Utilization and Drug Cost Outcomes of a Step-Therapy Edit for Generic Antidepressants in an HMO in an Integrated Health System

Blood Pressure Goal Attainment According to JNC 7 Guidelines and Utilization of Antihypertensive Drug Therapy in MCO Patients With Type 1 or Type 2 Diabetes

Administrative Claims Analysis of Asthma-Related Health Care Utilization for Patients Who Received Inhaled Corticosteroids With Either Montelukast or Salmeterol as Combination Therapy

The Cost-effectiveness of Lamotrigine in the Maintenance Treatment of Adults With Bipolar I Disorder

Drug and Medical Cost Effects of a Drug Formulary Change With Therapeutic Interchange for Statin Drugs in a Multistate Managed Medicaid Organization
CONTENTS

RESEARCH

294 Utilization and Drug Cost Outcomes of a Step-Therapy Edit for Generic Antidepressants in an HMO in an Integrated Health System
Jeffrey D. Dunn, PharmD, MBA; H. Eric Cannon, PharmD; Matthew P. Mitchell, PharmD; and Frederic R. Curtiss, PhD, CEBS

303 Blood Pressure Goal Attainment According to JNC 7 Guidelines and Utilization of Antihypertensive Drug Therapy in MCO Patients With Type 1 or Type 2 Diabetes
Vickie Andros, PharmD; Allison Egger, MPH; and Uma Dua, PharmD

310 Administrative Claims Analysis of Asthma-Related Health Care Utilization for Patients Who Received Inhaled Corticosteroids With Either Montelukast or Salmeterol as Combination Therapy
Felicia C. Allen-Ramey, PhD; Don Bukstein, MD; Allan Luskin, MD; Shiva G. Sajjan, PhD; and Leona E. Markson, ScD

322 The Cost-effectiveness of Lamotrigine in the Maintenance Treatment of Adults With Bipolar I Disorder
Neill W. Calvert, PhD; Steven P. Burch, PhD; Alex Z. Fu, PhD; Penny Reeves; and Thomas R. Thompson, MD

FORMULARY MANAGEMENT

331 Drug and Medical Cost Effects of a Drug Formulary Change With Therapeutic Interchange for Statin Drugs in a Multistate Managed Medicaid Organization
Brian Meissner, PharmD, PhD; Michael Dickson, PhD; Judy Shinogle, PhD, MSc; C.E. Reeder, PhD; Dea Betazi, PharmD, MPH, PAHM; and Viran Senevirante, PharmD

DEPARTMENTS

284 Cover Impressions
Phillip Singer
Sheila Macho
Cover Editor

341 Editorial
• PP-ICONS—Another Tool to Help Interpret Asthma Utilization Studies
Brian K. Crownover, MD, FAAPP, Lt. Col., USAF, MC
Associate Editor

343 Editorial Subjects—In This Issue and in Previous Issues
• More Evolution of the Evidence in Asthma Disease Management—SMART Versus GOAL Clinical Trials Debate the Cost-Benefit of LABA While the Value of LeukotrieneModifiers, Particularly Montelukast, Is Uncertain
Frederic R. Curtiss, PhD, RPh, CEBS
Editor-in-Chief
JMCP EDITORIAL POLICY

EDITORIAL MISSION AND POLICIES

JMCP publishes peer-reviewed original research manuscripts, subject reviews, and other content intended to advance the use of the scientific method, including the interpretation of research findings in managed care pharmacy. JMCP is dedicated to improving the quality of care delivered to patients served by managed care pharmacy by providing its readers with the results of scientific investigation and evaluation of clinical, health, service, and economic outcomes of pharmacy services and pharmaceutical interventions, including formulary management. JMCP strives to engage and serve professionals in pharmacy, medicine, nursing, and related fields to optimize the value of pharmaceutical products and pharmacy services delivered to patients.

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.

EDUCATIONAL CONTENT AND PEER REVIEW

All articles, editorials, and commentary in JMCP undergo peer review; articles undergo blinded peer review. Letters may be peer-reviewed to ensure accuracy. The fundamental departments for manuscript submission are:

- Research
- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Editorials/Commentary
- Letters

For manuscript preparation requirements, see "JMCP Author Guidelines" in this journal or at www.amcp.org.

RESEARCH

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.

SUBJECT REVIEWS

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

FORMULARY MANAGEMENT

These are well-referenced, comprehensive reviews of subjects relevant to formulary management methods or procedures in the conduct of pharmacy and therapeutics (P&T) committees and may include description and interpretation of clinical evidence.

CONTEMPORARY SUBJECTS

These are well-referenced submissions that are particularly timely or describe research conducted in pilot projects. Contemporary Subjects, like all articles in JMCP, must describe the hypotheses or hypotheses that guided the research, the principal methods, and results and include a Discussion section that includes a clear description of how this research adds information to the current literature.

EDITORIALS/COMMENTARY

These submissions should be relevant to managed care pharmacy and address a topic of contemporary interest.

LETTERS

If the letter addresses a previously published article, an author response may be appropriate. (See "Letter to the Editor" instructions at www.amcp.org.)

ADVERTISING/DISCLOSURE POLICY

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 or back of the journal; it is not accepted for placement opposite or near submitted editorial copy.

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

See "Advertising Opportunities" at www.amcp.org. Contact the Advertising Representative to receive a Media Kit.

