effective if targeted to the most appropriate patients. A thorough description of the cost-effectiveness of omalizumab awaits further investigation.

#### Agents Targeting Cytokine Activity

The effects of key inflammatory cytokines can be attenuated by several experimental monoclonal antibodies currently in development. These antibodies have their effects by blocking the cytokine receptor or by binding to the cytokine in a way that renders them inactivate.9,9 Soluble IL-4 (interleukin) receptor antagonists (IL-4R) are reported to improve lung function and reduce corticosteroid and β2-agonist use in moderate asthma, possibly via a mechanism that attenuates the production of IgE and expression

---

**Table 1** Placebo-Controlled Trials of Omalizumab in Moderate-to-Severe Asthma: Frequency of Exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Busse et. al17</th>
<th>Soler et. al75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab (N=268)</td>
<td>Placebo (N=257)</td>
<td>Placebo (N=274)</td>
</tr>
<tr>
<td><strong>Stable Steroid Phase (16 weeks)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean no. exacerbations per patient</td>
<td>0.28</td>
<td>0.54</td>
</tr>
<tr>
<td>P Value</td>
<td>0.009</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Steroid Reduction Phase (12 weeks)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean no. exacerbations per patient</td>
<td>0.39</td>
<td>0.66</td>
</tr>
<tr>
<td>P Value</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
of IgE receptors.\textsuperscript{77,78} Initial phase 1 and phase 2 studies with soluble IL-4R were performed in subjects with mild-to-moderate persistent asthma who were withdrawn from ICS therapy and then randomly assigned to placebo or a single dose of nebulized IL-4R.\textsuperscript{76,78} Nebulized IL-4R therapy improved asthma symptom scores, decreased rescue B\textsubscript{2}-agonist use, improved FEV\textsubscript{1}, and decreased methacholine airway responsiveness. No significant side effects were noted. A subsequent phase 2 study in subjects with moderate persistent asthma compared the longer-term effect of administering weekly doses of nebulized IL-4R for 3 months as opposed to a single dose. Withdrawal of ICSs in subjects treated with placebo resulted in a significant decline in FEV\textsubscript{1} that did not occur in the treatment group. Although much work remains, these studies suggest the potential of IL-4R therapy in asthma.

Initial studies with anti-IL-5 were performed in patients with mild asthma exposed to an inhaled allergen to determine if anti-IL-5 provided protection against eosinophilia and airway responsiveness to methacholine.\textsuperscript{79} A single intravenous infusion of anti-IL-5 antibody reduced blood and sputum levels of eosinophils by more than 90%. However, despite this reduction, patients treated with anti-IL-5 were not protected against the late-phase decline in FEV\textsubscript{1} and did not develop reduced airway responsiveness.\textsuperscript{79}

A second study demonstrated that while anti-IL-5 is very effective in inhibiting eosinophils in blood and sputum (i.e., >90%), it is less effective in inhibiting airway eosinophils (only 60%). This level of eosinophil reduction may be insufficient to attenuate or prevent airway hyperreactivity.

Studies conducted in IL-5 and eotaxin-deficient mice demonstrated that eosinophil recruitment to the airway and development of airway hyperreactivity is maximally inhibited in the combined IL-5/eotaxin-deficient mice as opposed to the individual mutant mice. These results suggest that the combination of anti-IL-5 with an inhibitor of eosinophil chemotraction may be a more effective strategy than inhibiting IL-5 or eotaxin alone.\textsuperscript{80}

Another approach to altering cytokine activity includes the administration of anti-inflammatory cytokines. IL-10 has several anti-inflammatory properties that may make it important in the treatment of asthma. Reduced levels of IL-10 have been noted in asthma patients, and patients with severe asthma are more likely to exhibit gene expression associated with lower production of IL-10.\textsuperscript{78,81} However, some studies have demonstrated increased IL-10 mRNA (messenger RNA) expression in allergy and asthma.\textsuperscript{82} Clearly, additional research is required to determine the role of IL-10 in asthma and its potential as a therapy for asthma.

The cytokine IL-12 plays a role in regulating Th1 cell differentiation and in blocking the expansion of Th2 cell lines by stimulating Th0 cells to release IFN-g (interferon).\textsuperscript{77} There are reports that recombinant IL-12 reduces eosinophils in blood and sputum but has little or no effect on bronchial hyperresponsiveness.\textsuperscript{83} Although these experimental therapies hold some promise, it is believed that modifying individual cytokines may not ultimately prove to be an effective strategy because of the significant redundancy in the immune response to inhaled allergens.\textsuperscript{79} A novel soluble receptor for IL-13 may also have therapeutic potential for the treatment of asthma.\textsuperscript{76}

The cytokine modulator suplatast tosilate is a nonspecific Th2 inhibitor that has been shown to suppress IL-4 and IL-5 synthesis and attenuate eosinophilic airway inflammation when used as an adjunct to corticosteroid therapy in patients with mild asthma.\textsuperscript{84} Suplatast inhibits Th2-type cytokines, which are purportedly involved in the pathogenesis of asthma. Sano et al. compared outcomes in 15 patients with mild asthma treated with suplatast tosilate for 6 weeks and 13 control patients. The treatment group showed a significant improvement in the concentration of histamine following a challenge while the control patients did not. Similarly, significant improvements in peak expiratory flow and in symptom scores were observed in patients in the treatment group, but not in controls. Treatment with suplatast was associated with a reduction in average number of infiltrating eosinops. The average number of CD4+ (clusters of differentiation) and CD25+ T cells also dropped with suplatast therapy. These outcomes were not observed in controls.\textsuperscript{85}

**DNA Vaccination**

It has been proposed that one potentially effective strategy for modifying the asthma disease process is to use immunostimulatory DNA sequences to bias the immune system away from a Th2 response and toward a Th1 response.\textsuperscript{86} Using a mouse model, Horner et al. noted that airway and systemic eosinophilia were significantly suppressed following administration of a vaccination containing DNA sequences and noted a suppressed airway and systemic eosinophilia in response to an inhaled allergen.\textsuperscript{86} Inhibition of airway inflammation and eosinophilia has also been noted in mice using a vaccine that induces an immune response directed at IL-5. Immunotherapy with vaccinations appears to be effective in animal models, but extensive further research is required to demonstrate their applicability in humans.

In summary, biologic agents under development for the treatment of asthma offer the promise of therapies that target specific steps in the pathogenesis of the disease. However, with the exception of the IgE blocker omalizumab, these experimental therapies are several years away from potential use in regular clinical practice. Because of their experimental status, no data exist comparing the cost-effectiveness of these agents with more conventional therapies. As novel biologic therapies become available, the most appropriate use will need to be determined, particularly considering the current availability of many safe and effective pharmacotherapies that provide sufficient asthma control in the majority of patients.

**Conclusions**

Asthma care remains suboptimal despite major therapeutic advances over the past decade and the widespread dissemination...
of asthma management guidelines. Asthma is associated with significant morbidity and mortality, and, clearly, the primary goals of therapy are to decrease the number of exacerbations, reduce the severity of symptoms, reduce ED use and hospital admissions, and improve QOL. While progress has been made in reducing the rates of adverse outcomes of asthma, there remain unacceptably high rates of adverse outcomes, particularly in patients with poorly controlled moderate-to-severe disease. It is these patients who are suboptimally controlled on current standard-of-care medications and who consume a disproportionate percentage of the health care resources used in asthma care.

Patients with poorly controlled asthma stand to benefit from management strategies that guide clinicians and managed care organizations in making appropriate treatment decisions. Numerous observational studies have shown that practitioner compliance with national treatment guidelines and patient adherence to treatment regimens is less than optimal. Targeted educational initiatives for pharmacists and other health care professionals, as well as for patients, may help improve clinical and economic outcomes.

Asthma patients will also benefit from the continuing development of novel biologic therapies that specifically target the mechanisms responsible for persistent airway inflammation. The recently approved IgE blocker omalizumab and the numerous cytokine modulators and other biologically engineered agents still in development offer patients with poorly controlled, moderate-to-severe asthma promising alternatives to currently available treatments. However, the cost-effectiveness of these agents has yet to be determined.

ACKNOWLEDGMENT
The research and editorial support of Keith Engelke is greatly appreciated.

DISCLOSURES
Funding for this research was provided by an unrestricted educational grant from Genentech Inc. and Novartis Pharmaceuticals Corporation, and was obtained by author William W. Storms. The author discloses participation in speakers’ bureaus or paid consultant work for AstraZeneca, Aventis, Genentech, Merck, Novartis, and Schering-Plough and work as principal investigator in research funded by 3M, Adams Labs, Aerogen, AstraZeneca, Aventis, Bayer, Immunex, Iva, Merck, Novartis, Pfizer, Schering-Plough, Sepcror, and others. Administrative and technical support for this study was provided by Keith Engelke, Dover Communications, Blue Bell, Pennsylvania.

REFERENCES
Unmet Needs in the Treatment of Allergic Asthma: Potential Role of Novel Biologic Therapies


71. Partridge MR. Delivering optimal care to the person with asthma: what are the key components and what do we mean by patient education? Eur Respir J. 1995;8:298-305.


Determinants of the Cost-Effectiveness of Statins

ALAN MORRISON, PhD, and HELENE GLASSBERG, MD

ABSTRACT

OBJECTIVE: To examine the cost-effectiveness of statins in relation to different measures of effectiveness, differences in efficacy among individual statins, and the risk of coronary heart disease. Efficacy is defined here as the magnitude of the effect produced by a given amount of drug, as demonstrated in placebo-control trials; i.e., the effectiveness per unit dose.

DATA SYNTHESIS: Treatment guidelines categorize patients by their risk of coronary events and set lower target cholesterol levels for patients at higher risk. Statins vary in their efficacy. If effectiveness is expressed as percent lowering in low-density lipoprotein cholesterol (LDL-C) and relatively little cholesterol lowering is required—as in low-risk patients—even statins of low efficacy provide adequate cholesterol lowering, and drug price is the determining factor of cost-effectiveness. For patients at high risk—the primary target group, which has been expanded in recent guidelines—high-efficacy statins are required to meet the more aggressive cholesterol goals, and efficacy is the important determinant of cost-effectiveness. When effectiveness is expressed in terms of life-years saved, the cost-effectiveness of statins as a class for treatment of high-risk patients compares favorably with the cost-effectiveness of generally accepted medical treatments.

CONCLUSION: In order to optimize cost-effectiveness, the level of effectiveness required to treat the specific patient or patient group must be considered. Statin efficacy is the major determinant of cost-effectiveness when greater cholesterol lowering is required, i.e., for high-risk patients, who make up the primary target group. Statin price is the more important factor if only limited cholesterol lowering (e.g., 35% or less reduction in LDL) is required.

KEYWORDS: Hydroxymethylglutaryl-CoA reductase inhibitors, Cost-effectiveness analysis, Drug therapy, Economics, Coronary disease

J Managed Care Pharm. 2003;9(6):544-51

Determinants of the Cost-Effectiveness of Statins

High blood cholesterol is a major modifiable risk factor for coronary heart disease (CHD), the primary cause of ill…
reviewed the statin pharmacoeconomic literature and examined the factors that determine the cost-effectiveness of statin treatment.

### Incremental Cost-Effectiveness

The cost-effectiveness ratio usually referred to in pharmacoeconomics is the incremental cost-effectiveness ratio, which compares the costs and effects of one treatment (here, statins) with those of another (typically patients’ usual care). The incremental cost-effectiveness ratio is defined as the difference in the cost of the 2 treatments (statin and usual care) divided by the difference in their effectiveness:

\[
\text{Cost/Effectiveness} = \frac{\text{Cost (statin)} - \text{Cost (usual care)}}{\text{Effectiveness (statin)} - \text{Effectiveness (usual care)}}
\]

Alternative treatments typically vary both in their cost and in their effectiveness. The goal is to find the treatment with the least cost for the greatest effectiveness, i.e., the treatment with the smallest (most favorable) cost-effectiveness ratio. It is evident from the above equation that the cost-effectiveness ratio can be minimized by decreasing the cost or increasing the effectiveness. The equation does not, however, specify how costs and effectiveness are to be defined. The cost is expressed in currency, but effectiveness can be expressed in a number of ways. The measures of effectiveness we shall consider are the average percent reduction in LDL-C per patient, the proportion of patients reaching their LDL-C goal, and number of life-years saved (LYS). These different measures imply different time horizons and corresponding differences in the costs that must be considered.

### Differences Among Statins in Efficacy and Price

Six statins—atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin—are currently marketed in the United States. These statins vary considerably in price and efficacy. Efficacy is defined here as the magnitude of the effect—or effectiveness—produced by a given amount of drug. It can be understood as the inverse of potency, which is the amount of drug required to produce a given effect.

Table 2 lists prices and effectiveness, expressed as percent reduction in LDL-C, for different statin dosages. The effectiveness of statins increases with dosage, but efficacy is a fixed property for each statin. There are 2 ways of increasing the effectiveness: (a) increasing the dose of a given statin or (b) using the same dose of another statin with greater efficacy. There are limits, however, to the extent to which the effectiveness of statins with relatively low efficacy can be increased by raising the dose. As an example, the effectiveness of pravastatin 80 mg (measured as percent reduction in LDL-C) is 65% greater than that of pravastatin 10 mg but still less than that of rosuvastatin 5 mg and considerably less than that of higher dosages of statins with greater efficacy. Although it has been argued that the statins are clinically interchangeable, the differences in efficacy and price have important consequences in the determination of cost-effectiveness of statins, as demonstrated below.

### Relationship Between Efficacy and Cost-Effectiveness

The relationship between the efficacy and cost-effectiveness of individual statins can be visualized in a scatter plot of the cost versus the effect. Figure 1 shows such a plot, where effectiveness is expressed as percent lowering of LDL-C and costs are expressed as annual drug costs, based on October 2003 prices from an online pharmacy. The line in Figure 1 describes the “efficient frontier,” consisting of those points representing the lowest cost at any given level of effectiveness. Rosuvastatin and generic lovastatin lie on the efficient frontier at higher and lower levels, respectively, of effectiveness; fluvastatin 80 mg and atorvastatin 10 mg lie on the efficient frontier at intermediate levels of effectiveness. If, for example, the level of effectiveness is set at 45% reduction in LDL-C, rosuvastatin 10 mg has the lowest cost; in the absence of rosuvastatin, atorvastatin 40 mg would have the lowest cost at that level of effectiveness. At higher lev-

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Description†</th>
<th>10-Year Risk of Coronary Events</th>
<th>LDL-C Goal (mg/dL)</th>
<th>LDL-C Level at Which to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD risk equivalents</td>
<td>&gt;20%</td>
<td>&lt;100</td>
<td>≥130 (100-129, drug therapy optional)</td>
</tr>
<tr>
<td>≥2 Risk factors</td>
<td>≤20%</td>
<td>&lt;130</td>
<td>≥130 if 10-year risk of events = 10%-20%; ≥160 if 10-year risk of events &lt;10%</td>
</tr>
<tr>
<td>0-1 Risk factors</td>
<td>&lt;10%‡</td>
<td>&lt;160</td>
<td>≥190 (160-189, drug therapy optional)</td>
</tr>
</tbody>
</table>

ATP = Adult Treatment Panel.
CHD = coronary heart disease.
LDL-C = low-density lipoprotein cholesterol.
NCEP = National Cholesterol Education Program.

* ATP III is based on the earlier ATP II and has the same LDL-C goals for the 3 risk categories. The highest risk category in ATP III includes patients with a risk of major coronary events equivalent to that of established CHD (in ATP II, only patients with established CHD were in the highest risk category). CHD risk equivalents include other forms of atherosclerotic disease, diabetes, and combinations of multiple risk factors conferring a 10-year risk of CHD of ≥20%. By focusing more on the 10-year risk of coronary events rather than simply on risk factors and placing more patient groups in the higher risk categories, ATP III expands the indications for intensive cholesterol-lowering therapy.

† Major risk factors (exclusive of LDL-C) that modify LDL-C goals include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or use of an antihypertensive medication), low HDL-C (<40 mg/dL), family history of premature CHD, age (men ≥45 years; women ≥55 years). Diabetes is considered as a CHD risk equivalent.

‡ Almost all people with 0-1 risk factors have a 10-year risk <10%; 10-year risk assessment in these patients is not necessary.
### TABLE 2: Statin Dosages by Effectiveness (Percent Reduction in LDL-C) and Price*

<table>
<thead>
<tr>
<th>Statin</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>-</td>
<td>39% / $2.04</td>
<td>43% / $3.07</td>
<td>50% / $3.07</td>
<td>60% / $3.07</td>
<td>-</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>-</td>
<td>22% / $1.56</td>
<td>25% / $1.56</td>
<td>35% / $1.97</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Lovastatin*</td>
<td>-</td>
<td>21% / $0.96</td>
<td>27% / $1.11</td>
<td>31% / $1.97</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>-</td>
<td>22% / $2.50</td>
<td>32% / $2.52</td>
<td>34% / $3.70</td>
<td>37% / $3.76</td>
<td>-</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>45% / $2.22</td>
<td>52% / $2.22</td>
<td>55% / $2.22</td>
<td>63% / $2.22</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>26% / $1.63</td>
<td>30% / $2.18</td>
<td>38% / $3.72</td>
<td>41% / $3.72</td>
<td>47% / $3.73</td>
<td>-</td>
</tr>
</tbody>
</table>

* Data presented as percent lowering of LDL-C / price per unit. Price per tablet based on price of 90 tablets listed on drugstore.com on October 10, 2003. Values for the percent reduction in LDL-C are as cited in the Physicians’ Desk Reference or at www.rxlist.com for patients with primary hypercholesterolemia.†

† Prices are shown for generic lovastatin. Brand lovastatin prices are $1.28, $2.20, and $3.94 for 10, 20, and 40 mg, respectively.

### FIGURE 1: Annual Statin Cost by Percent Reduction in LDL-C

![Graph showing annual statin cost by percent reduction in LDL-C.](image)

In this presentation of cost-effectiveness, drug acquisition costs are the only costs considered, and effectiveness is expressed as the percent reduction in LDL-C. The curve approximates the “efficient frontier,” which tracks the lowest cost at any given level of effectiveness. Statin dosages that lie on the efficient frontier are labeled: L10, L20, and L40 generic, generic lovastatin 10 mg, 20 mg, and 40 mg; R5, R10, R20, and R40, rosuvastatin 5 mg, 10 mg, 20 mg, and 40 mg. Annual drug costs are based on prices for 90-pill packages, as listed on drugstore.com on October 10, 2003. Effectiveness data are from the Physician’s Desk Reference or www.rxlist.com as indicated in the legend to Table 2.†

### NCEP ATP III Risk Groups

When effectiveness is measured in terms of the proportion of patients reaching a target LDL-C threshold, effectiveness is dependent on patients’ initial LDL-C level and on their target level. Since the LDL-C target levels recommended by the NCEP are lower for patients at higher risk of CHD, effectiveness (expressed as the percent of patients reaching their LDL-C goal) and, therefore, cost-effectiveness, are dependent on the risk of CHD. Figure 2 shows a scatter plot of annual statin cost versus percent of patients achieving their ATP III treatment goal for patients in the highest risk category (CHD and CHD-risk equivalents). The picture is similar to that in Figure 1 for the statins shown, which include the higher-efficacy statins (atorvastatin, rosuvastatin, and simvastatin) and pravastatin. Again, atorvastatin 10 mg and rosuvastatin 5 mg, 10 mg, 20 mg, and 40 mg lie on the efficient frontier. The lower-efficacy statins, including pravastatin, are not effective in the high-risk patient group.

For patients in the lower ATP III risk groups, the data points and the efficient frontier seen in Figure 2 are shifted to the right. Table 3 shows the percent patients reaching their LDL-C goal for each of the 3 ATP III risk categories. For patients in the lowest risk group (fewer than 2 CHD risk factors), even low-efficacy statins such as pravastatin can bring most patients to their treatment goal (Table 3). Under these circumstances, it is drug price rather than efficacy that is the more important determinant of cost-effectiveness.

Table 3 illustrates the concept that, as CHD risk decreases, statin efficacy is relatively less important. There are, however, some caveats to the interpretation of these results. First, the relationship between CHD risk and effectiveness seen in Figure 2 is a consequence of the method of expressing effectiveness and the fact that the NCEP target LDL-C levels are set lower for higher-risk groups. Second, it is generally not the case that all low-risk patients reach their LDL-C treatment goal.
Outcomes studies have shown that many patients in the low-risk category do not reach their LDL-C goal. The failure to reach LDL-C goal may be due, in part, to low adherence, but inadequate treatment, due to failure to titrate and low-efficacy therapies, also contributes to failure to reach LDL-C goal. Third, the use of the percent of patients reaching their LDL-C treatment goal as a measure of effectiveness ignores any potential benefit of reducing LDL-C levels to below recommended thresholds.

Preliminary data from the Heart Protection Study indicate that statin treatment reduces the risk of coronary events in some patient categories (those with a history of heart disease, stroke, other occlusive vascular disease, or diabetes) even when their cholesterol levels are normal. Furthermore, there appears to be no threshold cholesterol value below which statin therapy is not associated with a benefit, even among those with pretreatment cholesterol levels below current national recommended targets.

**Titration to LDL-C Treatment Goal**

The situation illustrated in Figures 1 and 2, in which patients continue with their initial statin dose, may, in fact, represent reality for many patients. Outcomes studies indicate that many patients—about half in some studies—do not receive LDL-C level monitoring or appropriate statin dose adjustment. In contrast, the NCEP guidelines recommend drug titration until patients reach their treatment goal (or the maximum dose) if the initial dose is inadequate. In this scenario, effectiveness is appropriately measured as the percent of patients reaching their LDL-C treatment goal.

The costs that must be considered are all those associated with measuring and remeasuring patients’ cholesterol levels, including the costs of office visits and laboratory tests, as well as drug acquisition costs. This scenario was examined in a pharmacoeconomic analysis based on a 54-week, randomized, multicenter trial in the United States, in which starting doses of 4 statins were titrated upwards until patients with and without atherosclerosis reached the ATP II goal for LDL-C (or the maximum dose was reached). All related medical costs (drugs, office visits, laboratory tests) were considered from the perspective of insurers and managed care organizations and were based on national averages. The statin with the greatest efficacy—atorvastatin, in that study—was “dominant,” i.e., it was both more effective and less costly than dose titration with the other statins. Note, however, that once drug titration has been completed, the costs of long-term maintenance therapy are principally the direct drug-acquisition costs.

**Cost per Life-Year Saved**

Since hypercholesterolemia is clinically silent, survival is the ultimate measure of statin effectiveness, not cholesterol lowering. When effectiveness is measured in terms of survival as the number of LYS, the costs that must be considered include not just statin therapy and dose titration but also medical treatments for CHD (which are reduced for patients treated with statins). More than 30 pharmacoeconomic analyses of the cost
### TABLE 4
Cost Per Life-Year Saved for Patients With and Without Preexisting Coronary Heart Disease in the United States

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>Cost per LYS ($1,000s)†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With Preexisting CHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ashraf et al. (1996)28</td>
<td>Pravastatin</td>
<td>13.0 – 1,500</td>
</tr>
<tr>
<td>Elliott 1999†‡*‡</td>
<td>Various</td>
<td>2.3 – 30.9</td>
</tr>
<tr>
<td>Gane 2000*‡‡</td>
<td>Pravastatin</td>
<td>5.4 – 97.8</td>
</tr>
<tr>
<td>Goldman 1991‡</td>
<td>Lovastatin</td>
<td>&lt;0 – 310</td>
</tr>
<tr>
<td>Grover 1999‡‡</td>
<td>Simvastatin</td>
<td>4.4 – 21.7</td>
</tr>
<tr>
<td>Huse 1998‡‡</td>
<td>Various</td>
<td>8.2 – 63.6</td>
</tr>
<tr>
<td>Johansson 1997‡‡</td>
<td>Simvastatin</td>
<td>3.8 – 27.4</td>
</tr>
<tr>
<td>Prosser 2000*‡‡</td>
<td>Pravastatin</td>
<td>1.8 – 40.0</td>
</tr>
<tr>
<td><strong>Without Preexisting CHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldman 1991‡</td>
<td>Lovastatin</td>
<td>6.0 – 297</td>
</tr>
<tr>
<td>Hay 1991‡</td>
<td>Lovastatin</td>
<td>1.500</td>
</tr>
<tr>
<td>Huse 1998‡‡</td>
<td>Various</td>
<td>4.3 – 46.3</td>
</tr>
<tr>
<td>Prosser 2000*‡‡</td>
<td>Pravastatin</td>
<td>54.0 – 1,400</td>
</tr>
</tbody>
</table>

LYS = life-years saved.
* Range of values (lower and upper) for the highest- and lowest-risk patient groups, respectively (except where indicated).
† Costs are unadjusted for inflation and are expressed in S.U.S. for 1989.27,28
‡ The lower and upper limits represent the most favorable and least favorable model scenarios rather than patient risk groups.
§ Cost per quality-adjusted life-year reported.

### TABLE 5
The Cost Per Life-Years Saved of Statin Treatment Decreases as the Risk Factors for Events Increase

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Sex</th>
<th>HTN</th>
<th>Obese</th>
<th>Smoker</th>
<th>CHD</th>
<th>Cost-Effectiveness ($/LYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥300</td>
<td>F</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>130,000</td>
</tr>
<tr>
<td>250-299</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>93,000</td>
</tr>
<tr>
<td>≥300</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>58,000</td>
</tr>
<tr>
<td>≥300</td>
<td>M</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>28,000</td>
</tr>
<tr>
<td>≥300</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>17,000</td>
</tr>
<tr>
<td>≥300</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>15,000</td>
</tr>
<tr>
<td>≥250</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17,000</td>
</tr>
<tr>
<td>≥250</td>
<td>F</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8,100</td>
</tr>
<tr>
<td>≥250</td>
<td>M</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1,468</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease.
HTN = hypertension.
LYS = life-years saved.
* Data of Goldman et al. for people 55 to 64 years of age treated with lovastatin 20 mg.27 Definitions: hypertensive, diastolic blood pressure ≥105 mm Hg; normotensive, diastolic blood pressure <95 mm Hg; obese, ≥130% of ideal weight; nonobese, <110% of ideal weight.

The cost per quality-adjusted life-year (QALY) was determined; this adjustment for quality of life increases cost-effectiveness ratios by about 10% to 20%.26

The cost per LYS for patients with preexisting CHD, and for those without CHD but with multiple risk factors, falls inside the threshold for an acceptable cost-effective ratio: the value of this threshold was about U.S. $30,000 in the early 1990s and $40,000 to $50,000 more recently. The cost-effectiveness values for statins also generally fall within the range of values for other currently accepted treatments: $7,700 to $10,000 for single-vessel angioplasty in patients with severe angina; $18,000 for annual screening for colorectal cancer with a fecal occult blood test; $108,000 to $112,000 for single-vessel angioplasty in patients with mild angina; $15,000 to $96,500 for treatment of hypertension in patients aged 35 to 64 years; and $150,000 for annual mammography in women aged 55 to 65 years (cost-effectiveness ratios expressed as 1995 U.S.$ per QALY).26,30

### Specific Risk Groups
In addition to patients with CHD, several at-risk patient groups have been subjected to cost-effectiveness analysis. Statin treatment of heterozygous familial hypercholesterolemia, which affects approximately 0.5 million people in the United States, is cost-saving for men and costs only $300 per LYS for women, even without additional risk factors.31 Patients with type-2 diabetes have a risk of coronary events comparable to that of non-diabetic patients with a history of myocardial infarction.32 This suggests that the cost-effectiveness of statin treatment of these
Determinants of the Cost-Effectiveness of Statins

2 populations should be equivalent; this has not, however, been demonstrated in the primary prevention cost-effectiveness literature, where diabetes has been treated as a risk factor for CHD comparable to smoking or hypertension. Secondary prevention of coronary events in diabetic patients was studied in post hoc analyses of patient subgroups of the 4S trial. The cost per LYS of simvastatin treatment was substantially lower for diabetic than for nondiabetic patients with CHD.

Statin Pricing

In Figures 1 and 2, we presented cost-effectiveness data using current statin prices from an online pharmacy. We note that there have been changes in pricing policy by drug manufacturers over the past several years, such as a switch for some statins from higher prices for higher doses to flat pricing, as well as the introduction of new statins. Rosuvastatin has displaced atorvastatin at the upper end of the efficient frontier seen in Figure 1, just as atorvastatin previously displaced simvastatin. Lovastatin, which was the first statin to be marketed in the United States (in 1987), became available as a generic drug in 2002. Generic lovastatin has replaced fluvastatin at the lower end of the efficient frontier shown in Figure 1. However, generic lovastatin 40 mg is comparable in effectiveness to simvastatin 10 mg or pravastatin 20 mg, which bring less than 20% of high-risk patients to their LDL-C goal (Figure 2), so that generic lovastatin can only compete (on the basis of price) at lower levels of effectiveness. Outcomes studies indicate that the majority of patients currently being treated with statins are in the CHD or risk-equivalent category.

Limitations

Managed care organizations typically contract for statin prices at discounts to the AWP. Discount prices for the statin drugs were obtained from an online pharmacy Web site to help account for the difference in AWP prices and the actual costs incurred by managed care organizations (MCOs), prior to member cost share. However, actual statin purchase costs will differ among MCOs, and this may change the cost-effectiveness rankings of statins at any given level of effectiveness. Nevertheless, in order to optimize cost-effectiveness, MCOs must consider the level of effectiveness that is required to treat individual patients or specific patient groups rather than simply the lowest purchase price.

Summary

In principle, the incremental cost-effectiveness ratio can be reduced by decreasing the cost or by increasing the effectiveness of the therapy. Both of these effects are evident in the comparisons of individual statins. When effectiveness is expressed as percent reduction in LDL-C and cost as statin price, increasing the efficacy (the effect per unit dose) decreases the cost-effectiveness ratio and, when greater LDL-C lowering is required (as is the case with patients with CHD or CHD-equivalent risk), the statins with the greatest efficacy have the lowest (most favorable) cost-effectiveness ratios. If limited LDL-C lowering is required (as may be the case for some low-risk patients), drug price may be the more important factor.

The same relationships between the cost-effectiveness ratio and statin efficacy and price are also seen when effectiveness is expressed as the proportion of patients reaching LDL-C goal. The inverse relationship between statin efficacy and the cost-effectiveness ratio holds up under the circumstances of statin titration to treatment goal and the inclusion of all related treatment costs. When effectiveness is expressed in terms of LYS and all long-term medical costs are taken into account, the incremental cost-effectiveness ratio decreases as the risk of CHD increases. For patients with preexisting CHD or CHD-equivalent risk of coronary events, the cost-effectiveness ratio of statins as a class compares favorably with generally accepted medical treatments.

The results suggest 3 strategies for minimizing the cost-effectiveness ratio of statin therapy. First, preferentially treat patients with existing CHD or equivalent risk; second, use statins with the greatest efficacy for these patients and for patients at low risk but with high baseline LDL-C levels; and third, use a less-expensive statin when less LDL-C lowering is needed, as in low-risk patients with lower baseline LDL-C levels.

DISCLOSURES

Funding for this study was provided by AstraZeneca LP and was obtained by author Alan Morrison. Morrison served as principal author of the study. Study concept and design and analysis and interpretation of data were contributed by Morrison. Drafting of the manuscript was the work of Morrison, and its critical revision was the work of Morrison and author Helene Glassberg.

REFERENCES

Determinants of the Cost-Effectiveness of Statins


42. Davidson M, Ma P, Stein EA, et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvast.


Longitudinal Assessment of a Diabetes Care Management System in an Integrated Health Network

DAVID L. LARSEN, RN, MHA; WAYNE CANNON, MD; and STEVEN TOWNER, MD

ABSTRACT

OBJECTIVE: To describe the results of longitudinal assessment of the results of a disease management process developed in a large integrated health care system that successfully improved care for patients with diabetes. Outcome measures included rates of testing of hemoglobin A1c (HbA1c) and low-density lipoprotein (LDL), rate of annual eye exams, and LDL and HbA1c values.

METHODS: Intermountain Health Care (IHC) initiated the development of a Diabetes Care Management System (DCMS) in early 1998. The DCMS was developed as a comprehensive population-based disease management system. It includes provider education programs; performance feedback to physicians; clinical quality performance incentives for physicians; patient education programs; patient incentive, reminder systems to encourage compliance with best care process models; and tracking of physician behavior change and patient compliance with diabetes therapy. A multifaceted intervention and education approach was chosen because of the complexity of the diabetes treatment process.

RESULTS: The percentage of patients with at least one annual HbA1c test increased from 78.5% in 1998 to 90.5% in 2002. During the same time period, the percentage of patients whose most recent HbA1c was less than 7.0 increased from 33.5% to 52.8%, average HbA1c decreased from 8.1 to 7.3, and the percentage of patients whose most recent HbA1c was greater than 9.5 decreased from 34.6% to 21.4%. The percentage of patients who had an LDL cholesterol screening test within the prior 2 years increased from 65.9% in 1998 to 91.7% in 2002. During the same time period, the percentage of patients whose most recent LDL cholesterol was less than 130 mg/dL increased from 39.9% to 69.8%. The percentage of diabetes patients who had an annual eye exam increased from 52% in 1998 to 62% in 2002.