JMCP

Academy of Managed Care Pharmacy
100 North Pitt St., Suite 400
Alexandria, VA 22314
Tel: (703) 683-6116
Fax: (703) 683-6117
E-mail: jmcpreview@amcp.org

Advertising Sales Office
Professional Media Group, Inc.
40 N. Woodbury Rd.,
Pitman, NJ 08071
Tel: (800) 466-5454
or (856) 589-5454
Fax: (856) 582-7611
E-mail: peters@ymailgroup.net

www.amcp.org  Vol. 12, No. 4  May 2006  JMCP  Journal of Managed Care Pharmacy 279
JMCP publishes peer-reviewed original research manuscripts, subject reviews, and other content intended to advance the use of the scientific method, including the interpretation of research findings in managed care pharmacy. JMCP is dedicated to improving the quality of care delivered to patients served by managed care pharmacy by providing its readers with the results of scientific investigation and evaluation of clinical, health, service, and economic outcomes of pharmacy services and pharmaceutical interventions, including formulary management. JMCP strives to engage and serve professionals in pharmacy, medicine, nursing, and related fields to optimize the value of pharmaceutical products and pharmacy services delivered to patients.

JMCP employs extensive bias-management procedures intended to ensure the integrity and reliability of published work.

EDITORIAL MISSION

Journal of Managed Care Pharmacy (ISSN 1083–4087) is published 9 times per year and is the official publication of the Academy of Managed Care Pharmacy (AMCP), 100 North Pitt St., Suite 400, Alexandria, VA 22314. (ISSN 1083–4087) is published 9 times per year and is the official publication of the Academy of Managed Care Pharmacy (AMCP), 100 North Pitt St., Suite 400, Alexandria, VA 22314. (703) 683-8416, (800) TAP-AMCP, (703) 683-8417 (fax). The paper used by the Journal of Managed Care Pharmacy meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper) effective with Volume 7, Issue 5, 2001; prior to that issue, all paper was acid-free. Annual membership dues for AMCP include $60 allocated for the Journal of Managed Care Pharmacy. POSTMASTER: Send address changes to JMCP, 100 North Pitt St., Suite 400, Alexandria, VA 22314.
Phillip Singer was born in 1966 in Philadelphia, Pennsylvania. As a young boy, one of his favorite pastimes was paging through his family's collection of art books. He found the books about Norman Rockwell especially appealing. Perhaps it was seeing Rockwell's idealized vision of reality that ultimately influenced Singer to develop his own depiction of reality. His unique artistic style is a fascinating mix of realism and surrealism, blended with a dash of wit.

Singer was “bitten by the drawing bug” in high school after years of admiring the work of great masters and famous illustrators. Encouraged by his parents and teachers, he eventually earned a full scholarship to The School of Visual Arts in New York City. “Art was one thing I was truly passionate about. I wasn’t sure if I could ever be good enough to be a professional artist, but the challenge gave me focus and direction in my life,” Singer said. He proved that he was indeed good enough when he won The School of Visual Arts’s illustration portfolio cover competition in his senior year. Singer’s professional illustration career started the day after graduating with a bachelor’s degree in illustration, and has lasted for 16 years. His illustration credits include more than 100 book covers for Avon Books, HarperCollins, Viking Books, Simon & Schuster, and Warner Books. He has also done numerous illustrations for magazines such as Forbes and National Geographic and promotional illustrations for corporations such as Merck & Co. and Celestial Seasonings Tea.

Even after achieving great success in his illustration career, Singer wanted more—he yearned to make the transition from illustration to fine art. This move began in a real sense when he created Delicate Balance. “I painted Delicate Balance over 15 years ago, when I was strictly an illustrator. I wasn’t getting the kind of freelance illustration work that I longed for, so I set out to show people what I could do. I wanted to paint living, breathing things, but I also wanted to show art directors that I could put together a compelling image. I wanted them to use me as a creative resource, not just a pair of hands. I really don’t know how that image came together, but I think I did over 100 thumbnail sketches. Finally, I had the idea of all the animals being carried by a single bird,” explained Singer. Delicate Balance not only symbolizes the balance between his illustration and fine art careers but also serves to remind us of our world’s delicate ecological balance. The painting also exemplifies Singer’s ability to make a surreal image seem so real that the impossible somehow seems possible.

In 1999, he made the final leap of faith from illustration to fine art when the Singer Fine Art Collection made its debut at a handful of fine art festivals on the East Coast. His charming collection features original oil paintings and limited-edition giclée prints. Singer’s spectacular paintings can take him more than a month to produce, and he has been able to sell them almost as fast as he paints them. Although he occasionally shows his work in galleries such as the Langman Gallery in Willow Grove, Pennsylvania, he makes his living primarily by showing his art at art fairs throughout the country. Singer currently participates in approximately 15 art fairs a year, which are listed on his Web site, The Art of Phill Singer (www.psingerart.com). He also illustrates about four book covers a year for the murder mystery novels written by Elizabeth Peters.

When asked if he had any favorite artists, Singer replied, “I have always loved the surreal images painted by René Magritte. There’s a certain combination and juxtaposition of objects and people that speaks to me. However, I would have to say that I prefer the work of the more traditional Realists. William Bouguereau is my all-time favorite. To me, there is nothing more magical than creating the illusion of three dimensions on a flat canvas. I also like Frederic Lord Leighton, Jean Auguste Dominique Ingres, Johannes Vermeer, John Singer Sargent, and William McGregor Paxton.” Commenting on Realism in today’s world, Singer said, “It’s very difficult to dazzle people with a straightforward image. Therefore, I think I’ve stumbled onto a way to combine my sense of humor with the kind of [realistic] painting I like to do.” For instance, Singer’s work titled Pie in the Sky is literally a picture of a big slice of apple pie suspended in a small room with walls rendered to look like a sky. He has painted the pie slice so realistically—from the flaky crust to the gooey filling—that one can almost smell it. This painting, as well as many other fascinating works of art, can be seen in the gallery section of Singer’s Web site.

Singer said that with every composition he paints, he strives for beauty, yet hopes the audience also finds it challenging, bold, smart, funny, and imaginative. “When you find the ‘unexpected’ in a piece of art, that makes it worth taking home,” he remarked. Singer now enjoys a growing following, and he remains focused on creating the paintings he has always dreamed of—with an emphasis on the word “dream.”
Manuscript Preparation

Manuscripts should include, in this order: title page, abstract, text, references, tables, and figures (see Submission Checklist for details).