CONCLUSION: A multifaceted approach to improving diabetes management has led to improved performance in clinical measures related to diabetes care that have been shown to reduce the risk of patients with diabetes developing diabetes-related complications. All components of the diabetes management continuum of care, including primary care physicians, specialists, office staff, patients, diabetes educators, and others, were involved in the care improvement activities.

KEYWORDS: Diabetes, Disease management, Clinical practice guideline, Care process model, Integrated health system, Registry

J Managed Care Pharm. 2003;9(6):552-58

A ggressive management of diabetes is well known to decrease both mortality and morbidity from complications related to the disease. From 1998 to 2003, Intermountain Health Care (IHC) developed a system-wide initiative to improve care for patients with diabetes. This initiative is known as the Diabetes Care Management System (DCMS). It is a coordinated effort involving IHC senior management, IHC-employed physicians, network physicians not employed by IHC who see IHC Health Plans patients, and IHC Health Plans, all of which is coordinated through the Primary Care Clinical Program of IHC. Specific goals of the DCMS include the following:

1. increase the annual testing rate of hemoglobin A1c (HbA1c) in adult patients with diabetes,
2. increase the percentage of adult diabetes patients with favorable HbA1c values,
3. decrease the percentage of adult diabetes patients with unfavorable HbA1c values,
4. increase the percentage of adult patients with diabetes tested at least once every 2 years for low-density lipoprotein (LDL) cholesterol,
5. increase the percentage of adult diabetes patients with favorable LDL values,
6. decrease the percentage of adult diabetes patients with unfavorable LDL values, and
7. increase the percentage of adult diabetes patients with an annual diabetes eye exam.

IHC is an integrated health network with 400 employed physicians, 100 outpatient clinics, 22 hospitals, and a health plan that insures 467,000 members. There are also approximately 800 affiliated non-IHC-employed primary care physicians.

Disease management activities throughout the system are led by “clinical programs.” Clinical programs established to date include cardiovascular, women and newborn, neuromusculoskeletal, pediatric subspecialty, oncology, behavioral health, intensive medicine, and primary care (Figure 1). Clinical programs are formed around like processes of clinical care such as the Primary Care Clinical Program. Each clinical program builds Care Management Systems (disease management programs) around the highest-volume clinical processes such as asthma, diabetes, depression, hypertension, heart failure, otitis media, and attention deficit hyperactivity disorder for primary care. Each clinical program provides the resources necessary to focus on the development, implementation, and outcomes measurement of each clinical process.

Each clinical program has its own work group and develop-
Diabetes Care Process Model

The center of the DCMS is an evidence-based diabetes best-care practice model (CPM). This detailed CPM is based on nationally recognized guidelines from the American Diabetes Association, with updates from current scientific literature, and was developed by a multidisciplinary group of providers, including endocrinologists, primary care physicians, pharmacists, diabetes educators, and nurses. Pharmacists are included on all development teams and in work groups, where appropriate, to provide input on fundamental knowledge and expert advice in CPM development. They also are valuable in providing input regarding drug formulary preferences and other health plan issues. The diabetes CPM was distributed to physicians via academic detailing of small groups of 6 to 8 primary care physicians, conducted by an endocrinologist, to discuss the science of the disease management system, which is then refined by the larger development team. This is then coordinated through central leadership and a large guidance council of approximately 25 members, composed of primary care medical directors and nurse managers, all under the direction of the Primary Care Clinical Program staff.

Diabetes Performance Measurement

System and Diabetes Registry

The second part of the DCMS was the development of a measurement system founded on diabetes best-care practices. A diabetes datamart (registry) was established by combining data from 5 different data sources: electronic laboratory, health plan claims, physician billing, clinical information system, and case mix (from hospital/facility billing data). These 5 databases comprise the available outpatient clinical information and financial data used to identify patients with diabetes to populate the registry and then match patients with the dates and results of their lab tests, e.g., HbA1c and LDL cholesterol. These databases were also used to identify and match patients with their primary care physician and specialist, if applicable. The registry was initially populated in July 1999 with approximately 18,000 patients and has been updated quarterly; the most recent update period ended June 30, 2003, and includes approximately 25,500 patients.

The 5 databases are updated each calendar quarter, and the registry is refreshed using a multiple-step process to import the new data into the registry. Of the 25,500 patients in the registry, approximately 9,500 are members of IHC Health Plans (a multiproduct health plan with a health maintenance organization and point-of-service options). The remaining 16,000 patients consist of patients with diabetes not insured by IHC Health Plans but treated by IHC-employed physicians from the IHC Physician Division.

The 25,500 patients in the diabetes registry are treated by approximately 750 primary care physicians. The primary care physician with the most diabetes patients in the registry has 278 patients, and the registry is used to produce reports for physicians who have as few as 1 or 2 patients.

Patient detail reports are produced quarterly for each primary care physician from the diabetes registry. The reports include: (1) name, medical record number, and phone number for each patient; (2) the most recent values for HbA1c, LDL, and urine microalbumin; and (3) the date of the patient’s last eye exam. Patients are sorted by risk (lack of needed test or abnormal test result).

A Provider Summary Report (Figure 2) is included with this patient detail report; it shows a physician his or her testing rates compared with peers in both the physician’s geographical region and the entire IHC system. The Provider Summary Report also shows relative values of HbA1c and LDL in patients cared for by the provider and how those values compare with the region or system. These results are also available through a password-protected site on the IHC intranet. On this Web site, a physician can view his or her Provider Summary Report and the same patient detail report that is distributed quarterly. The patient detail report may be sorted by risk (HbA1c values higher than 9), or alphabetically. The intranet Web site also has performance reports for these same measures by quarter over the last 4 years for the region or system.

Patient Education and Self-Management

The third part of the DCMS is a broad array of patient education programs. These include IHC-developed patient handouts, outpatient programs that bring a certified diabetes educator and
a registered dietician into physician offices, and Web-based patient education programs. Patient handouts are available to physicians through the electronic medical record used by IHC-employed physicians, the IHC intranet, or on the Internet (www.IHC.com). Hard copies can be ordered for the cost of shipping and handling. These materials are also available to patients at the Diabetes Online Resource Center Internet site (www.IHC.com). Telephone-based care management is provided for patients with diabetes who are high risk (HbA1c values higher than 9), and many large IHC-employed physician clinics have on-site nurse care managers to assist with patient self-management.

Pharmacists at IHC participate in the diabetes CMS in several ways. Clinical pharmacists from IHC Health Plans provide routine consultation with disease state managers on complicated cases. IHC clinic-based pharmacists work closely with patients to educate them on the importance of glucose testing and medication compliance. Pharmacists in all IHC facilities work to make sure all diabetics have glucose meters, understand how to use them, and provide additional training to supplement training received from diabetes educators. All pharmacists throughout the IHC system continually work to help patients avoid drug interactions and adverse events.

**Physician Office Implementation Tools**

The fourth part of the DCMS includes tools that were developed for physicians and their office staff to facilitate the implementation of the DCMS in their office. The tools include:

1. templates on the electronic medical record (EMR) to make charting easier for patients with diabetes;
2. a report, produced by the EMR, for patients with diabetes in advance of their medical visit that provides an electronic flowchart of all of the patient's key diabetes management parameters and alerts the physician to interventions that need to occur at that medical visit;
3. manual diabetes data flowsheets that record lab values and

---

**FIGURE 2** Examples of Provider Summary Report for Diabetes Patient

**Diabetes Summary Report**

**Provider:**

**Period:** January 2002-December 2002

**Patients Tested (Proportion of Total Patients %) - All Patients**

<table>
<thead>
<tr>
<th>Provider</th>
<th>Region</th>
<th>System</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>190 (99%)</td>
<td>1,326 (90%)</td>
</tr>
<tr>
<td>LDL/Trig</td>
<td>185 (96%)</td>
<td>1,357 (92%)</td>
</tr>
<tr>
<td>Eye exam</td>
<td>28 (78%)</td>
<td>156 (50%)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>172 (90%)</td>
<td>1,064 (72%)</td>
</tr>
<tr>
<td>Total patients</td>
<td>192</td>
<td>1,481</td>
</tr>
</tbody>
</table>

- LDL measures represent 2 years, ending in the chosen period.
- Eye exam % calculated using IHC Health Plans patients only.
- Includes spot microalbuminuria or 24-hour microalbuminuria or positive UA tests for protein, within the reporting period, or any history of treatment for nephropathy.
clinical findings at each visit and can therefore be easily trended across multiple visits;
4. patient self-history forms;
5. methods to alert the physician that the patient has diabetes;
6. monofilament fibers and training in their use for foot exams; and
7. organized resources such as the American Diabetes Association or the Juvenile Diabetes Foundation for patients in financial need or with other socioeconomic problems.

To introduce and implement the DCMS, small-group meetings of 6 to 8 physicians were conducted, with separate small-group meetings for the physicians’ office staff. These meetings allowed a physician-educator who was a diabetes expert to present the CPM, answer questions, and then present to each physician the diabetes Provider Summary Report related to that physician’s practice. This report allowed each physician to compare his or her performance with the CPM. The first encounter with the performance reports for many physicians resulted in a predictable response—the physician-specific data did not match the physicians’ perception of their level of testing and control for their diabetic patients. Initial physician challenge of the data in the performance reports evolved into familiarity and confidence in the data and cooperation in using the reports to improve their clinical performance.

After the initial DCMS implementation meetings, including the important opportunity for physicians to challenge the data, the diabetes Provider Summary Reports were distributed to each physician on a quarterly basis. These reports became a means of identifying patients that required direct physician contact and follow-up. Periodic small-group follow-up meetings were held to introduce revisions to the CPM, introduce new data included on the performance reports, and conduct more detailed implementation education.

## Diabetes Quality Improvement Financial Incentive

A quality improvement (QI) financial incentive program was also developed by IHC Health Plans to improve physician performance on the measured data elements. The QI financial incentive represents 0.5% to 1% of total physician compensation, and one half of the total managed care QI financial incentive for physicians is based on diabetes measures. The 2 diabetes CPMs that are tied to the QI financial incentive are (1) the percentage of diabetes patients who received an HbA1c test in the past year and (2) the percentage of diabetes patients who had an LDL test in the past 2 years.

## Direct Patient Outreach

In addition to these aforementioned interactions with physicians, direct outreach to patients was initiated in 1998. Diabetes patients who did not schedule routine diabetes-related office visits or did not have an HbA1c test in the previous 12 months were invited to diabetes screening clinics.

Diabetes calendars were distributed by mail to all IHC Health Plan members with diabetes. The calendars focused on a different diabetes self-management concept each month, with...
Longitudinal Assessment of a Diabetes Care Management System in an Integrated Health Network

reminders for appropriate self-management activities indicated on various days throughout the month. Each month, a reminder postcard that correlated to the diabetes self-management concept depicted on the calendar was mailed to each of the members with diabetes.

Patients with diabetes received a status report by mail regarding their own compliance with appropriate tests or exams to screen for diabetes complications. The report contained dates and laboratory values for the patient’s most recent HbA1c and LDL tests and the date of the patient’s most recent eye exam.

To encourage eye exams, patients were offered a 60-minute, long-distance telephone debit card as an incentive to complete their annual eye exam. During the time the calling card incentive was in place, the eye exam rates increased by approximately 5%, from 37% to 42%.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Diabetes Management Performance Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance Measurement</td>
<td>1998</td>
</tr>
<tr>
<td>Annual HbA1c†</td>
<td>78.5%</td>
</tr>
<tr>
<td>HbA1c &gt; 9.5†</td>
<td>34.6%</td>
</tr>
<tr>
<td>Average HbA1c</td>
<td>8.1</td>
</tr>
<tr>
<td>HbA1c &lt; 7</td>
<td>33.3%</td>
</tr>
<tr>
<td>Biannual LDL†</td>
<td>65.9%</td>
</tr>
<tr>
<td>LDL &lt; 130†</td>
<td>39.9%</td>
</tr>
<tr>
<td>Annual eye exam†</td>
<td>52.0%</td>
</tr>
</tbody>
</table>

* Number of patients in the diabetes datamart (registry).
† HEDIS measure.
‡ A chi-square test of proportions with uncorrected P value was used to measure the statistical difference between each of the listed performance measures in 1999 and 2002.

Results

The improvement in each of the key performance measures in diabetes management is both clinically important and statistically significant (Table 1). This CPM was implemented for all patients with diabetes in the IHC system. Thus, there is not a control group. However, compared with national benchmarks, currently, these results exceed the 90th percentile in all areas except annual eye exam.14

The percentage of patients with at least one annual HbA1c test increased from 78.5% in 1998 to 90.5% in 2002 (Figure 3). As the DCMS was implemented, the first emphasis was on improving the percentage of patients with at least one HbA1c measurement. The rate of testing has leveled out at approximately 91% over the last 3 years, without improvement, and is thought to be reflective of a harder-to-reach population to improve beyond the current level of performance. Accordingly, we have implemented a new lab requisition program to address this challenge. This program is described in “Summary and Future Plans” below.

The percentage of patients whose most recent HbA1c value was less than 7 increased from 33.5% in 1998 to 52.8% in 2002 (Figure 4), and the average HbA1c decreased from 8.1 to 7.3 (Figure 5). Improved HbA1c levels have been clinically proven to result in reduction of diabetes complications.7-9 The percentage of patients whose most recent HbA1c value was greater than 9.5 decreased from 34.6% in 1998 to 21.4% in 2002 (Figure 6). The percentage of patients who had an LDL cholesterol screening test within the last 2 years increased from 65.9% in 1998 to 91.7% in 2002 (Figure 7), and the percentage of patients whose most recent LDL cholesterol was less than 130 mg/dL increased from 39.9% in 1998 to 69.8% in 2002 (Figure 8). These achievements in quality improvement should significantly reduce the risk of cardiovascular complications in these diabetes patients.7-9

The percentage of patients who had an annual eye exam increased from 52.0% in 1998 to 62.0% in 2002 (Figure 9).
Improving the rate of eye examinations for patients with diabetes proved to be one of the most difficult performance levels to affect. We found that primary care physicians have relatively little control over whether patients follow their advice to obtain an eye exam. Also, primary care physicians may not focus on this outcome because of the general lack of communication between primary care and secondary care providers. These difficulties led to the development and implementation of the patient incentive program for eye exams.

Summary and Future Plans

A multifaceted approach to improving diabetes management resulted in improved intermediate outcomes in diabetes care (Figure 10) and should result in less risk of long-term diabetes complications for these patients. A multispecialty diabetes work group of 10 members, including primary care physicians, endocrinologists, physician office staff, diabetes educators, and pharmacists led by a physician diabetes champion, developed and implemented the DCMS. Many of the interventions initiated through the IHC DCMS are replicable in other managed care settings. Plans for the future include further enhancements to the patient education materials for diabetes, expansion of the resources devoted to diabetes education and care management, and further development of the EMR system related to tracking and monitoring diabetes patients. The diabetes registry will be used to develop additional patient care management reports such as medication compliance reporting and predictive modeling of patients to identify those patients most likely to incur significant future health care expenditures.

While our integrated health system has used physician-specific performance reports for diabetes care for several years, many physicians have expressed concern regarding the time and office resources that are necessary to schedule patients for routine and follow-up testing and subsequent office visits. In response to this concern, the health system has developed a laboratory requisition direct-mailing process that includes HbA1c, lipid profile, and microalbumin screening.

Diabetes laboratory requisition direct mailing has been piloted in several physician offices. This new enhancement in DCMS identifies diabetes patients who do not have a record of receipt of the appropriate diabetes complication screening tests in the time period specified. Laboratory requisition forms for direct mailing are produced in bulk, aggregated, and then forwarded to each primary care physician’s office. The laboratory requisition is produced with prepaid postage and includes space for the physician to personalize the mailing with a signature. The patient direct-mail letters include the list of locations where the lab tests can be performed. The actual tear-off laboratory requisition includes all of the required information necessary to process the laboratory tests automatically. The primary care physician verifies that the patient is active in the practice, personalizes the requisition with a signature, seals the trifold requisition, and either mails

---

**FIGURE 8** Percent of Diabetes Patients With LDL Cholesterol <130 mg/dL

**FIGURE 9** Percent of Diabetes Patients Who Received an Eye Exam in Previous 12 Months

**FIGURE 10** Diabetes Care Management System (DCMS) Results, 1998-2002
it to the patient directly or returns the requisitions in bulk to be mailed to patients by the health system.

This laboratory requisition process allows for personalized outreach to patients from each physician's office while incurring minimal use of office staff. This process is expected to reduce the number of physician office visits, and the health system plans to expand the laboratory requisition program to all primary care offices that have patients in the diabetes registry.

ACKNOWLEDGMENTS

The authors wish to acknowledge the following contributions in the preparation of this research and manuscript: Ilene Tippets for her input on study concept and design and analysis and interpretation of data, Matt Snell for his statistical expertise and analysis and interpretation of data, and Steven Barlow, Jonathan Despain, and David Hale, for their administrative and technical support related to the building of the diabetes registry and the reports included in this manuscript.