JMCP abstracts should be carefully written narratives that contain all of the principal quantitative and qualitative findings, with the outcomes of statistical tests of comparisons where appropriate. Abstracts are required for all articles in Research, Subject Reviews, Formulary Management, and Contemporary Subjects. The format for the abstract is Objective, Methods, Results, Conclusion, Keywords. Editorials and Commentary do not include abstracts.

For descriptions of editorial content, see “JMCP Editorial Policy” in this Journal or at www.amcp.org.

Please note:
• The JMCP Peer Review Checklist is the best guide for authors to improve the likelihood of success in the JMCP peer-review process. It is available at www.amcp.org (Peer Reviewers tab).
• A subsection in the Discussion labeled “Limitations” is generally appropriate for all articles published in JMCP.
• Most articles published in JMCP, particularly Subject Reviews, should incorporate or at least acknowledge the relevant work of others published previously in JMCP (see “Article Index by Subject Category” at www.amcp.org).
• For most articles in JMCP, a figure is recommended for making the effects of the inclusion and exclusion criteria clear to readers (see JMCP examples in 2003;9(4):320 [Figure 1] or 2003;9(3):258 [Table 1]).
• Product trade names may be used only once, for the purpose of providing clarity for readers, generally at the first mention of the generic name in the article but not in the abstract.

Reference Style

References should be prepared following modified AMA style. All reference numbers in manuscript should be superscript (e.g., 1). See the following 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

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. Paper (or Poster) presented at a meeting

9. Newspaper

10. Web site

Manuscript Submission

A paper copy of the manuscript, including original figures and tables and author attestations (see Submission Checklist), should be submitted to the JMCP Peer Review Administrator at the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314; Tel: (800) 827-2627 or (703) 483-8416 or Fax: (703) 683-8147. The paper copy is necessary to ensure proper presentation and placement of text, figures, tables, and graphs. Please submit the manuscripts electronically at jmcp.msubmit.net. 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 the paper copy of your manuscript to the Journal of Managed Care Pharmacy, please check to see that your package includes the following:

❑ Cover letter
❑ Manuscript: prepared in 12-point type, 1.5 line spacing, including abstract; no more than 500 words
❑ Keywords: follows the abstract
❑ References: cited in numerical order as they appear in the text (use superscript numbers) and prepared following modified AMA style; do not include footnotes in the manuscript
❑ 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) at the end of the manuscript; match symbols in tables and figures to explanatory notes, if included. May use 10-point font.
❑ Disclosures and conflict-of-interest forms: completed and signed author attestation forms (available at www.amcp.org); clearly indicate source(s) of funding and financial support.

Note: Please do not include author identification in the electronic manuscript document.

For “Manuscript Submission Checklist” and “Peer Review Checklist,” see www.amcp.org

REFERENCE


www.amcp.org    Vol. 12, No. 4    May 2006 JMCP    Journal of Managed Care Pharmacy    289
Utilization and Drug Cost Outcomes of a Step-Therapy Edit for Generic Antidepressants in an HMO in an Integrated Health System

JEFFREY D. DUNN, PharmD, MBA; H. ERIC CANNON, PharmD; MATTHEW P. MITCHELL, PharmD; and FREDERIC R. CURTISS, PhD, CEBS

ABSTRACT

OBJECTIVE: Antidepressants do not differ significantly in their ability to treat depression. Excluding the tricyclic antidepressants (TCAs), these drugs also do not differ significantly in their incidence of adverse events. Therefore, the initial choice of antidepressant medication should be based, in part, on cost. The objective of this study was to evaluate the impact on utilization and costs of a generic step-therapy edit for antidepressant drugs excluding TCAs in a health maintenance organization (HMO) in an integrated health system (IHS).

METHODS: The pharmacy department of the 440,000-member HMO in an IHS collaborated with the Behavioral Health Clinical Program to design an intervention that required generic antidepressants as first-line pharmacotherapy. Under the GenericStart! Program, a brand-name antidepressant was covered only after trial with a generic antidepressant, excluding TCAs. A step-therapy edit was added to the pharmacy claims processing system on January 1, 2005. All new starts, defined as members with no claims history of antidepressant treatment within the preceding 6 months, were required to use a generic antidepressant. The member copayment was waived for the first prescription. All generic antidepressants were in tier 1 of the drug formulary, with an average copayment of $5 to $10. All brand-name antidepressants were in either tier 2 (preferred brand), with an average copayment of $20 to $25 or 25% coinsurance, or tier 3 (nonformulary brand), with an average copayment of $40 to $45 or 50% coinsurance. Pharmacy claims data from a national pharmacy benefit manager (PBM) without interventions for antidepressants in 2004 or 2005 were used for the comparison group.

RESULTS: The generic antidepressant dispensing rate increased by 20 points (32.5% to 52.5%) in the intervention group but only 7.4 points (24.9% to 32.3%) in the comparison group in 2005 compared with 2004. The principal measure of antidepressant drug cost per day of therapy in the intervention group decreased by 11.7% (from $2.40 to $2.12) in 2005 compared with 2004 versus a 2.1% decrease (from $2.60 to $2.53) in the comparison group (P < .001). Days of antidepressant drug therapy per member per month (PMPM) dropped by 1.5% (from 1.74 to 1.71) in the intervention group versus a decrease of 5.0% (from 1.37 to 1.30) in the comparison group in 2005 compared with 2004. The combination of change in drug cost and utilization resulted in a 13.0% decrease in antidepressant drug cost, from $4.16 PMPM in 2004 to $3.62 in 2005, compared with a 7.6% decrease (from $3.57 to $3.30 PMPM) in the comparison group. The 9.0% difference in drug cost per day represents drug cost savings of approximately $0.36 PMPM or $1,880,562 in 2005 dollars for this HMO of approximately 440,000 members.