DISCLOSURES

No outside funding supported this study. Author David L. Larsen served as principal author of the study. Study concept and design were contributed by Larsen and authors Wayne Cannon and Steven Towner. Drafting of the manuscript and its critical revision were the work of Larsen and Cannon. Analysis and interpretation of data was contributed by Larsen, Cannon, and Towner, and statistical expertise was contributed primarily by Matt Snell.

REFERENCES

ABSTRACT

OBJECTIVES: (1) Describe the relevance of off-label use of gabapentin to managed care pharmacy; (2) summarize recent FDA warnings and media reports related to off-label gabapentin use; (3) review medical information pertaining to the off-label use of gabapentin; (4) outline alternatives to off-label use of gabapentin in an evidence-based fashion, where literature exists to support such alternatives; and (5) encourage key clinicians and decision makers in managed care pharmacy to develop and support programs that restrict the use of gabapentin to specific evidence-based situations.

SUMMARY: Gabapentin is approved by the U.S. Food and Drug Administration (FDA) for adjunctive therapy in treatment of partial seizures and postherpetic neuralgia. Various off-label (unapproved) uses have been reported, and the use of gabapentin for off-label purposes has reportedly exceeded use for FDA-approved indications. Pharmaceutical marketing practices and physician dissatisfaction with currently available pharmacological treatment options may be key factors that contribute to this prescribing trend.

Recently, the media has focused on these issues, noting that many cases of reported safety and effectiveness of gabapentin for off-label use may have been fabricated. A thorough review of the medical and pharmacy literature related to off-label use of gabapentin was performed, and a summary of the literature for the following conditions is presented: bipolar disorder, peripheral neuropathy, diabetic neuropathy, complex regional pain syndrome, attention deficit disorder, restless legs syndrome, trigeminal neuralgia, periodic limb movement disorder of sleep, migraine headaches, and alcohol withdrawal syndrome. A common theme in the medical literature for gabapentin is the prevalence of open-label studies and a lack of randomized controlled clinical trials for all but a small number of indications.

CONCLUSIONS: In the majority of circumstances where it has reported potential for “off-label” use, gabapentin is not the optimal treatment. The off-label use of gabapentin for indications not approved by the FDA should be reserved for cases where there is solid research support (e.g., diabetic neuropathy and prophylaxis of frequent migraine headaches). Managed care pharmacists should develop programs to restrict the use of gabapentin to these specific evidence-based situations, and key decision makers in managed care practice should feel confident in supporting these use restrictions for gabapentin.

KEYWORDS: Neurontin, Gabapentin, Off-label, Comparison, Bipolar, Restless legs, Trigeminal neuralgia, Migraine, Peripheral neuropathy, Diabetic neuropathy, Complex regional pain syndrome, Attention deficit disorder, Periodic limb movement disorder of sleep, Alcohol withdrawal syndrome

J Managed Care Pharm. 2003;9(6):559-68

Gabapentin (Neurontin) was approved by the U.S. Food and Drug Administration (FDA) on December 30, 1993, for adjunctive therapy in the treatment of partial seizures, with and without secondary generalization, in patients above the age of 12 years. The FDA approved the indication for adjunctive therapy for partial seizures in children aged 3 to 12 years in October 2000 and the indication for postherpetic neuralgia in adults in May 2004.

Gabapentin is an amino acid that is structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA); however, its antiepileptic activity appears unrelated to any direct effects on the GABAergic system. The mechanism of action of the drug has led to tremendous scientific speculation as to the potential merits of the drug in other clinical conditions.

Since its introduction to the market in 1993, gabapentin has gained widespread use, and a significant portion of this use has been for non-FDA approved uses (Figure 1). A retrospective review of one managed Medicaid plan demonstrated that 95% of patients were using gabapentin for off-label diagnoses. The manufacturer of gabapentin has been accused of illegal promotion of the drug to prescribing physicians for at least 10 “off-label” medical conditions. The FDA has issued various warning statements to the manufacturer as a result of these marketing practices.

While various summaries of these issues are accessible in the public domain, a more thorough evaluation of the issues from a clinical standpoint is warranted. The intent of this review is to tie the media concerns to clinical evidence obtained from a thorough literature review so that managed care pharmacists and physicians will be better prepared to address the subject of appropriate use of gabapentin.
Examination of the Evidence for Off-Label Use of Gabapentin

TABLE 1: Summary of Open-Label Trials and Case Reports With Gabapentin in Bipolar Illness

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Population</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghaemi SN, Goodwin FK, Open, prospective chart review</td>
<td>8 patients received gabapentin monotherapy; 13 received adjunctive therapy</td>
<td>21 outpatients meeting DSM-IV criteria for bipolar spectrum disorder (type I, type II, NOS cyclothymia) who were treated with gabapentin</td>
<td>Alone, or as adjunct, gabapentin appeared moderately effective in treating depression. Using the CGI-BP, gabapentin was moderately to markedly effective in 43% of patients for overall bipolar illness, 38% for depressive symptoms, and 25% for manic symptoms.</td>
<td>J Affect Disord. 2001,65(2):167-71.</td>
</tr>
<tr>
<td>Altshuler LL, Keck PE, McElroy SL, et al. Open</td>
<td>Adjunctive therapy with gabapentin 600 mg-3,600 mg/day</td>
<td>28 bipolar patients, 5 experiencing manic symptoms, 5 experiencing depressive symptoms, and 5 experiencing rapidly cycling symptoms refractory to at least 1 mood stabilizer</td>
<td>As adjunctive therapy, gabapentin appears to have acute antimanic and antidepressant properties. Fourteen of the 18 (78%) mania or hypomania patients had a positive response. All of the patients treated for depression had positive response. (Positive response was a CGI response of much or very much improvement.)</td>
<td>Bipolar Disord. 1999;1(1):61-65.</td>
</tr>
<tr>
<td>Carta MG, Hardoy MC, Dessi I, et al. Open</td>
<td>Adjunctive therapy with gabapentin 300 mg-900 mg</td>
<td>10 patients with intellectual disability and demonstrable increases in symptomatology during significant life events that had interfered with or induced interruption of their rehabilitation programs</td>
<td>A positive response to therapy was observed with subsequent improvement of psychopathological conditions, particularly for anxiety and depressive symptoms.</td>
<td>J Intellect Disabil Res. 2001;45(pt 2):139-45.</td>
</tr>
<tr>
<td>Sokolski KN, Green C, Maris DE, et al. Open label</td>
<td>Adjunctive therapy for 1 month</td>
<td>10 bipolar patients with mixed symptoms who had previously demonstrated only partial treatment responses</td>
<td>Decreases in Hamilton depression (P&lt;0.05) and Bech mania ratings (P&lt;0.01) were evident in the first week of treatment and were sustained. Potent early improvements were noted in early, middle, and late insomnia.</td>
<td>Ann Clin Psychiatry. 1999;11(4):217-22.</td>
</tr>
<tr>
<td>Young LT, Robb JC, Hasey GM, et al.</td>
<td>Adjunctive treatment for up to 6 months</td>
<td>37 patients with bipolar type 1 or II with or without rapid cycling course</td>
<td>Using HamD and YMS scales, mood symptoms were assessed and both depressive and manic symptoms were found to be significantly reduced with gabapentin.</td>
<td>J Affect Disord. 1999;55(1):73-77.</td>
</tr>
<tr>
<td>Erfurth A, Kammerer C, Grunze H, et al. Open label</td>
<td>6 add-on cases and 8 high-dose monotherapy cases; dose range of 1,200 mg-4,800 mg/day; treatment for up to 21 days</td>
<td>14 patients with acute mania</td>
<td>The study suggested that gabapentin monotherapy may be useful in treating modest but not severe manic states. In conjunction with other mood stabilizers such as lithium or depakote, it may be useful. Of note, there was not a comparison arm to the mood stabilizers alone, so any advantage of the combination over monotherapy with these agents remains unproven.</td>
<td>J Psychiatr Res. 1998;32(5):261-64.</td>
</tr>
<tr>
<td>Soutullo CA, Casuto LS, Keck PE. Case report</td>
<td>Add-on to carbamazepine</td>
<td>One boy, aged 13 years, with bipolar disorder, manic episode, and ADHD</td>
<td>Patient remained euthymic 7 months after gabapentin was added. Young Mania Rating Scale (YMRS) score was 27 when gabapentin was added, 9 after 1 month, 15 after 4 months, and 6 after 7 months.</td>
<td>J Child Adolesc Psychopharmacol. 1998;8(1):81-85.</td>
</tr>
</tbody>
</table>

A follow-up story in January 2003 about a “whistle-blower” lawsuit related to allegedly illegal marketing practices included an explanation of some of the issues, with particular emphasis on the clinically inappropriate promotion of gabapentin for bipolar disorder. The lawsuit involves charges made by a for-

label conditions; company medical science liaisons were also alleged to have been involved in this practice. The authors of one news article noted that many reported cases of safety and effectiveness with unapproved use of the drug appeared to be fabricated by the manufacturer.
## Table 2: Summary of Selected Primary and Tertiary References

**Using Gabapentin in Management of Neuropathic Pain**

<table>
<thead>
<tr>
<th>Publication Type</th>
<th>Treatment or Method</th>
<th>Population</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Symptom-based, 8-week study design of patients receiving gabapentin in doses up to 2,400 mg/day or placebo</td>
<td>153 patients randomized to gabapentin and 152 patients randomized to placebo</td>
<td>Over the study, the average daily pain diary score improved by 1.5 (21%) in gabapentin-treated patients and by 1.0 (14%) in placebo-treated patients. ($P=0.048$, rank-based analysis of covariance). Significant differences were shown in favor of gabapentin ($P&lt;0.05$) for the clinician and patient global impression of change and some domains of the Short-Form McGill Pain Questionnaire.</td>
<td>Serpell MG. <em>Pain</em>. 2002;99(3):557-66.</td>
</tr>
<tr>
<td>Pilot study</td>
<td>Gabapentin was administered orally in gradually increasing doses up to a maximum of 2,400 mg/day</td>
<td>18 patients with peripheral nerve injuries or central lesions</td>
<td>Gabapentin induced a moderate and statistically significant relief of ongoing or spontaneous pain and was particularly effective in reducing paroxysmal pain. A striking finding was the significant effect on brush-induced cold allodynia. In contrast, no effects were observed on detection of pain thresholds to static mechanical and hot stimuli.</td>
<td>Brasseur AN, Parker F, Chauvin M, et al. <em>Eur Neurol.</em> 1998;40(4):191-200.</td>
</tr>
<tr>
<td>Retrospective chart review</td>
<td>Patients receiving gabapentin for at least 30 days were studied</td>
<td>122 patients divided into 3 groups based on pain diagnosis of low back, myofascial, or neuropathic pain</td>
<td>Significant decrease in pain scores with gabapentin in the neuropathic pain group but not in the low-back-pain group. Patients with postherpetic neuralgia had the greatest decrease in pain scores. Patients who were taking opiates had significantly less benefit with gabapentin in terms of pain score.</td>
<td>Rosenberg JM, Harrell C, Ristic H, et al. <em>Clin J Pain</em>. 1997;13(3):351-55.</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>Extensive search of several electronic databases for controlled and uncontrolled studies. Efficacy was assessed through meta-analyses of randomized controlled trials (RCTs). Effectiveness of gabapentin in uncontrolled studies was assessed via a novel system of dichotomous classification of bad versus good results.</td>
<td>35 papers involving 727 patients with multiple neuropathic pain conditions met inclusion criteria</td>
<td>The meta-analysis of the 2 high-quality placebo-controlled randomized trials showed positive effect of gabapentin in diabetic neuropathy and postherpetic neuralgia. Addition of 2 low-quality PC, RCTs did not alter the magnitude or duration of the observed effect. The uncontrolled studies demonstrated positive effect on pain in different neuropathic syndromes as well as benefit for different types of neuropathic pain; highest dose administered and rate of dose escalation showed wide variability between prescribers. Fewer and less-severe side effects were reported in the uncontrolled studies.</td>
<td>Mellegers MA, Purlan AD, Mailis A. <em>Clin J Pain</em>. 2001;17(4):284-95.</td>
</tr>
<tr>
<td>Randomized controlled clinical trial</td>
<td>Gabapentin 3,600 mg/day (forced max) 67% achieved max dose</td>
<td>Uncontrolled diabetes (75% type 2) n=84 gabapentin, n=81 placebo</td>
<td>Gabapentin versus placebo difference in mean pain score at endpoint = -1.2 ($P&lt;0.001$); difference in mean sleep interference score = -1.47 ($P&lt;0.001$).</td>
<td>Backonja M, Beydoun A, Edwards K, et al. <em>JAMA</em>. 1998;280:1831-36.</td>
</tr>
<tr>
<td>Randomized controlled clinical trial</td>
<td>Gabapentin 3,600 mg/day (65% achieved max dose) versus placebo</td>
<td>Postherpetic neuralgia n=113 gabapentin, n=112 placebo</td>
<td>Decrease in average daily pain score = 33% gabapentin, 7% placebo ($P&lt;0.001$).</td>
<td>Rowbotham M, Harden N, Stacey B, et al. <em>Ann Pharmacother</em>. 2000;34:802-07.</td>
</tr>
</tbody>
</table>
Examination of the Evidence for Off-Label Use of Gabapentin

Review of the Clinical Literature

Off-label use of gabapentin has been reported in bipolar disorder, peripheral neuropathy, diabetic neuropathy, complex regional pain syndrome, attention deficit disorder, restless legs syndrome, trigeminal neuralgia, periodic limb movement disorder of sleep, migraine headaches, and drug and alcohol withdrawal syndrome. A recurring theme in the literature, with the exception of neuropathic pain and migraine, is a prevalence of open-label studies with a lack of randomized controlled clinical trials. It is important to consider that an inherent problem with open-label trial design is the potential for introduction of bias because the treatment assignment is known.

Gabapentin in the Treatment of Bipolar Disorder

Extensive review confirms that current published literature on gabapentin is primarily based on open-label trials that evaluate small numbers of patients (Table 1). The few randomized controlled trials designed to investigate the efficacy of gabapentin in treating bipolar disorder have concluded that there is no significant difference in the effects of the drug compared with placebo. This supports the likelihood of bias in the various open-label studies since these results have not been confirmed in the randomized controlled trials. Various authors of medical reviews on this subject have concluded that gabapentin should not be recommended for treatment of bipolar disorder and that double-blind, randomized controlled trials are needed to confirm any true efficacy of the drug in management of this condition.

Real-life practice involves instances of refractory bipolar disorder that exhaust the current treatment options. The Texas Medication Algorithm Project (TMAP) lists lamotrigine or gabapentin only as salvage therapy. Therefore, these 2 agents should be reserved for unstable patients at the seventh stage of treatment in hypomanic/manic episodes. In all other forms of bipolar disorder, gabapentin is not recommended at any phase of therapy.

Although limited comparative data are available on the subject, results from a cross-over study suggest that lamotrigine may be superior to gabapentin as well as placebo for the management of refractory mood disorders. The investigators studied 31 patients who had either bipolar I, bipolar II, or unipolar disorder and failures of other mood stabilizing agents. Lamotrigine was titrated to 300 mg–500 mg by weeks 5 and 6, and gabapentin was titrated to 4,800 mg daily by week 6. At week 6, based on the Clinical Global Impression Score, 52% of patients responded to lamotrigine, 26% responded to gabapentin, and 23% responded to placebo. The results of this study suggest that lamotrigine might be considered in cases of treatment refractory to first-line agents in bipolar disorder.

Gabapentin in the Treatment of Pain Syndromes, Peripheral Neuropathy, and Diabetic Neuropathy

The exact mechanism of action of gabapentin in managing neuropathic pain is unknown; however, it is speculated to work via

### TABLE 3 Price Comparisons for Gabapentin Versus Various Tricyclic Antidepressants Used in the Management of Neuropathic Pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose for Management of Neuropathic Pain†*</th>
<th>FDA Approval</th>
<th>Cost per Unit† per Month</th>
<th>Tablet or Capsules Maximum Average Cost per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>300 mg/day up to 1,800 mg/day</td>
<td>No</td>
<td>100 mg cap ($0.51 ea) up to 540</td>
<td>$275.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>300 mg ($1.23 ea) up to 180</td>
<td>$221.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>400 mg ($1.47 ea) up to 135</td>
<td>$199.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>600 mg ($1.98 ea) up to 90</td>
<td>$178.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>800 mg ($2.38 ea) up to 68</td>
<td>$162.44</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10 mg-25 mg orally, at bedtime, up to</td>
<td>No</td>
<td>10 mg tab ($0.09 ea) up to 600</td>
<td>$54.00</td>
</tr>
<tr>
<td></td>
<td>150 mg-200 mg/day</td>
<td></td>
<td>25 mg ($0.12 ea) up to 240</td>
<td>$28.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 mg ($0.09 ea) up to 120</td>
<td>$10.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75 mg ($0.12 ea) up to 90</td>
<td>$10.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 mg ($0.13 ea) up to 60</td>
<td>$7.80</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>10 mg/day orally, increase by 10 mg/day</td>
<td>No</td>
<td>10 mg cap ($0.14 ea) up to 180</td>
<td>$25.20</td>
</tr>
<tr>
<td></td>
<td>every 3 to 5 days as needed; doses up to 60 mg/day</td>
<td></td>
<td>25 mg cap ($0.21 ea) up to 60</td>
<td>$12.60</td>
</tr>
<tr>
<td></td>
<td>have been reported</td>
<td></td>
<td>50 mg cap ($0.25 ea) up to 30</td>
<td>$7.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75 mg cap ($0.28 ea) up to 30</td>
<td>$8.40</td>
</tr>
</tbody>
</table>


Dose for Management of Tablet or Capsules Maximum Average

**Journal of Managed Care Pharmacy**

November/December 2003 Vol. 9, No. 6 www.amcp.org
Examination of the Evidence for Off-Label Use of Gabapentin

Table 4: Published Reports Related to Use of Gabapentin in Complex Regional Pain Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Population</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case study</td>
<td>Gabapentin</td>
<td>6 patients, aged 42-68 years, with severe, refractory RSD</td>
<td>Satisfactory pain relief was obtained in all patients</td>
<td>Mellick GA, Mellick LB. Reflex sympathetic dystrophy treated with gabapentin. Arch Phys Med Rehabil. 1997;78(1):98-103.</td>
</tr>
</tbody>
</table>

In the Morello study, the agents were proven comparable in clinical efficacy. In fact, these authors suggested a slight advantage to using amitriptyline over gabapentin, although the difference was not statistically significant. Comparing prices of the agents given in doses for the management of neuropathic pain, amitriptyline and nortriptyline cost only a small fraction of the significant direct drug cost associated with gabapentin (Table 3). Therefore, the tricyclics appear to offer a lower-cost therapeutically equivalent alternative to gabapentin in many situations.

Gabapentin in the Treatment of Complex Regional Pain Syndrome

There are no reports that confirm efficacy of gabapentin in management of complex regional pain syndrome, also known as reflex sympathetic dystrophy (RSD). The literature is sparse and primarily anecdotal in nature, composed of 2 reports involving a total of 7 patients in addition to 2 letters (Table 4) that offer little scientific value. From an evidence-based standpoint, the available information is insufficient to support use of gabapentin in this condition. Recognized medical treatments for RSD include adrenergic blockers, nonsteroidal anti-inflammatory drugs, calcium channel blockers, phenytoin, opioids, and calcitonin.

Gabapentin in the Treatment of Attention Deficit Disorder

There are 3 published reports related to behavioral disturbances and the use of gabapentin, none of which were clinical trials. One case report is specific to the use of the drug in attention deficit hyperactivity disorder (ADHD). A second case report involved 7 patients who experienced behavioral side effects with gabapentin. The third citation was a letter (Table 5). Thus, the evidence related to the use of gabapentin in ADHD is insufficient to warrant its use for this condition.

Stimulants have been the mainstay of ADHD therapy for decades, but there is a rising trend in pediatric polypharmacy with little or no research to support this phenomenon. Since there is no evidence to support the use of gabapentin in ADHD, alternative clinically appropriate and supportive treatment options should be given primary consideration when formulating treatment plans for cases refractory to stimulants in ADHD. Current treatment guidelines suggest a trial with a stimulant along with diet, behavior management, special education, and perhaps psychotherapy in ADHD disease management.
Gabapentin in the Treatment of Restless Leg Syndrome

Restless leg syndrome (RLS) is an awake phenomenon characterized by an intense, irresistible urge to move the legs, usually associated with sensory complaints, motor restlessness, worsening of symptoms at rest and relief with motor activation, and increased severity in the evening or during the night. Sparse case reports have suggested potential use of gabapentin in RLS, but again, there are no controlled clinical trials that assess its safety and effectiveness in treatment of this condition.45-49

The Standards of Practice Committee of the American Academy of Sleep Medicine (AASM), in conjunction with specialists and other interested parties, developed guidelines for managing RLS that were subsequently approved by the Board of Directors of AASM. The recommendations were identified as standards, guidelines, or options, based on the strength of evidence from published studies that meet criteria for inclusion (Table 6).

The AASM guideline classifies the following agents as having sufficient evidence to support their use in RLS treatment: (1) levodopa with decarboxylase inhibitor and pergolide, (2) oxycodone and propoxyphene, or (3) carbamazepine. AASM has reported that the dopaminergic agents are notably the best studied and most successful agents for the treatment of RLS.50 Alternatively, they have commented that gabapentin has limited “Level V” evidence (case-series reports only), consisting of only 2 case studies. For this reason, AASM has classified use of gabapentin in RLS as a patient-care strategy that reflects uncertain clinical use. The members of the panel felt that there is inconclusive data, conflicting evidence, or conflicting expert opinion on the use of gabapentin for managing RLS.56

Gabapentin in the Treatment of Trigeminal Neuralgia

Conclusive studies confirming the efficacy of gabapentin in the treatment of trigeminal neuralgia are lacking. To date, literature supporting the effectiveness of gabapentin in trigeminal neuralgia is limited to case studies in aggregate of less than 30 patients.51-53 Carbamazepine remains the drug of first choice.54 If paroxysms of pain still occur with therapeutic blood levels, phenytoin or baclofen should be added.54 Lamotrigine was recently validated for use in refractory trigeminal neuralgia, especially due to multiple sclerosis.51,52,55

Gabapentin in the Treatment of Periodic Limb Movement Disorder of Sleep

Periodic limb movements of sleep occur as an asleep phenomenon and are characterized by periodic episodes of repetitive and highly stereotyped limb movements. These patients typically have complaints of insomnia or excessive sleepiness with no other disorder to explain the symptoms. RLS and periodic limb movement disorder (PLMD) of sleep are distinct disorders by definition, but they have been reported to coexist in approximately 80% of cases. However, the treatment of the 2 conditions is not always the same. There is no reference to the use of gabapentin in PLMD, and there is no mention of gabapentin in recommendations of AASM.50 There is no published evidence demonstrating efficacy of gabapentin in the management of PLMD. Experts have reported that symptoms may respond to correction of a coexisting iron deficiency anemia or to treatment with dopaminergic medication (such as levodopa or bromocriptine), benzodiazepines (diazepam or clonazepam), or opiates (codeine, propoxyphene, or oxycodone).50

Gabapentin in the Treatment of Migraine

Pharmacoeconomic analyses reveal that gabapentin is only cost effective for migraine prophylaxis in patients who experience very frequent migraine headaches. Adelman et al. studied the costs for acute migraine care following initiation of prophylactic medications. They reported that divalproex patients must have

<table>
<thead>
<tr>
<th>Study type</th>
<th>Treatment</th>
<th>Population</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case report</td>
<td>Gabapentin 200 mg/day added to methylphenidate 30 mg/day</td>
<td>1 boy, aged 12 years, with ADD, reading disorder, mixed receptive and expressive language disorder, encopresis, and bipolar disorder II</td>
<td>Within 3 weeks, mother, teacher, and clinician noted improvement and stabilization of mood symptoms as remarkable; it remained so for 6 months of follow-up.</td>
<td>Hamrin V, Bailey K. Gabapentin and methylphenidate treatment of a preadolescent with attention deficit hyperactivity disorder and bipolar disorder. J Child Adolesc Psychopharmacol. 2001;11(3):301-09.</td>
</tr>
<tr>
<td>Case report</td>
<td>Gabapentin as adjunct</td>
<td>7 children with baseline ADD and developmental delay</td>
<td>Children consequentially developed behavioral side effects, including tantrums, aggression toward others, hyperactivity, and defiance. All behavioral changes were reversible and were managed by dose reduction or discontinuation of gabapentin.</td>
<td>Lee DO, Steingard RJ, Casena M, et al. Behavioral side effects of gabapentin in children. Epilepsia. 1996;3(1):87-90.</td>
</tr>
</tbody>
</table>

**TABLE 5** Published Reports of Gabapentin and Behavior in Children
more than 10 migraine episodes per month while gabapentin patients must have more than 24 migraine episodes per month before these drugs can be considered cost effective.51-60

While there are clinical trials of gabapentin in migraine prophylaxis, outstanding questions remain regarding the drug’s utility in clinical practice. One randomized, placebo-controlled study of 63 patients showed that gabapentin in daily prophylactic doses of 1,200 mg is well tolerated and reduces headache frequency and the use of drugs to produce symptomatic relief.61 While gabapentin appeared to be effective in this particular trial, it is still unclear how gabapentin would compare to other more-established pharmacotherapy for migraine prophylaxis. Thus, gabapentin should be considered for use in migraine syndrome management only after failure of standard prophylaxis regimens (Table 7).

Gabapentin in the Treatment of Drug and Alcohol Withdrawal Seizures

Mayo-Smith published an evidence-based practice guideline for the pharmacological management of alcohol withdrawal.62 He completed a meta-analysis of prospective controlled trials only, with methodologically sound endpoints (e.g., withdrawal severity, delirium, seizures, completion of withdrawal, entry into rehabilitation, adverse events) corresponding to the Diagnostic and Statistical Manual of Mental Disorders. Mayo-Smith concluded that benzodiazepines remain the gold standard for management of alcohol withdrawal and that dosage should be individualized based on withdrawal severity.

According to this analysis, the author notes that beta-blockers, clonidine, and carbamazepine may be considered as adjunctive therapy.62 There was no mention of gabapentin in this guideline since published reports of gabapentin for these indications are limited to case reports, open-label studies, and anecdotal letters.63-67 Thus, gabapentin cannot be recommended for use in any aspect of the management of alcohol withdrawal seizures, either as initial or add-on therapy.

<table>
<thead>
<tr>
<th>TABLE 6A</th>
<th>American Academy of Sleep Medicine Classification of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation Grade</td>
<td>Evidence Level</td>
</tr>
<tr>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>C</td>
<td>III</td>
</tr>
<tr>
<td>C</td>
<td>IV</td>
</tr>
<tr>
<td>C</td>
<td>V</td>
</tr>
</tbody>
</table>

*Alpha error refers to the probability (generally set at 95% or greater) that a significant result (e.g., $P<0.05$) is the correct conclusion of the study or studies. Beta error refers to the probability (generally set at 80% or 90% or greater) that a nonsignificant result (e.g., $P>0.05$) is the correct conclusion of the study or studies. The estimation of beta error is generally the result of a power analysis. The power analysis includes a sample size analysis that projects the size of the study population necessary to ensure that significant differences will be observed if actually present.


<table>
<thead>
<tr>
<th>TABLE 6B</th>
<th>American Academy of Sleep Medicine Recommendations for Restless Legs Syndrome or Periodic Limb Movement Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>Standard</td>
<td>This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term “standard” generally implies the use of Level I evidence, which directly addresses the clinical issue or overwhelming Level II evidence.</td>
</tr>
<tr>
<td>Guideline</td>
<td>This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term “guideline” implies the use of Level II evidence or a consensus of Level III evidence.</td>
</tr>
<tr>
<td>Option</td>
<td>This is a patient care strategy that reflects uncertain clinical use. The term “option” implies either inconclusive or conflicting evidence or conflicting expert opinion.</td>
</tr>
</tbody>
</table>


In the majority of circumstances where it has reported potential for indications not approved by the FDA (i.e., off-label use), gabapentin is not the optimal treatment. The reader should remain cautious regarding claims that gabapentin offers any benefit in treating conditions other than those with FDA approval. Hamer et al. concluded, “While case reports and open-label trials are valuable for directing further research, they are generally not sufficient as the basis of treatment decisions.”

Gabapentin is not recommended in the clinical guidelines or established treatment algorithms (e.g., American Academy of Neurology or AASM guidelines or TMAP algorithm) for any of the off-label indications. Considering the evidence, gabapentin should be used almost exclusively for the FDA-approved indications—treatment of seizures and postherpetic neuralgia.

Off-label use of gabapentin should be reserved for patients who have failed standard treatment options and in those cases where randomized controlled clinical trials have demonstrated gabapentin efficacy (i.e., diabetic neuropathy and migraine headaches). Cost-effectiveness ratios tend to be high (unfavorable) for the use of gabapentin in diabetic neuropathy and migraine syndrome except in those patients who experience a high frequency of acute episodes.

Pharmaceutical manufacturer marketing practices appear to

Conclusions

Examination of the Evidence for Off-Label Use of Gabapentin
Examination of the Evidence for Off-Label Use of Gabapentin

be a key contributor to the use of gabapentin in excess of its scientifically proven value. One additional factor is the perceived need for treatment options among clinicians dissatisfied with currently available therapies. The financial success of gabapentin could be at least partially attributable to the placebo effect since the majority of the off-label conditions are associated with an underlying psychological component.

DISCLAIMER
Since various disease states are discussed in this review, it is essential to note that the references to treatment guidelines and algorithms are summary in nature and are in no way intended to replace the various expert consensus and more thorough reviews on the various subjects.

ACKNOWLEDGMENTS
The author would first like to acknowledge Robert Mack for his patience and encouragement throughout the process of developing and writing this manuscript. The author would also like to acknowledge the following individuals at Three Rivers Administrative Services, LLC: Warren Carmichael, CEO, for the opportunity to be a part of this organization and pursue this project; Robert Baker, MD, MMM, FAAP, senior medical director, for thoughtful comments that made a valuable contribution to this manuscript; Jessica Neely, PharmD, clinical pharmacist; and Jim Hancovsky, RPh, MSHA, pharmacy director, for helpful review of an earlier version of this manuscript.

DISCLOSURES
No outside funding supported this study. The author discloses that she has no financial affiliation with or interest in any company, product, or service that is discussed in this article.

### TABLE 7  AAA Migraine Prophylaxis Guidelines: Assessment of the Relative Value of Preventive Therapies for Migraine Available in the United States

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacious Doses in Clinical Trials</th>
<th>Drug</th>
<th>Efficacious Doses in Clinical Trials</th>
<th>Drug</th>
<th>Efficacious Doses in Clinical Trials</th>
<th>Drug</th>
<th>Efficacious Doses in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>30 mg-150 mg/day</td>
<td>Aspirin†</td>
<td>1,300 mg/day</td>
<td>Cyprophedrine</td>
<td>Not established</td>
<td>Methysergide</td>
<td>6 mg/day</td>
</tr>
<tr>
<td>Divalproex</td>
<td>500 mg-1,500 mg/day</td>
<td>Atenolol</td>
<td>100 mg/day</td>
<td>Bupropion</td>
<td>Not established</td>
<td>Carbamazepine</td>
<td>Not established</td>
</tr>
<tr>
<td>Propranolol</td>
<td>80 mg-400 mg/day</td>
<td>Fenoprofen</td>
<td>1,600 mg/day</td>
<td>Dilatazep</td>
<td>Not established</td>
<td>Conipramine</td>
<td>Not established</td>
</tr>
<tr>
<td>Timolol</td>
<td>20 mg-30 mg/day</td>
<td>Flurbiprofen</td>
<td>200 mg/day</td>
<td>Doxepin</td>
<td>Not established</td>
<td>Clonazepam</td>
<td>Not established</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg every other day to 40 mg/day</td>
<td>Fluvoxamine</td>
<td>Not established</td>
<td>Lamotrigine</td>
<td>Not established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900 mg-2,400 mg/day</td>
<td>Ibuprofen</td>
<td>Not established</td>
<td></td>
<td>Lamotrigine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanfacine</td>
<td>1 mg/day</td>
<td>Imipramine</td>
<td>Not established</td>
<td></td>
<td>Nembrutone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>150 mg/day</td>
<td>Mirtazapine</td>
<td>Not established</td>
<td></td>
<td>Nicardipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>400 mg-600 mg/day</td>
<td>Nortriptyline</td>
<td>Not established</td>
<td></td>
<td>Nifedipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mefanamic acid</td>
<td>1,500 mg/day</td>
<td>Paroxetine</td>
<td>Not established</td>
<td></td>
<td>Pindolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>200 mg/day</td>
<td>Propranolol</td>
<td>Not established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>80 mg-240 mg/day</td>
<td>Sertraline</td>
<td>Not established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>1,100 mg/day</td>
<td>Tiagabine</td>
<td>Not established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nimodipine</td>
<td>120 mg/day</td>
<td>Topiramate</td>
<td>Not established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolermamic acid</td>
<td>300 mg/day</td>
<td>Trazadone</td>
<td>Not established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>240 mg/day</td>
<td>Venlafaxine</td>
<td>Not established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B2</td>
<td>400 mg/day</td>
<td>Methylsergonovine</td>
<td>Not established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Group I = Medium to high efficacy, good strength of evidence, and a range of severity (mild to moderate) and frequency (infrequent to frequent) of side effects.
† Group II = Lower efficacy than those listed in the first column, or limited strength of evidence, and mild to moderate side effects.
‡ Group III = Clinically efficacious based on consensus and clinical experience, but no scientific evidence of efficacy.
§ Group IV = Medium to high efficacy, good strength of evidence, but with side concerns.
|| Group V = Evidence indicating no efficacy over placebo
¶ Does not include combination products.