CONCLUSION: A step-therapy edit requiring HMO members to use a generic antidepressant, excluding tricyclics, prior to use of a brand-name antidepressant resulted in drug cost savings of 9.0% for the entire class of antidepressants, equal to $1,880,562 ($0.36 PMPM) in 2005 dollars in the first year of the intervention. A small (-1.5%) decrease in use of antidepressants occurred in the intervention group, which was less than the 5.0% decrease in utilization of antidepressants in the comparison group.

KEYWORDS: Antidepressant, Drug benefit design, Generic drug, Step therapy, Utilization management

J Manag Care Pharm. 2006;12(4):294-302

T he direct cost of antidepressant drug therapy should be of interest to managed care organizations, such as health maintenance organizations (HMOs), for several reasons. First, the antidepressants, excluding the tricyclic antidepressants (TCAs), do not significantly differ in their ability to treat depression or in their incidence of adverse events (with some interpatient variability), creating an opportunity for achieving similar or better clinical outcomes at lower cost. Second, active drug is not necessary to obtain a clinical response in many patients. In a meta-analysis of original data from 7 randomized controlled trials, Thase et al. found that 51% of outpatients with major depressive disorder responded to placebo, and 36% of the patients randomized to placebo experienced remission during follow-up. Third, many managed care patients who receive antidepressant drugs may not have major depression. Theobald et al. found that only 7% of the medical charts for patients who had received antidepressant drug therapy had documentation of 5 of the 9 symptoms required to make a diagnosis of major depression, and 40% of the medical charts did not include a single symptom necessary to make a diagnosis of major depressive disorder.

Given the lack of a significantly superior choice among the antidepressants, the initial choice of antidepressant medication should be made based, in part, on cost considerations. The availability of multiple generic antidepressant medications creates the opportunity to improve the cost-effectiveness of treatment and lower the cost of treatment for patients as well as HMOs. Three of the selective serotonin reuptake inhibitors (SSRIs) currently on the market are available by generic name. Fluoxetine (Prozac) became available in generic form in August 2001. The first abbreviated new drug application (ANDA) for

Authors

JEFFREY D. DUNN, PharmD, MBA, is formulary and contract manager, H. ERIC CANNON, PharmD, is director, Pharmacy, and director, Health and Wellness, MATTHEW P. MITCHELL, PharmD, is clinical pharmacy coordinator, SelectHealth, Intermountain Healthcare, Salt Lake City, Utah; FREDERIC R. CURTISS, PhD, CEBS, is editor-in-chief, JMCP, Alexandria, Virginia.

AUTHOR CORRESPONDENCE: Jeffrey D. Dunn, PharmD, MBA, Formulary and Contract Manager, SelectHealth, 4646 West Lake Park Blvd., Suite N3, Salt Lake City, Utah 84120. Tel: (801) 442-7984; Fax: (801) 442-3006; E-mail: jeffrey.dunn@selecthealth.org

Copyright © 2006, Academy of Managed Care Pharmacy. All rights reserved.
generic Paxil (paroxetine) was approved on September 29, 2003, by the U.S. Food and Drug Administration (FDA), and the FDA approved ANDAs from 5 manufacturers of generic citalopram (Celexa) on October 28, 2004.

In addition to the 3 generic SSRIs, 2 other non-TCA antidepressants are available generically. An ANDA for bupropion SR (Wellbutrin SR), a weak inhibitor of norepinephrine and dopamine uptake, was approved by the FDA on March 22, 2004, which was preceded by the ANDA for immediate-release bupropion that was issued by the FDA on April 17, 2000. The first ANDA for mirtazapine (Remeron), a serotonin, alpha-adrenergic, and histamine antagonist, was approved by the FDA on January 24, 2003. Some of the antidepressants have FDA-approved label indications for conditions other than treatment of depression. The vast majority of patients will both tolerate and respond to one of these 5 generic medications.

In light of multigeneric, multisource availability of the antidepressants, on January 1, 2005, IHC Health Plans and the IHC Behavioral Health Clinical Program introduced the GenericStart! Program. Patients new to antidepressant drug therapy (having no claims history of antidepressant treatment within the previous 6 months) were required to use a generic antidepressant medication (excluding TCAs) prior to coverage of a brand-name antidepressant.

The GenericStart! intervention in 2005 was preceded by the GenericSample program that had been in effect since 2003 for generic fluoxetine and was later expanded to include generic bupropion SR, generic citalopram, and generic paroxetine as these drugs became available generically. The GenericSample program waives the copayment or coinsurance for the first fill of the generic antidepressant when obtained at a participating community pharmacy.

Implementation of the GenericStart! Intervention in 2005 included a notice to all participating physicians. This notice included several key points: (a) generic antidepressants offer a dramatic improvement in cost-effectiveness over the brand-name equivalents because of their low expense with the same efficacy and safety profile as the higher-cost brand antidepressants; (b) generic antidepressants should be considered as the initial choice for a patient presenting with depression; (c) most patients respond within the first 4 to 6 weeks of drug treatment, but a substantial minority of patients may require 8 to 12 weeks of therapy with an antidepressant before response is observed; and (d) the possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs and, therefore, close supervision of high-risk patients should accompany drug therapy.

This research with administrative pharmacy claims was approved by the IHC Institutional Review Board and IHC Patient Privacy Board on February 17, 2006.

**Methods**

The drugs included in this study are shown in Table 1, which includes the copayment tier and formulary status of each drug. Generic drugs in this study are shown with the preface “generic” in Table 1 and include bupropion, citalopram, fluoxetine, mirtazapine, and paroxetine. Pharmacy claims with dates of service from January 1, 2004, through December 31, 2005, were included in the study if the National Drug Code (NDC) on the pharmacy claim was grouped under 1 of 4 Medispan Generic Product Indicators (GPIs): GPI starts with 5802 (mirtazapine), GPI starts with 5816 (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline), GPI starts with 5818 (duloxetine and venlafaxine), or GPI starts with 5830 (bupropion, maprotiline, and venlafaxine prior to the market introduction of duloxetine in August 2004).

The administrative claims data fields for this analysis were actual allowed drug (ingredient) cost, total days supply of antidepressant drug therapy, total pharmacy claims, total generic drug claims, and total eligible member-month counts. The principal outcome measures were generic dispensing ratio (GDR, the number of generic drug claims divided by the total number of drug claims), days of therapy per claim (prescription [Rx]), drug cost per claim, drug cost per day, and drug cost per member month (PMPM).

The study design involved a 12-month preperiod (calendar...
Utilization and Drug Cost Outcomes of a Step-Therapy Edit for Generic Antidepressants in an HMO in an Integrated Health System

Table 2A: Utilization and Cost for Antidepressants—Intervention Group

<table>
<thead>
<tr>
<th>Intervention Group</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>Total days of therapy</td>
<td>2,222,985</td>
<td>2,210,707</td>
</tr>
<tr>
<td>Utilizing members</td>
<td>31,303</td>
<td>30,554</td>
</tr>
<tr>
<td>Ingredient cost†</td>
<td>$5,403,976</td>
<td>$5,354,397</td>
</tr>
<tr>
<td>Generic Rx ratio</td>
<td>28.51%</td>
<td>31.61%</td>
</tr>
<tr>
<td>Units per day</td>
<td>1.21</td>
<td>1.21</td>
</tr>
<tr>
<td>Days per Rx</td>
<td>32.96</td>
<td>33.03</td>
</tr>
<tr>
<td>Ingredient costs per Rx</td>
<td>$80.14</td>
<td>$80.01</td>
</tr>
<tr>
<td>Ingredient cost per utilizing member</td>
<td>$172.63</td>
<td>$175.24</td>
</tr>
<tr>
<td>Eligible members</td>
<td>427,791</td>
<td>426,671</td>
</tr>
<tr>
<td>Prevalence of use</td>
<td>7.3%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Days PMPM</td>
<td>1.73</td>
<td>1.73</td>
</tr>
<tr>
<td>Rxs PMPM</td>
<td>0.0526</td>
<td>0.0523</td>
</tr>
<tr>
<td>Cost per day</td>
<td>$2.43</td>
<td>$2.42</td>
</tr>
<tr>
<td>Average cost PMPM</td>
<td>$4.22</td>
<td>$4.18</td>
</tr>
</tbody>
</table>

* Antidepressants exclude tricyclic antidepressants and include the selective serotonin reuptake inhibitors (SSRIs, Medispan Generic Product Indicator [GPI] beginning with 5816), serotonin and norepinephrine reuptake inhibitors (SNRIs, GPI beginning with 5818), bupropion (GPI beginning with 5830), and mirtazapine (GPI beginning with 5803).
† Ingredient cost is the actual allowed drug cost without dispense fees and before member cost-share.
PMPM = per member per month; Rx = prescription.

Year 2004 and a 12-month postperiod (calendar year 2005). To control for change in new generic drug introduction (e.g., citalopram in November 2004); new label warnings for antidepressants regarding suicidality; and antidepressant market dynamics, including drug promotion to consumers and physicians and other factors, a comparison group of similar size (total membership) was identified from the pharmacy claims data for a national pharmacy benefit manager (PBM) without interventions for antidepressants during the 24-month study period. Approximately one third of members in the PBM data were subject to a 3-tier copay design (e.g., copayments of $5 for generic drugs, $15 for formulary brand drugs, and $30 for nonformulary brand drugs); the remaining two thirds of members in the PBM data were subject to a 2-tier copayment design (e.g., $10 generic, $20 brand).

For the intervention groups, all generic antidepressants had a tier-1 copayment, which was waived for the first fill for the 4 GenericSample drugs (generic bupropion, generic citalopram, generic fluoxetine, and generic paroxetine). Paxil CR (paroxetine), Wellbutrin XL (bupropion), and Effexor XR (venlafaxine) were in the second copayment tier in 2004 and 2005. Lexapro (escitalopram) was in the third copayment tier, and Zoloft (sertraline) moved from tier-2 to tier-3 copayment on April 1, 2005. Cymbalta (duloxetine) moved from tier-3 to tier-2 copayment on July 1, 2005 (Table 1).

The t test (MS Excel) was used to test the null hypothesis that the change in average drug cost per day of therapy in 2005 compared with 2004 was no different in the intervention group compared with the comparison group.

Results

The intervention group was similar to the comparison group in the number of total eligible members, the number of utilizing members (patients), and total antidepressant drug costs (Tables 2a and 2b). For the principal measure of drug (ingredient) cost per day of therapy, the comparison group experienced a small dip in average cost, from $2.60 per day in the first quarter (Q1) of 2004 to $2.53 per day in 2005 Q4 (Figure 1). The intervention group experienced a cost per day nearly parallel to the comparison group until the first quarter of the intervention (2005 Q1), and the reduction in drug cost became increasingly evident over the 4 calendar quarters of the 12-month intervention period.