REFERENCES


SUGGESTED READING


### Article Index by Subject Category

**JMCP – July/August 1995 through November/December 2003**

#### Adherence, Compliance, and Persistence
- Patient adherence with HMG reductase inhibitor therapy among users of two types of prescription services. 2002;8(3):186-91.
- Adherence, compliance, and persistence in drug therapy. 2002;8(3):177-78.
- Evaluating medication adherence: which measure is right for your program? 2000;6(6):499-504.

#### Adverse Drug Events
- Medical errors, adverse medical events, and PDRM. 2002;8(5):400.
- Evaluation of resources used to treat adverse events of selective serotonin reuptake inhibitor use. 2001;7(5):402-06.

#### Behavioral Health

#### Biotechnology

#### Capitation and Risk-Financing Methods

#### Clinical Pharmacy Interventions – Quality, Service, and Cost Outcomes
- Assessment of clinical pharmacist management of lipid-lowering therapy in a primary care setting. 2003;9(3):269-73.
- Determining the value of pharmacy services—the search for rigorous research designs. 2002;8(2):152-53.
Clinical Pharmacy—Patient Consultation


Clinical Pharmacy—Payment for Services


Clinical Pharmacy Quality Improvement—Patient Safety and Prevention of ADEs

- Preventing medication errors and adverse drug events. 2003;9(1):92-93.

Clinical Practice Guidelines (CPGs) and Quality Improvement

- Crossing the quality chasm—incremental change through clinical practice guidelines (CPGs) (editorial). 2002;8(5):400-01.

Clinical Quality Improvement

- Managing drug therapy decisions: pay me now or pay me later. 1998;4(3):242, 245.

Collaboration—Physicians and Others

- Pharmacy practice in the long-term care environment. 1997;3(2):189-94.

Collaboration—Pharmacy Education

- Oregon State University partners with Medicaid and a managed care organization. 2001;7(3):185-86.
- The University of Colorado School of Pharmacy and the University of Colorado Health Plan forge a PBM partnership. 1998;4(3):478, 480.

Collaborative Practice—Pharmacists as Prescribers


Database Analyses of Drug Utilization (see also Research Methods)

- Claims data and drawing appropriate conclusions. 2002;8(2):152.
• Basics of managed care claims processing: from claims payment to outcomes management. 1999;1(6):200-05.

Decision Support Systems (DSS)

Direct-to-Consumer Advertising (DTCA)
(see also Drug Promotion and Advertising)
• Direct-to-patient advertising (DTPA) and direct-to-consumer advertising (DTCA) of prescription drugs. 2002;8(6):521.
• Responding to direct-to-consumer advertising. 2000;6(3):201-02.
• Direct-to-consumer advertising provides challenge to managed care. 1999;5(2):101-03, 106.

Disease Management—ALS (Amyotrophic Lateral Sclerosis)

Disease Management—Angina, CHD, and CHF

Disease Management—Arthritis and Joint Pain
• Relationship of clinical factors to the use of COX-2 selective NSAIDs within an arthritis population in a large HMO. 2002; 8(4):252-58.
• Economic considerations in the management of arthritis. 1999;5(6):476-78, 481-82, 484.

Disease Management—Asthma or Allergic Rhinitis
• Optimizing clinical and economic outcomes in asthma management: individualizing drug therapy to address dual components of asthma. 2002;8(5):S1-S25.
• Evaluating asthma medication use before and after an acute asthma-related event. 2001;7(4):303-08.

Disease Management—Atopic Dermatitis
• The effect of atopic dermatitis on total burden of illness and quality of life on adults and children in a large managed care organization. 2002;8(5):333-42.

Disease Management—Attention Deficit Hyperactivity Disorder (ADHD)
• Physician perceptions of the use of medications for attention deficit hyperactivity disorder. 2003;9(5):416-23.

Disease Management—Cancer

Disease Management—Deep Vein Thrombosis

Disease Management—Depression
• Documentation of indicators for antidepressant treatment and response in an HMO primary care population. 2000;6(6):494-98.
• Utilization patterns of antidepressant medications in a patient population served by a primary care medical group. 1999; 5(3):243-49.
• The treatment of depression with newer antidepressants: phar-
Disease Management—Diabetes (see also Clinical Pharmacy Interventions)

Disease Management—Heartburn

Disease Management—Hypercholesterolemia

Disease Management—Hypertension
- Impact of the ALLHAT study results on managed care. 2003;9(1):84-86.

Disease Management—Multiple Sclerosis

Disease Management—Obesity
Disease Management—Osteoporosis

- Tablet splitting to improve the value-for-money equation in cholesterol management. 2002;8(6):519.

Disease Management—Otitis Media and Infectious Disease

- Fluoroquinolone-use evaluation by acute cystitis. 1996;2(5):564-68.

Disease Management—Seizure Disorders


Disease Pathology


Dose Optimization

- Dose optimization: an opportunity for pharmacy administrative services. 2002;8(2):81.

Drug Benefit Management—Benchmarks and Measures

- Searching for drug benefit benchmarks—cost per day of therapy. 2002;8(1):54-55.

Drug Benefit Management—Efficiency and Patient Safety

- Weight uniformity of split tablets required by a Veterans Affairs policy. 2003;9(5):401-07.

Drug Benefit Management—Employee Benefits and Coverage

- New generic and OTC drugs provide opportunities for drug benefit managers. 2002;8(6):520.

Drug Benefit Management—Patient Satisfaction, Benefit Knowledge, and Consumer Behavior


• Consumer preferences for types of cost containment in prescription drug programs. 2002;8(3):192-98

• Drugs, PPOs, tiered cost-share for beneficiaries, and consumer preferences. 2002;8(3):177.

• Patient satisfaction with and knowledge of their prescription drug coverage. 2001;7(1):34-42.


• A comparison of satisfaction with mail versus traditional pharmacy services. 1997;3(3):327-37.


Drug Benefit Management—Pharmacy Providers


Drug Benefit Management—Quantity Limits and Prior Authorization (PA)


• Evaluation of a monthly coverage maximum (drug specific quantity limit) on the 5-HT1 agonists (triptans) and dihydroergotamine nasal spray. 2003;9(4):335-45.


• Prior authorization to manage drug utilization and costs. 2003;9(1):95.

• Analysis of a prescription drug prior authorization program in a Medicaid health maintenance organization. 2003;9(1):36-44.


• A neurologist’s perspective on quantity limits. 2002;8(3):184.

• Triptan quantity limits. 2002;8(3):182-84.

• Medical and pharmacy cost and utilization outcomes of a quantity limit on 5-HT1 agonists (triptans) by a managed care organization. 2001;7(6):468-75.


Drug Benefit Management Methods—Benefit Design

• Benefit maximums versus drug benefit needs for Medicare beneficiaries. 2002;8(5):402-03.

• Prescription use behavior among Medicare beneficiaries with capped prescription benefits. 2002;8(5):360-64.


Drug Promotion and Advertising (see also Direct-to-Consumer Advertising (DTCA))


• Health care communications agencies respond to managed care. 1998;4(1):9-12.

• Information requirements of health systems as drug purchasers: does the FDA have a role in setting evidentiary standards? 1996;2(6):593-98.

Drug Spending, Utilization, and Cost Trends


• Drug costs out of control—check your assumptions. 2002;8(2):81.


• Too much or too little? The role of pharmaceuticals in the health care system. 1999;5(4):296-97, 301-02.

• Local area market dynamics. 1998;4(2):115-17, 120.
Drug Therapy and Therapeutic Selection

- Cost and utilization comparisons among propensity score-matched insulin lispro and regular insulin users. 2003;9(3):263-68.
- Improvements in glycemic control in type 2 diabetes patients switched form sulfonylurea coadministered with metformin to glyburide-metformin tablets. 2003;9(3):256-62.

Drug Therapy—Natural Products


Drug Utilization Review (DUR) or Drug Utilization Management—Appropriate Drug Use

- Gabapentin may be appropriate for off-label uses (editorial). 2003;9(6):569-70.
- Examination of the evidence for off-label use of gabapentin. 2003;9(6):559-68.
- The pharmacist's assessment of second generation online...

Ethics


Formulary Management—Methods and Effects—Pharmacoeconomics

• Industry’s perception of presenting pharmacoeconomic models to managed care organizations. 2003;9(2):159-67.
• Summary quality scores for pharmacoeconomic studies: balancing validity with need. 2003;9(1):87-88.
• Examining the value and quality of health economic analyses: implications of utilizing the QHES. 2003;9(1):53-61.
• Meta-analysis of oral triptan therapy for migraine: number needed to treat and relative cost to achieve relief within 2 hours. 2003;9(1):45-52.
• Exploring the methodological challenges of investigating comparison groups with different underlying characteristics: a case study. 2002;8(5):353-59.
• Outcome analysis of a formulary transition from nifedipine to felodipine at a Veterans Affairs Medical Center. 1999;5(5):425-28.
• Formulary management by an on-site school of pharmacy faculty member in a Medicaid managed care organization. 1998;4(4):407-10.
• DODs Pharmacoeconomic Center: translating research into good patient care practices. 1997;3(6):662-64, 666.
• Drug formularies: real opportunities to improve MCO efficiency. 1997;3(3):254, 375-76.
• Using outcomes as a tool to evaluate formulary selection decisions: hypercholesterolemia as a case example. 1996;2(4):396-404.

Formulary Management—P & T Committees


Health Care Delivery

• International markets offer new opportunities for MCOs and PBMs. 1997;3(4):403-04, 409-10.
• Integration takes managed care in different directions: horizontal, vertical, and beyond. 1997;3(3):260, 263-64.
• Alternative medicine in managed care pharmacy. 1997;3(1):77-80, 83-86.
• Indian Health Service: paving the way for pharmaceutical care. 1997;3(1):36,41-43.
• While health care evolves, antitrust law endures. 1996;2(6):679-86.

**Health Care Quality Improvement**

• Information technology to cross the quality chasm. 2002;8(5):401-02.
• Quality improvement opportunities in health care—making it easy to do it right. 2002;8(5):394-99.
• Quality measures: looking in all the wrong places. 2001;7(2):88.
• Medical and medication errors: a partial summary of reports by the Institute of Medicine and the quality interagency coordination task force. 2001;7(1):62-68.
• How to evaluate disease state management programs. 1997;3(3):270, 273-74, 277-78.
• Managed care and the quest for quality measures. 1997;3(3):255, 258-89.
• Successful CQI-based programs in a group-model managed care setting. 1995;1(5):134, 137.

**Health Care Spending and Health Economics**

• Is there no prescription to decrease health care outlays in the face of an aging population? 2000;6(6):450-51.
• Health economics II: some unique aspects of health economics. 2000;6(2):173-78.

**Health Insurance and Health Care Finance**

• Direct contracting: the next purchaser strategy. 1996;2(1):11-12, 14, 16.

**Institutional Managed Care**

• Managed pharmaceutical care within a criminal justice system. 2001;7(3):182.

**Internet Pharmacy**

• Concern about foreign-source pharmacy Internet providers. 2001;7(5):335-36.
• The Internet and PBMs: new business model or business as usual? 2000;6(2):102,105-07.

**Lifestyle Drugs**


**Managed Care Pharmacy Practice**

• John Ogden talks about managed care in the Veterans Administration. 2002;8(2):91-93.
• Managed care and the pharmacy profession revisited. 1999;5(2):78.
• The importance of communication skills for the managed care pharmacist. 1998;4(2):102.
• The changing face of managed care pharmacy and the role of PBMs. 1997;3(3):494, 497-98.
• Blue Cross and Blue Shield: making pharmaceutical care a key
• Professional opportunities in managed care pharmacy. 1995;1(5):80, 82, 86-87.

Managed Health Care

• Medicare PPOs and managed care. 2003;9(1):91.
• Examining the managed health care continuum. 1997;3(5):511-12, 515-16, 518.

Manpower and Job Satisfaction

• A closer look at pharmacy technicians. 2003;9(1):84.
• How many pharmacists are in our future? The Bureau of Health Professions projects supply to 2020. 2000;6(6):474-82.
• Burnout in a sample of HMO pharmacists using the Maslach Burnout Inventory. 1998;4(5):495-503.

Medicaid


Medicare (see also Drug Benefit Management Methods—Benefit Design)


Pain Management

• Beyond narcotics for effective pain management. 2003;9(2):175-76.
• It’s a pain. 1999;5(6):558.

Pharmaceutical Industry


Pharmacogenomics

• Drug therapy customized to individual patients. 2002;8(4):296-97.
• Health care professionals’ perceptions of the role of pharmacogenomic data. 2002;8(4):278-84.

Pharmacy Education

• Managed care and the University of Texas College of Pharmacy. 2001;7(6):490.
• University of Michigan College of Pharmacy and managed care partner to enhance drug therapy. 2001;7(5):345-46.
• An inside look at the benefits of a student pharmacy and therapeutics (P & T) committee competition from the University of Illinois at Chicago. 2001;7(4):259-60.
• Managed care concepts prominently featured in innovative management programs at Duquesne University. 2001;7(2):94,96.
• Synergy between the University of Louisiana at Monroe and the...
• College offers certified managed care pharmacist program. 2000;6(3):262-63.
• The University of Maryland’s Center on Drugs and Public Policy. 2000;6(2):184-85.
• Managed care pharmacy practice at the Texas Tech University Health Sciences Center School of Pharmacy. 1999;5(6):556-57.
• Description of a formal affiliation between a school of pharmacy and a managed care organization. 1999;5(5):433-37.
• Students gain exposure to managed care principles at a new school of pharmacy. 1999;5(4):371.
• Improving efficiency and effectiveness in managed care: ongoing efforts at the University of New Mexico College of Pharmacy. 1999;5(2):111.
• First managed care pharmacy course at the University of Illinois at Chicago. 1998;4(1):80-81.
• Linking the ivory tower and real-world practice: building a synergy bridge in managed care pharmacy. 1997;3(1):107-08, 110.
• Pharmacy internship offers real-world exposure to managed care pharmacy practice. 1996;2(6):605-06.
• Managed care pharmacy at the St. Louis College of Pharmacy. 1996;2(4):439, 442.
• Managed care pharmacy education at the University of Washington School of Pharmacy. 1996;2(3):319-20.
• Managed care pharmacy education at MCP. 1996;2(1):53.

### Physician Education-Intervention—Academic Detailing

- Selection bias in physician education-intervention programs. 2002;8(2):82.
- UIC students mobilize first student chapter of AMCP. 1995;1(6):185-86.

### Population Health—Interventions and Prevention of ADEs


### Prior Authorization (PA) (see Drug Benefit Management—Quantity Limits and Prior Authorization (PA))

### Privacy of Health Information

- The Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the pharmacy benefit: implications for health plans, PBMs, and providers. 2003;9(1):66-71.

### Quality Assurance


### Research Methods (see also Survey Methods)

• Method is everything: evaluating results by study design. 1997;3(1):66-68, 71-72, 75-76.
• Epidemiological techniques. 1997;3(1):30-32, 35.
• Interface between pharmacoepidemiology and pharmacoconomics in managed care pharmacy. 1996;2(3):282-89.
• Outcomes research, pharmacoconomics, and the pharmaceutical industry. 1996;2(1):48-52.

Safety—Health Care Worker

Safety—Patient Care (see also Drug Utilization Review (DUR))

Specialty Pharmacy
• The emergence of specialty pharmacy. 2000;6(4):280-84.

Survey Methods (see also Research Methods)
• Constructing mail survey questionnaires to maximize the rates of return and assure the validity and reliability of responses. 2002;8(3):225-31.

Technology—Automation

Technology—Education and Information
• Use of technology throughout the curriculum. 2002;8(2):86.

Technology—Electronic Prescribing
• Extent of electronic prescribing implementation as perceived by MCO pharmacy managers. 2002;8(1):41-47.

Therapeutic Interchange—Therapeutic Selection
• Utilization of pharmacy claims data to evaluate therapeutic interchange programs. 1999;5(4):331-34.

Value of Pharmacotherapy
• RxHealthValue offers three recommendations and cost research. 2001;7(1):17-20.