The source of the drug cost savings is found in the generic dispensing ratio (Figure 2). The slope of the GDR was similar for the intervention and comparison groups until 2004 Q4, and the GDR became increasingly divergent throughout the 12-month intervention period, ending in a GDR of 52.5% for
Utilization and Drug Cost Outcomes of a Step-Therapy Edit for Generic Antidepressants in an HMO in an Integrated Health System

Utilization and Cost for Antidepressants*—Comparison Group

<table>
<thead>
<tr>
<th>Comparison Group†</th>
<th>2004</th>
<th></th>
<th></th>
<th>2005</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx</td>
<td>59,982</td>
<td>57,325</td>
<td>55,590</td>
<td>55,050</td>
<td>53,122</td>
<td>53,180</td>
<td>49,700</td>
</tr>
<tr>
<td>Total days of therapy</td>
<td>2,099,305</td>
<td>2,024,803</td>
<td>1,978,274</td>
<td>1,962,688</td>
<td>1,882,799</td>
<td>1,892,078</td>
<td>1,771,615</td>
</tr>
<tr>
<td>Utilizing members</td>
<td>30,942</td>
<td>29,413</td>
<td>29,274</td>
<td>28,245</td>
<td>27,843</td>
<td>27,487</td>
<td>26,036</td>
</tr>
<tr>
<td>Ingredient cost‡</td>
<td>$5,528,569</td>
<td>$5,309,003</td>
<td>$5,116,906</td>
<td>$5,052,124</td>
<td>$4,806,113</td>
<td>$4,819,268</td>
<td>$4,438,808</td>
</tr>
<tr>
<td>Generic Rx ratio</td>
<td>21.98%</td>
<td>25.62%</td>
<td>25.48%</td>
<td>26.86%</td>
<td>29.59%</td>
<td>34.19%</td>
<td>33.26%</td>
</tr>
<tr>
<td>Units per day</td>
<td>1.22</td>
<td>1.22</td>
<td>1.21</td>
<td>1.20</td>
<td>1.20</td>
<td>1.20</td>
<td>1.20</td>
</tr>
<tr>
<td>Days per Rx</td>
<td>35.00</td>
<td>35.32</td>
<td>35.59</td>
<td>35.65</td>
<td>35.44</td>
<td>35.38</td>
<td>35.65</td>
</tr>
<tr>
<td>Ingredient cost/Rx</td>
<td>$92.17</td>
<td>$92.61</td>
<td>$92.05</td>
<td>$91.77</td>
<td>$90.47</td>
<td>$90.62</td>
<td>$89.31</td>
</tr>
<tr>
<td>Ingredient cost per utilizing member</td>
<td>$178.68</td>
<td>$180.50</td>
<td>$174.79</td>
<td>$178.87</td>
<td>$172.61</td>
<td>$175.33</td>
<td>$170.49</td>
</tr>
<tr>
<td>Eligible members</td>
<td>509,044</td>
<td>495,930</td>
<td>489,086</td>
<td>463,057</td>
<td>443,444</td>
<td>470,330</td>
<td>462,699</td>
</tr>
<tr>
<td>Prevalence of use</td>
<td>6.1%</td>
<td>5.9%</td>
<td>6.0%</td>
<td>6.1%</td>
<td>5.8%</td>
<td>5.8%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Days P/P</td>
<td>1.37</td>
<td>1.36</td>
<td>1.35</td>
<td>1.41</td>
<td>1.30</td>
<td>1.34</td>
<td>1.28</td>
</tr>
<tr>
<td>Rx P/P</td>
<td>0.039</td>
<td>0.039</td>
<td>0.038</td>
<td>0.039</td>
<td>0.037</td>
<td>0.038</td>
<td>0.036</td>
</tr>
<tr>
<td>Cost per day</td>
<td>$2.63</td>
<td>$2.62</td>
<td>$2.59</td>
<td>$2.57</td>
<td>$2.55</td>
<td>$2.55</td>
<td>$2.51</td>
</tr>
<tr>
<td>Average cost P/P</td>
<td>$3.62</td>
<td>$3.57</td>
<td>$3.49</td>
<td>$3.62</td>
<td>$3.31</td>
<td>$3.42</td>
<td>$3.20</td>
</tr>
</tbody>
</table>

* Antidepressants exclude tricyclic antidepressants and include the selective serotonin reuptake inhibitors (SSRIs, Medispan Generic Product Indicator [GPI] beginning with 5816), serotonin and norepinephrine reuptake inhibitors (SNRIs, GPI beginning with 5818), bupropion (GPI beginning with 5830), and mirtazapine (GPI beginning with 5803).
† The comparison group comprises approximately 500,000 beneficiaries who were not subject to interventions involving antidepressant drug therapy in either 2004 or 2005. Approximately 36% of these beneficiaries were enrolled in 3-tier copayment plans in 2004 and about 30% in 2005, and the remainder was enrolled primarily in 2-tier copayment plans. The common copayments were $5-$10 for tier 1 for community pharmacy drugs, $15-$25 for tier-2 drugs, and $30-$45 for tier-3 drugs. Mail-service copayments were generally 2 times the community pharmacy copayment amounts.
‡ Ingredient cost is the actual allowed drug cost without dispense fees and before member cost-share.
PMPM=per member per month, Rx=prescription.

antidepressant drugs for the intervention group in 2005 Q4 versus 32.3% for the comparison group.

Utilization of antidepressant drugs as measured by the days of drug therapy PMPM changed very little during the 8 calendar quarters of observation (Figure 3). For the intervention group, the days of drug therapy PMPM was 1.73 in 2004 Q1 and 1.75 days PMPM in 2005 Q4. The days of antidepressant drug therapy PMPM was lower for the comparison group, 1.37 PMPM in 2004 Q1 and 1.30 in 2005 Q4, but the slope of the lines showing this utilization measure were similar throughout the 8 calendar quarters of observation.

The combination of drug cost (per day of therapy) and utilization (days PMPM) are shown in Figure 4 for the 8 calendar quarters. The average drug cost PMPM for antidepressant drugs was parallel for the 2 groups in the preperiod in 2004 and converged during the intervention period in 2005.

There are some interesting trends within the average utilization of antidepressants in the intervention. The increase in market share of generic citalopram at the end of 2004 and throughout 2005 is approximately equal to the sum of the decline in brand citalopram plus the decline in the chemically similar escitalopram (Table 3). The Rx market share of both bupropion XL and venlafaxine XR dipped in 2005 compared with the end of the preintervention period in 2004, while the large decline in Rx market share of bupropion SR was balanced closely by a corresponding increase in the Rx market share of generic bupropion SR.

Generic fluoxetine maintained its position as the most commonly dispensed non-TCA antidepressant, accounting for about 22% of all non-TCA antidepressant pharmacy claims at the end of the observation period in 2005 Q4 (Table 3). The Rx market share for generic citalopram rose dramatically to more than 15% in 2005 Q4, at the apparent expense of branded sertraline (Zoloft), which dropped in Rx market share from 16% in the 4 quarters of 2004 to 12% in 2005 Q4.

The intervention group experienced a relative 61.5% increase in the generic utilization ratio, from 32.5% of all non-TCA antidepressants in 2004 to 52.5% in 2005, versus a 29.7% relative increase in the comparison group, from 24.9% in 2004 to 32.3% in 2005 (Table 4). For the principal measure of average drug (ingredient) cost per day of therapy, the intervention group experienced a relative decrease of 11.7%, from $2.40 in 2004 to $2.12 in 2005, versus a 2.7% relative decrease in the comparison

www.amcp.org Vol. 12, No. 4 May 2006 JMCP Journal of Managed Care Pharmacy 297
group, from $2.60 per day in 2004 to $2.53 in 2005 (t value 23.78, P <0.001). The 9.0% relative savings in actual drug cost translates into total savings of $1,880,562 in 2005 (actual drug ingredient cost of $19,014,580 versus projected drug cost of $20,895,142 absent the intervention).

Discussion

The principal measure in this study was the drug cost per day of drug therapy. This step-therapy intervention requiring first-line therapy with a generic antidepressant was not expected to adversely affect utilization of antidepressant drugs. Implementation of a generics-first, step-therapy protocol for antidepressant drug therapy in this HMO with approximately 440,000 members reduced the average drug cost per day of therapy by 9.0%. The utilization of antidepressant drugs, as measured by either the prevalence of use of antidepressants or the days of drug therapy PMPM, was not adversely affected.

On June 30, 2005, the FDA released a public health advisory regarding the risk of suicidality in adult patients treated with antidepressants and, specifically, all of the drugs in the present study. This announcement drew increased attention from the public as well as health care professionals to the potential risk associated with a class of drugs formerly thought to be virtually risk free. In October 2004, the FDA requested new “black box” labeling on 32 antidepressants, warning of increased risk of suicidality when used in children. This was followed by a request for all manufacturers to include notice of the new risk warning in direct-to-consumer advertisements on or before February 11, 2005.

The attention to possible threats to safety in the use of antidepressants during the study period would be expected to have a downward influence on the utilization of these drugs. Market data from Verispan for 54,000 community pharmacies in 2005 showed that SSRI utilization declined in 2005, with volume in prescriptions down 4.1% compared with 2004 and sales down 13.9% in dollars. This market-wide influence may be reflected in the days of antidepressant drug therapy PMPM, particularly in 2005 Q1 (Figure 3). The prevalence of use of antidepressants, excluding TCAs, dipped slightly by a relative 5.4% in 2005 (10.5%) compared with 2004 (11.1%) in the intervention group and by nearly the same relative decline (-6.7%) in the comparison group, from 10.5% in 2004 to 9.8% in 2005.

Over the entire 24-month study period, the average days of antidepressant drug therapy PMPM declined by only 1.5% in the intervention group, from 1.74 in 2004 to 1.71 in 2005, and by 5.0% in the comparison group, from 1.37 days PMPM in 2004 to 1.30 days PMPM in 2005 (Table 4). This slightly deeper decline in utilization in the comparison group contributed to the 7.6% drop in antidepressant drug cost PMPM, from $3.57 in 2004 to $3.30 in 2005, versus a 13.0% drop in antidepressant drug cost PMPM in the intervention group, from $4.16 in 2004 to $3.62 in 2005.

The 9.0% savings in cost per day of non-TCA antidepressant drug therapy compares favorably with other managed care interventions. In a study of the cost and utilization outcomes following the implementation of prescriber profiles (report cards) with academic detailing, Yokoyama et al. found 7.4% cost savings per day of SSRI therapy, from $2.43 per day in 1998 to $2.25 in 1999, and 4.0% additional savings, to $2.16 per day in 2000. These savings translated into $0.07 PMPM in the first year and $0.04 PMPM in the second year, compared with $0.36 PMPM in drug cost savings in the present study.

The step-therapy intervention implemented in this HMO did not permit prior authorization (PA) or medical exception. In a study of 3 step-therapy programs for one Midwest employer of approximately 20,000 beneficiaries, Motheral et al. found savings in PMPM drug costs for the proton pump inhibitors (for heartburn) and for the nonsteroidal anti-inflammatory drugs
but not for the SSRIs.\textsuperscript{1} One of the major differences in the intervention described by Motheral et al. and the present study was the opportunity for exceptions and the outcome that 23% of affected members reported receiving a medical exception to the first-line therapy.