Women’s Health
Gabapentin May Be Appropriate for Off-Label Uses

In this issue, Alicia Mack, PharmD, discusses the clinical literature of the “off-label” uses of gabapentin (Neurontin) to prepare managed care practitioners for the appropriate uses of gabapentin.1 In the review, Mack examines several off-label uses of gabapentin, leading her to the conclusion that patients should only receive gabapentin when they have failed standard treatment options and when efficacy has been demonstrated in a randomized controlled trial.1

The methods by which gabapentin has become a drug with more than a billion dollars in annual sales in the United States are being examined in the federal court system.2 Regardless of the outcomes of the federal investigation of marketing practices, the use of gabapentin for off-label indications far surpasses its FDA-approved indications.3 Gabapentin may have become a “catch-all” medication for practitioners because its exact mechanism of action remains unknown and because it can be prescribed to patients with hepatic and/or renal insufficiencies.4 Furthermore, data ranging from case studies to randomized double-blind, placebo-controlled studies suggest that gabapentin may have positive effects on patients with a variety of disease states.

Randomized double-blind studies are the gold standard when researchers are trying to compare medication regimens. However, the studies must be critically evaluated to ensure that the results can be applied to a specific patient population.

Mack cites a study by Morello4 that was a randomized double-blind study comparing the efficacy of gabapentin to amitriptyline on diabetic peripheral neuropathy pain. The results state that there is no statistically significant difference between the 2 medications. However, the study was conducted in the Veterans Affairs (VA) San Diego Healthcare System.3 The demographics of the study—24 men and 1 woman—do not accurately depict the American population of diabetics, which is more than 50% female.6 The study was well designed and the results are accurate, but they may not be generalized to patient populations outside the VA system.

A similar study performed by Dallocchio et al. states that gabapentin significantly reduced pain scores, improved paresthesia scores, and had a better safety profile when compared with amitriptyline.7 The study was an open-label design, but the authors lessened possible biases by randomizing the patients to treatment arms.7 In addition, the patient population was also more representative of the American diabetic population (11 males, 14 females). Even though the study lacked blinding, the results may be considered as more applicable based upon the generalizability of the results. Moreover, all published data must be assessed to determine their applicability to specific patient cases.

The evidence-based practice of medicine allows therapies to evolve in search of the optimal treatment. A recent example utilizes metformin as adjunctive therapy in adolescents with type 1 diabetes.8 Another article by Gomez9 states that metformin adjunctive therapy may improve glycemic control in type 1 diabetic patients. If several articles are published about metformin use in type 1 diabetes, a meta-analysis can be performed to determine treatment effectiveness.

A meta-analysis, such as the one performed by Backonja and Glanzman10 for gabapentin, provides an immense amount of data on the treatment of painful diabetic neuropathy, postthermal neuralgia, and other neuropathic pain syndromes. Meta-analyses of well-designed studies provide greater generalizability when compared with smaller well-designed, randomized controlled trials, due to greater statistical power. Therefore, a practitioner can confidently apply the data to treat a more diverse patient population. Off-label uses may become clinically acceptable without having an FDA-approved indication.

Speculation arises concerning consistency of gabapentin off-label use due to a lack of manufacturer prescribing guidelines. A retrospective study in a managed Medicaid population (N=105) by Hamer et al. demonstrated that 95% of patients received gabapentin for off-label uses.11 Results indicated that 99% of patients receiving gabapentin continued treatment with the initial prescriber; 47% of patients received gabapentin 3 times daily, the usual dosing frequency; 40% of patients had no documented follow-up related to gabapentin; and 65% of patients discontinued therapy by the end of the study period.11 Additionally, the average dose received was predominately at the lower end of published dosage ranges.11 Based on the review, Hamer concluded that patients did not appear to receive benefit from gabapentin.11 Consequently, are the results due to gabapentin ineffectiveness, improper titration and follow-up, poor patient compliance, an atypical population, or a combination thereof? Health professionals choosing to practice evidence-based medicine must adhere to the published literature in regard to dosing, titration, and follow-up to accurately medicate their patient population.

The medical community has helped to make gabapentin a blockbuster drug, in part through prescribing for off-label uses. Gabapentin is used to treat some patients with unexplainable pathophysioologies; in patients with multiple, complex disease states; and in patients who have demonstrated intolerance to other therapies.

John Barbuto, MD, a practicing neurologist, observed in a previous issue of the Journal that logic drives the use of gabapentin because of its (a) few major side effects (and lower risk of malpractice lawsuits); (b) few drug interactions, a consideration more important for this patient population that has a relatively high incidence of affective disorders and chronic pain and tends to be taking multiple drugs; (c) favorable tolerance for these patients with affective disorders and chronic pain who are more prone to complain of side effects; and (d) relative ease of use (e.g., less need for follow-up laboratory monitoring).12

In many cases, practitioners are unable to pinpoint the mechanism causing relief; critics refer to this as the placebo effect and demand randomized controlled trials to justify the cost of gabapentin. Is it financially responsible to conduct a randomized controlled study to demonstrate results beyond a rea-
reasonable doubt when conclusions from a meta-analysis of all published data suggest clinical effectiveness and certain patients seem to respond favorably to gabapentin?

Limiting the use of gabapentin to an alternative status for only times when the patient is intolerant of the standard treatment option(s) or only when it has been studied in randomized controlled trials would be practicing “black and white” medicine in an environment that is actually various shades of gray. Practicing evidence-based medicine requires the health care professional to critically evaluate the literature, consider all possible therapeutic options, select therapy that will adequately treat the patient, and properly follow the patient in order to minimize the cost to the health care system.

**Shawn Davis**
PharmD Candidate, 2004
The Ohio State University College of Pharmacy
Columbus, Ohio
E-mail: davis.1685@osu.edu

The author discloses no financial interest or bias regarding gabapentin or Pfizer, Inc.

**REFERENCES**


**Use of Drugs for Off-Label Indications: Living in the Same World**

Learning is acquired by reading books; but the much more necessary learning, the knowledge of the world, is only to be acquired by reading man, and studying all the various editions of them.

—Philip Dormer Stanhope, statesman and writer (1694-1773)

In this issue Alicia Mack, PharmD, discusses a proposal that gabapentin use be restricted to its label indications. While her argument is based on perspectives of documented science, it may miss the point. Medical care is based on serving patients. The demands of this are a far cry from rigorous science. In the real world, the perspectives of Mack are, in my opinion, impractical. Scientifically, it would be ideal if medical care proceeded as a rigorous science. Yet, it doesn’t. Ultimately, medical care is about patient satisfaction. Patients do not go to the doctor to be provided rigorous science. Patients go to the doctor to meet their medical desires. There is only a partial correlation between these and the interests of science. If you were to attempt to provide medical care based on rigorous science (and I, more or less, have tried this), you would find that what you receive is patient dissatisfaction, even hostility. The average patient is only interested in rigorous science when this happens to be consistent with beliefs and desires.

What is the proof for this? The proof is plentiful indeed. Let’s start with some very simple perspectives: smoking, obesity, narcotic addiction. Is there evidence that smoking is bad for health? Do people continue to smoke? Do a lot of people continue to smoke? Or, is there evidence that obesity is bad for health? Do people continue to overeat? Do a lot of people continue to overeat? Or, is there evidence that drug addiction is bad for health? Do a lot of people abuse drugs? What do we learn from these observations? What are these people doing? Are they looking for the answers of rigorous science, or something else?

Now, let’s consider more subtle proof. There are countries of the world that have life expectancies equal to ours but that also have far lower health care costs. Widely available statistics (from the U.S. Census Bureau’s International Data Base, for instance) reveal that the United States is certainly not heading the list of life expectancy. By some measures, we’re down around rank 20. Yet, our health care costs are not only the highest in the world in terms of percent GNP but also are about double the costs for some other countries whose life expectancies are similar (or greater) than ours, such as England and Japan. Why is this proof for the tenet above? Science would dictate that all of our cost is not necessary. Yet, people of America do seek and consume health care to a greater extent than anywhere in the world. So, is this meeting the needs revealed by science, or is this consumption driven by something else? Information on health care costs across the world are widely available. If we are so interested in reducing costs, why do we not, as scientists, look at outcomes across the world? Part of the reason is simply that medical care is only part
ly interested in science.

In the real world of the doctor in the office, medical care is about people who are ill or worried and who seek to assuage their illness or fears. They come as humans, driven by emotion and personal life needs or desires. They do not come as computers, satisfied with the best solution to the equation.

This then brings us to gabapentin. This is a drug that patients find to “work” for them. How do we know this? They buy it—or have an insurance company buy it for them. They buy it not because they find taking pills an inherently joyful activity. They buy it, and continue to buy it, because, at one level or another, it proves itself to them. And, doctors provide it because, at one level or another, the drug proves itself to them also. For doctors in America, the keys to success of gabapentin are few drug interactions and few major side effects. In other words, providing the drug is not likely to get the patient or the doctor in trouble. This is the key to its widespread use.

While these perspectives paint a sobering picture of the practical use of gabapentin, we must also recognize that a great deal of off-label use of medications later becomes on-label use. Obtaining a specific indication for a drug is an economic decision. A manufacturer must decide whether the potential market opportunities of the medication warrant the costs of the research that might support it. The manufacturer must decide whether the formal studies would generate more business or simply provide a costly “I told you so.” And, yes, the company must decide what would happen if science did not support their current use patterns. This set of issues largely becomes a commentary on market economics, not scientific applicability. Yet, we must recognize that when there is widespread use of a medication for a problem, it may be reasonably likely that there is some foundation for the behavior. Just because a use is off-label does not mean it is scientifically wrong.

The move to control a drug by demanding that its use be limited to formal indications is a doomed strategy. There is very extensive information supporting the perspective that very frequently a drug comes to be recognized as useful for a condition via serendipity. Some physician somewhere either observes a fortuitous effect or correctly guesses a probable applicability. In the early stage of such use, the application is off-label.

For many drugs and many conditions, well-established uses may stay off-label. So, the hope of curtailing use to those situations that have formal labeling is an approach that will be rejected. To recognize this truth is not to advocate “do whatever you want.” Certainly, I do not believe nor support this. Rather, we simply know that there is a large gray area where science has not rigorously resolved questions. Where this is true, we would be wrong to presume that science will be unsupportive of extant behaviors.

I have no personal or economic interest in gabapentin or the company that manufactures it. Support of the behaviors surrounding gabapentin is not about supporting the drug itself. It is about recognizing how real medical care works. Real medical care is about taking care of emotional, personally interested human beings in a way that is satisfying to the patient and allows the doctor a successful life. Real medical care is about people. It is only about science as a secondary issue. Human beings are drawn to science where it serves their desires; however, few humans are drawn to science truly as a life grail. This should not surprise us—in spite of our trappings, we are barely emerged from the forest, so to speak.

So, as I have advocated before in the pages of this Journal, if we wish to control costs, we need to understand the real dynamics of American health care. I deeply believe in science. Yet, I also know the limits of its application to most human beings. This is not a criticism. This is a science.

More wisdom is latent in things-as-they-are than in all the words men use.

—Antoine-Marie-Roger de Saint Exupéry (1900-1944).

John P. Barbuto, MD
Neurology In Focus
An Outpatient Neurology Clinic at HealthSouth
Sandy, Utah
E-mail: doctorbarbuto@aol.com

REFERENCES
Contractual Arrangements Between HMOs and Medical Groups to Manage Drug Costs

In the middle 1980s, a national for-profit health maintenance organization (HMO) signed pharmacies, physicians, and hospitals to full-risk (capitation) financial arrangements that left many of these contract providers bankrupt or financially devastated. Many medical and hospital providers have come to more fully appreciate that financial risk can, in fact, be very risky. Several pharmacy administrative service organizations ceased to exist in the swath of the lopsided risk-contracting methods.

Financial-risk contracting between HMOs and provider groups is an ongoing tug of war. From one perspective, financial risk that can be fully managed by the provider group should be fully transferred (capitated) to the provider group from the HMO. Ideally, financial risk that is less manageable by the provider group should be retained by the HMO in increments proportional to the manageability of the financial risk, including volume (units) and price per unit. In general, pharmacy providers have very little control over either price or volume and generally should not assume financial risk associated with a prescription drug benefit. The HMO (insurer) controls the drug benefit design, including scope of drug coverage, copayment amounts, and days supply per copayment, etc. The HMO (or health plan), not the pharmacy provider, controls the rebates obtainable from pharmaceutical manufacturers, and pharmacy providers have little opportunity to influence (reduce) price except for small discounts earned through volume purchasing or through therapeutic selection if the HMO administers a true low net-cost drug formulary.

Physician medical groups have some degree of control over volume and price in prescription drug benefits of HMOs and may, therefore, reasonably assume some degree of shared financial risk. Physicians can control price through therapeutic selection of generic drugs and lower-cost brand drugs. Physicians also have a considerable amount of control over the volume of prescription drugs provided to a given population of patients.

Drug benefit financial risk is measurable and even predictable for large HMOs, and historical experience, measured per member per month (PMPM) with defined populations of continuously enrolled members-patients, can help reduce the uncertainty of unknown future costs. However, physician medical groups are also dependent on HMOs to share reliable information to help predict future costs. In the 1990s, allegations were made that some HMOs were setting PMPM capitation rates, including drug benefit financial risk, as a percentage of premium, using unadjusted historical costs and growing enrollment through artificially low monthly premium rates. A Texas state court judge ruled in May 1998 that a given HMO must stop immediately its practice of penalizing physicians who exceeded their pharmacy risk-budgets, calling the policy “probably illegal.” An executive at the HMO acknowledged that the first drug benefit capitation rate was “too low” (at 9.6% of premium). In October 1998, a large medical service organization (MSO) representing an independent practice association (IPA) of physicians in North Texas terminated its risk-contract with one of the largest HMOs in the country for not providing claims data in a timely and complete manner, making it impossible for the MSO to manage financial risk. Subsequent negotiations between the large HMO-insurer and the MSO resulted in some strong-arm tactics that attracted national attention and the intervention of the American Medical Association. The presidents of the Dallas County Medical Society and the Texas Medical Association (Austin) released a joint statement that included the following assertion: “Remember, this is an HMO that cannot, on a daily basis, tell its contracting doctors where or who its patients are, what kind of medications they are taking, or even what hospital they are in.” The dispute attracted the attention of the Texas Department of Insurance and the U.S. Justice Department, which penalized the insurer in a consent decree that required significant asset divestures in key Texas markets.

In early 1999, an independent practice association in San Mateo, California, notified the same large national insurer that it would not renew its contract, in part because the IPA could not obtain accurate and timely medical claims data. The IPA claimed that “We could never seem to get information on admissions, bed-days, etc.”

Business practices that either leave provider groups with unmanageable medical or drug costs or fail to provide the risk-contracted providers with the claims data necessary to manage the financial risk may result in state restrictions on risk contract terms. The Texas Department of Insurance, for example, prohibited HMOs from transferring financial risk for prescription drugs to medical groups following the unfair capitation rates and financial-risk practices for prescription drug benefits risk that devastated several physician groups in North Texas in the late 1990s. HMOs in Texas may provide financial incentives to physician groups for managing prescription drug costs but are not permitted to transfer financial risk for prescription drug benefits to physicians.

In this issue of the Journal, Agnew, Stubbins, Hickman, and Lipton describe the results of a survey of physician groups surrounding the subject of the management of financial risk associated with the growing use of self-administered injectable (SAI) drugs. As the relative magnitude of cost of this category of medical costs grows, more attention will be paid to the methods to manage these SAI drug costs effectively. The present survey, sponsored by a grant from the Robert Wood Johnson Foundation, seemed to find that many physician groups under contract with HMOs had not, as of early 2001, adopted a sophisticated or thorough cost management strategy for SAI drugs. This finding is really not surprising because the utilization of SAI drugs has grown more dramatically since that time, particularly in the categories of SAI drugs for hepatitis C virus (e.g., interferon SAIIs with ribavirin), multiple sclerosis (e.g., beta interferons and glatiramer acetate) and rheumatoid arthritis (e.g., etanercept). What is surprising is that at the time...
of this survey, the 18-month period ended in June 2001, the 20 physician groups almost universally did not know their actual SAI drugs costs, even for those medical groups that reported risk contracts with HMOs for these costs.

Some readers may have difficulty understanding why and how a physician group would agree to accept financial risk for a cost center, in this case SAI drugs, that is poorly measured and not clearly defined. However, a survey performed a year earlier, in 1999, by Evergreen Re, a reinsurer based in Stuart, Florida, produced results that may have predicted the results found by Agnew, Stebbins, Hickman, and Lipton. As many as 30% of hospital and physician medical group executives in markets with considerable HMO penetration—at least 30%—had little understanding of their level of exposure to financial risk through their capitated contracts. The hospital and medical groups in the survey reported an average 36% of revenues from capitated contracts, and the average provider organization had capitated agreements with 5 HMOs.

Many of the SAI drugs have a monthly drug cost of more than $1,000 per patient. There is probably the temptation for some HMOs to consider the transfer of financial risk, in this case for SAI drugs, to physician provider groups. This will also be a short-run game if (a) the expenditures for SAI drugs become significant and (b) the physicians groups do not have control over benefit design (e.g., out-of-pocket cost-share amount, scope of coverage, and criteria for coverage). SAI drug cost is probably best managed by a shared financial risk arrangement in which the physician groups assume a relatively small portion (e.g., 20%) of the total financial risk and also enjoy a reasonable financial cap on losses (i.e., aggregate or patient-specific stop-loss).

**Evidence-based Medicine, Practice Guidelines, and Disease Management**

Early in 2003, the Agency for Healthcare Research and Quality launched the Web-based National Quality Measures Clearinghouse to function as a repository for evidence-based quality measures and measure sets.

In January 2003, Kaiser Permanente announced that it would make available on its Web site more than 100 clinical practice guidelines (CPGs) that are used by Kaiser doctors for treatment of Kaiser HMO members. CPGs are the operational (process) part of interventions to improve clinical, service and cost outcomes. CPGs are necessary to operationalize the evidence that results from the conduct of randomized controlled trials (RCTs). Without CPGs, it is possible to systematically apply RCT evidence to real-world clinical practice. When CPGs are defined clearly and in sufficient detail, it is possible to use feedback from performance measures to continually improve care in a disease management program.

Disease management programs are difficult to design, implement, operate, and maintain, and, even today, there remains considerable frustration over the inability to reliably measure the financial value of disease management programs. In this issue of the *Journal*, Cannon, Larsen, Towner, et al. describe a health system-wide effort to improve clinical outcomes in diabetes. The authors report statistically significant and clinically important improvement in diabetes care according to 6 key performance measures: percentage of diabetics with at least 1 recorded hemoglobin A1c measurement per year, percentage of diabetics with hemoglobin A1c greater than 9.5, percentage of diabetics with hemoglobin A1c less than 7, percentage of diabetics with at least 1 recorded low-density lipoprotein (LDL) measurement per year, percentage of diabetics with recorded LDL value less than 130 mg/dL, and percentage of diabetics with at least 1 eye exam per year. The authors do not report an estimated return on investment in the diabetes care management system (DCMS) at this integrated health system.

The investment in care process models (CPMs) at Intermountain Health Care (IHC) is, in fact, large. Brent James, MD, and his colleagues at IHC have worked for nearly 20 years to create CPMs and measure their effects on clinical and service outcomes. James is fond of saying that clinical practice improvement will result in greater efficiency and, therefore, have a favorable effect on cost outcomes as well as clinical and service outcomes.

The results of the DCMS reported in this issue of the *Journal* are nothing short of exciting. Yet, readers should recognize that (a) this integrated health network (IHN) has been in the business of producing, implementing, and continually improving CPMs for nearly 20 years and (b) this is not just another integrated health system. SMG Marketing, now Verispan, has found IHC to be among the top integrated health systems in the United States since it began the measurement of integrated health systems 5 years ago. As of March 1999, this IHN ranked number 15 among all IHNs in the United States. SMG Marketing ranked IHC number one among 532 IHNs in 1999.

In year 2000, Sentara Healthcare (Norfolk, VA) edged out IHC as the most integrated health network in the United States by these measures, but IHC reclaimed the top spot in 2001 and held on to the top spot among 472 IHNs assessed in 2002. IHC had about 2,000 beds among 21 hospitals in 2002, in addition to the physician division and insurance division, including IHC Health Plans.

**The Relative Value of Disease Management Programs Versus Drug Manufacturer Rebates**

When the State of Florida in 2001 proposed a plan to extract additional rebates from prescription drug manufacturers through imposition of a preferred drug list (PDL) tied to a prior-authorization process, selected prescription drug manufacturers made counter proposals to sponsor disease management programs in lieu of paying additional rebates. In September 2001, Florida agreed to a proposal that projected savings of $16.3 million from establishment of 2 community-based disease management programs, one to hire health professionals and social workers to attend to Hispanic and Mexican-American Medicaid recipients with depression, HIV/AIDS, breast cancer, cervical cancer, or lung cancer. The explicit goal of this disease management program was to improve compliance with health regimens, including drug regimen adherence. The second disease
management program would hire and train community residents to help overcome language and cultural barriers to obtaining access to care for Medicaid recipients with depression and cardiovascular disease. The “savings” would apparently be measured in reduced emergency room visits and hospitalizations. The Pharmaceutical Research and Manufacturers of America (PhRMA) contested the Florida Medicaid program efforts to extract “supplemental” rebates, but a federal judge in the U.S. District Court in northern Florida (Tallahassee) ruled on December 28, 2001, that the Florida Medicaid list of preferred drugs may influence patient and physician behavior but did not prevent access to nonpreferred drugs, which would be illegal under federal law. In September 2002, the Eleventh Circuit Court of Appeals (Atlanta) upheld the lower court’s ruling regarding the Florida program, and the legality of Medicaid supplement rebate programs based upon PDLs with prior authorization was bolstered by the decision from Federal Court Judge John Bates in Washington, DC, on March 28, 2003, regarding a similar program in Michigan that employed a PDL with prior authorization.

The value of disease management programs in lieu of concessions in direct drug cost was disputed by a report from the Office of Program Policy Analysis & Government Accountability (OPPAGA) of the Florida legislature in early 2003. OPPAGA found that the disease management programs in Florida sponsored by prescription drug manufacturers saved the state about $35M in 2002, about $30M short of the amount that the drug companies would have paid in supplemental rebates. In 2001, Florida’s PDL saved the state $123M, including $46M (37.4%) from supplemental rebates. OPPAGA recommended to the Florida legislature that supplemental rebates be required for all drugs on the PDL and that the disease management programs be funded from a portion of the supplemental rebate income. OPPAGA analysts also said that the methodologies used by the drug companies to calculate savings from the disease management programs were vague, and some experts opined that the drug manufacturers had not been able to show that their disease management programs save money despite offering these programs to health insurers and others since the mid-1990s.

From another perspective, it is easy to see why the pharmaceutical manufacturers are opposed to the heavy-handed managed care method imposed by prior authorization (PA). The PA process in Florida produced dramatic market share changes that would be the envy of managed care pharmacists in the private sector. In just 90 days, the market share of lansoprazole increased by an absolute 21 percentage points, or 55% in relative terms, from 38% of prescriptions for proton-pump inhibitors in the second quarter of 2001 to 59% of prescriptions for proton-pump inhibitors in the third quarter of 2001. Lansoprazole market share increased further, to 67% of prescriptions in the fourth quarter of 2001. Stated another way, by paying supplemental rebates, the manufacturer of lansoprazole was able to nearly double its market share, a relative increase of 76%, or 29 absolute percentage points, in just 6 months, at the expense of competitor omeprazole, which experienced a market share drop of 33 percentage points, from 49% in the second quarter of 2001 and to 16% in just 90 days in the third quarter of 2001. The market share erosion for omeprazole was essentially 100%, to a residual of 1% of prescriptions for proton-pump inhibitors in the first quarter of 2002, a period of just 9 months.

### Disease Management, Pay-for-Performance, and Clinical Pharmacist Interventions in Diabetes Care

The April 2003 issue of a business news magazine contained 2 articles on the same subject, but the editor did not make an apparent connection between the articles and their common subject. More surprising, both articles were written by the same author. Certainly, the titles of the articles were different and would not suggest a connection: “Pay-for-performance plans seek to cut costs,” and “Pharmacist oversight cuts cost of chronic disease.” One article touted the “unique” notion of paying physicians to attain certain measures of disease management, in an employer-sponsored program called “Bridges to Excellence.” The separate, front-page article, touted the value of pharmacists in managing chronic disease, particularly diabetes; incidentally, the pharmacists were compensated for the professional interventions. The former article reported that several large employers had invested in a scheme, labeled Bridges to Excellence, with the intended purpose of reducing future costs of chronic disease, specifically diabetes. The (physician) pay-for-performance program had the same expected outcomes as the pay-pharmacist program, the regular, routine use by patients of measures to better control serum glucose and thereby delay the onset and reduce the magnitude of complications of diabetes.

The pharmacist pay-for-outcomes program, the “Asheville Project,” involved payment of $38 per monthly visit to participating pharmacists who monitor medication adherence and the routine use of serum glucose measures and perform basic physical exams to detect foot care or other health problems that may warrant a medical visit to a physician. The City of Asheville, a primary sponsor of the pay-pharmacist disease-management program for diabetes, reported savings of $2,000 per diabetic patient per year, largely as a result of reduced hospital costs. Average total medical costs per diabetic patient were reported to be $7,082 prior to implementation of the pharmacist disease management program for diabetes, an average $5,210 (26% less) in the first year and $4,651 in year 2, a 34% reduction compared to base-year costs. The Asheville Project included incentives for patient participation, including the elimination of copayments for visits to pharmacists and diabetes drugs and supplies, and provided each participating patient with a glucose meter.

### Consensus Panel, National Guidelines, and Other Potentially Misleading Terms

A recent article trumpeted in its title, “Consensus Panel Recommendations” for “Asthma Treatment Guidelines.” The
panel of 16 physicians and 2 pharmacists appeared to have the credentials necessary to adequately address the subject. However, the work of the panel and the article that was derived from this work were funded by the manufacturer of the drug that the panel recommended for use in patients with moderate to severe asthma that is “suboptimally controlled.” This observation gives the reader pause. Should not national treatment guidelines be based upon evidence from randomized clinical trials and developed by independent experts who do not benefit from or have a direct commercial interest in the recommendations that evolve from such panels?

What is the necessary amount of independence for these experts? Some may argue that experts employed by health plans are biased toward treatments and care processes that are concerned about cost. On the other hand, physicians and other providers engaged in clinical practice generally want what is best for their patients and may have little interest in cost, particularly for insured patients. Disclosure of potential conflicts of interest and sources of funding is a fundamental tool to manage bias, but most would agree that consensus panel guidelines should not be developed by persons compensated by the company that stands to benefit from the use of these guidelines. For busy readers, perhaps such treatment guidelines should include titles such as “Consensus Panel Recommendations Sponsored by XYZ Company.”

Frederic R. Curtiss, PhD, RPh, CEBS
Editor-in-Chief
E-mail: fcurtiss@amcp.org

REFERENCES

5. Patients and physicians are influenced by financial incentives in use of pharmaceuticals. Man Healthcare. 1997;May:70.
Transparency Needed for Economic Analyses of PA Programs

Dear Editor,

I am writing in response to the article “Pharmacoeconomic Modeling of Prior-Authorization Intervention for COX-2 Specific Inhibitors in a 3-Tier Copay Plan” in the July/August 2003 issue of the Journal of Managed Care Pharmacy.1 While the authors are to be commended for using an economic analysis to assess the impact of a prior-authorization (PA) program, I have some objections with the paper that I wish to express. My primary objection addresses the lack of transparency in methods used. When conducting pharmacoeconomic analyses, it is essential that the methods be made explicit to the reader. Otherwise, there is no way of knowing of the validity or applicability of the conclusions. In this study, there are several key variables that are insufficiently explained or ignored entirely.

1. The model assumes a drug cost savings of $0.31 per member per month (PMPM) exclusive of the PA program. This savings estimate was calculated based on the difference between the plan’s market share of COX-2s to nonspecific NSAIDs with that of other managed care populations across the nation according to IMS Health. The assumption is that the PA plan is responsible for that difference. This is a rather weak assumption upon which to base an entire analysis without additional substantiation. The discrepancy in COX-2 use between this plan and that of other plans across the nation could be explained by a variety of alternative causes other than the PA program. The variance could just as easily be explained by differences in population characteristics or variations in practice patterns.

2. The paper fails to mention that a significant portion of the savings resulted from denying care to 13% of people who have a prescription from their doctor.

3. There was no information provided about how the cost of the PA program was calculated. Readers were told that the PA program cost $0.07 per call but were not told whether that sum included costs due to start-up, office space and equipment, employee salaries and benefits, employee training, computing, and administration or how those costs were allocated. At a minimum, 25% of all costs associated with the PA plan-wide should be allocated toward this program since 25% of all calls were for COX-2 inhibitors.

4. There was no discussion about the possible relationship between the PA requests for COX-2 inhibitors and PA for proton-pump inhibitors (PPIs). Would a COX-2 PA request to switch to a NSAID and PPI initiate another PA for the PPI? If so, how many PAs for PPIs (20% of all PAs plan-wide) were generated due to a switch from a COX-2 drug? Were these costs included in the analysis?

5. The study only examined the cost of serious GI events and ignored the costs of other less-serious events. Symptoms of dyspepsia related to the treatment of arthritis have been associated with higher health care resource utilization (e.g., outpatient visits, inpatient admissions).2

6. Insufficient details are provided regarding the PA process and its impact on physician, pharmacist, and patient time. How much time was spent by persons affected by the PA burden? For example, how much time did patients, pharmacists, and physicians spend in switching from a prescribed COX-2 to an approved drug? There were no data or discussion relating to these potential time costs.

7. The model does not address costs associated with the requirement that a patient fail on 2 NSAIDs before becoming eligible for a COX-2 drug.

8. Figure 3 suggests that sensitivity analyses were conducted for all probabilities. However, they were not conducted on key assumptions such as the PMPM drug cost, PMPM cost of the PA, risk factors such as age or prior GI event, or percent compliance with medications. In addition, no 2-way or 3-way sensitivity analyses were conducted on any variables, although they are warranted.

9. The limitations section failed to acknowledge many of the study’s limitations described above.

My primary concern with this paper is that it presents conclusions with insufficient transparency of methods. Outcomes researchers can make a model agree with any conclusion they desire. Therefore, it is critical that authors make their methods and underlying assumptions as explicit as possible. Casual readers of this paper may accept the conclusions on face value without any understanding of their limitations. Worse, the conclusions may be cited by others to justify similar PA programs.

In conclusion, I want to express a final point relating to the issue of bias or conflict of interest. In the disclosure section at the end of the article, the authors “reported no biases or conflicts of interest in the preparation of this manuscript.” This statement lacks credibility given the fact that the authors are all employed by Humana, a health benefits company. Clearly, the authors’ interests are advanced if their PA intervention is shown to be cost effective. That does not imply that they are conducting biased research; it only suggests that their source of employment makes it that much more important to be explicit in their methods.

David Holdford, RPh, PhD
Department of Pharmacy, Medical College of Virginia
Richmond, Virginia
E-mail: david.holdford@vcu.edu

REFERENCES


For author response, see following page.
The Authors Respond

Dr. Holdford raises some good questions regarding our study.\textsuperscript{1} Our point-by-point response is as follows:

1. It is reasonable that population differences or practice variation can contribute to utilization variance. However, the size of the study population does represent broad geographic, demographic, and treatment patterns.

2. There is strong evidence regarding overprescribing of COX-2 specific inhibitors. The number of requests for COX-2 drugs suggests that many prescriptions are written for patients with no risk. The prior-authorization (PA) process is put in place to provide COX-2 drugs based on established risk criteria.

3. The administrative cost per call for the call center in 2000 reflected all costs, including office space and equipment, employee salaries and benefits, training costs, etc. The stated cost savings for the PA program on COX-2 specific inhibitors was adjusted for the entire operation of the call center. If only 25% of all costs of the call center were used, the cost savings of $0.24 per member per month (PMPM) would be more favorable.

4. Concomitant use of proton-pump inhibitors (PPIs) with COX-2 specific inhibitors and nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs) was reflected in the population of our model (see Figure 1). The membership is allowed 90-day PPI treatment without a PA. The actual influence of PA rate change for PPIs was not in the scope of the study.

5. This study, along with many in the current literature regarding NSAID treatment, focuses on only serious GI events. The study cited by Holdford used claims data from 1992-1993, before the availability of COX-2 drugs. It would probably be of value to repeat this analysis using more recent claims data.

6. The issues of PA impact on physician and patient time were addressed in the second-to-last paragraph of the Results section. It was acknowledged that the value of PA might decrease due to the level of patient and provider satisfaction and its impact on member retention and burden of use (see bottom of page 332).

7. We agree that the costs associated with treatment failure for nonspecific NSAIDs were not measured in the scope of this study.

8. Sensitivity analysis was conducted on the probabilities in which the assumptions were made. The areas of PMPM drug cost, cost of PA, and risk factors were calculated numbers that we feel were very real estimates with a smaller range of variability. Although this was only a preliminary study, a 2-way sensitivity analysis may prove valuable for future evaluations to determine how one variable affects the other. Regarding the issue of bias or conflicts of interest, this study was done to help make administrative decisions about benefit design and the true value of PA to the health plan. The results were not biased to sway the outcomes one way or the other.

Jane Stacy, PharmD
Clinical Pharmacist, Outcomes Analysis
Humana, Louisville, Kentucky
E-mail: jstacy1@humana.com

REFERENCE