Review of the medical literature through a PubMed/MEDLINE search conducted in March 2006 using the keywords “step therapy and depression” revealed only 20 published studies. None of these 20 studies addressed directly the subject of using generic antidepressants as first-line therapy in major depressive disorder. One study did report that drug switching is an important strategy in the treatment of depression since half of all treated depressed patients fail to respond adequately to the first prescribed antidepressant.\textsuperscript{25}

Fleck and Horwath concluded, from a MEDLINE review for the years 1999 to 2004, that antidepressant clinical trials are typically inadequate in the stratification of patients by disease severity to better manage difficult to treat depression.\textsuperscript{26} A 2-step approach is necessary to achieve better outcomes in pharmacologic treatment of major depression. Factors such as comorbid medical and psychiatric conditions are considered first in evaluation of patients nonresponsive to pharmacotherapy. The second step involves 4 strategies for enhancing the efficacy of antidepressant therapy: optimization of dose, augmentation, combination, and drug switching. Given the high rate of drug switching in the effective pharmacological management of depression, first-line treatment with a generic non-TCA agent seems particularly cost effective.

Utilization of antidepressants is an important consideration in clinical outcomes of patients with major depressive disorder, but the issue is far from simple.\textsuperscript{27} In the ARTIST (A Randomized Trial Investigating SSRI Treatment) study, 46% of patients (n = 256) with major depressive disorder treated with an SSRI were nonresponders at 6 months, and 53% of the patients (n = 222) who received SSRI therapy for at least 6 months did not achieve remission.\textsuperscript{28} While a minimum of 6 to 8 weeks of antidepressant drug therapy is considered to be necessary to determine if antidepressant drug therapy will be effective,\textsuperscript{29} 30% to 50% of patients have substantial residual symptoms after adequate first-line therapy,\textsuperscript{30} and the absence of improvement after 4 weeks of treatment with an adequate dose of a given antidepressant predicts an ultimate inadequate response.\textsuperscript{31}

**Limitations**

This study examined only the effects of a managed care protocol on direct drug costs. While there is no expectation that the use of generic SSRIs as first-line therapy in depression would have an influence on medical or other health system costs, these other costs were not measured in the present study. The only study specific to this issue of total medical costs associated with an SSRI generic step-therapy program was published in a sponsored supplement that may or may not have received adequate peer review.\textsuperscript{32} Second, any managed care intervention is likely to have an effect on humanistic outcomes, including patient satisfaction, and these outcomes were not measured in the present study.

The savings in cost per day in the present study was probably influenced, in part, by the implementation in mid-2005 of a dose-optimization intervention for generic fluoxetine. At the time, the maximum allowable cost (MAC) for fluoxetine 40 mg capsules was $1.59, and the MAC for fluoxetine 20 mg capsules was $0.15. HMO members who were using 40 mg per day of fluoxetine were switched by community pharmacists from one 40 mg capsule to two 20-mg capsules. This fluoxetine dose-optimization intervention did not affect utilization, but undoubtedly had some influence on the average cost per day of drug therapy in 2005 compared with 2004 even though it was in effect for only half of 2005. Another consideration in the
The present study was the temporary market unavailability of Paxil CR, which is evident in the Rx share data in Table 3 beginning in 2005 Q2. However, the comparison group was similarly affected.

The present study was designed to assess aggregate drug cost and drug utilization outcomes associated with a step-therapy requirement for HMO members to use a generic SSRI as first-line therapy prior to coverage of a brand-name antidepressant. No attempt was made to determine how many HMO members were affected or how much of the observed reduction in aggregate SSRI drug cost was due to first-time SSRI users who were affected directly or indirectly by the SSRI step-therapy edit. Also left to future research is the subject of adherence and persistence with SSRI therapy. McManus et al. found that 38% of “new users” of SSRIs were still receiving SSRIs 6 to 8 months later, but this research was conducted among patients eligible for social security entitlements in Australia and did not address generic versus brand-name SSRIs.

The present study was conducted in an HMO that is part of an integrated health system that has been ranked consistently as #1 or #2 in the top 100 health systems in the United States by the measure of degree of integration. However, the results of this study should be generalizable to other populations since the intervention involved primarily an administrative change in pharmacy benefits, an intervention that did not necessarily involve either physician or pharmacy provider cooperation and support.

There are administrative costs associated with step-therapy interventions, and these costs were not measured in this study. The step-therapy intervention employed in the present study used pharmacy claims history to identify prior antidepressant drug use and thereby avoided some of the administrative burden for pharmacists, members, and prescribers that would have otherwise been incurred by a simple PA requirement for brand-name SSRIs. Nevertheless, community pharmacists undoubtedly did incur some administrative costs associated

<table>
<thead>
<tr>
<th>Drug</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic fluoxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic paroxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine (Paxil) CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic citalopram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic bupropion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (Wellbutrin) SR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (Wellbutrin) XL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic mirtazapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (Effexor XR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total brand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic fluoxetine</td>
<td>20.59</td>
<td>20.25</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>0.94</td>
<td>0.89</td>
</tr>
<tr>
<td>Generic paroxetine</td>
<td>5.89</td>
<td>6.01</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>0.98</td>
<td>0.71</td>
</tr>
<tr>
<td>Paroxetine (Paxil) CR</td>
<td>5.07</td>
<td>4.86</td>
</tr>
<tr>
<td>Generic citalopram</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>10.49</td>
<td>9.91</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>11.06</td>
<td>11.25</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>16.19</td>
<td>16.12</td>
</tr>
<tr>
<td>Generic bupropion</td>
<td>0.47</td>
<td>0.48</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin) SR</td>
<td>0.35</td>
<td>4.04</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin) XL</td>
<td>5.70</td>
<td>7.37</td>
</tr>
<tr>
<td>Generic mirtazapine</td>
<td>0.78</td>
<td>0.83</td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td>0.26</td>
<td>0.14</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>0.44</td>
<td>0.46</td>
</tr>
<tr>
<td>Venlafaxine (Effexor XR)</td>
<td>12.67</td>
<td>12.92</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total generic</td>
<td>28.08</td>
<td>31.61</td>
</tr>
<tr>
<td>Total brand</td>
<td>71.49</td>
<td>67.02</td>
</tr>
<tr>
<td>Other</td>
<td>0.43</td>
<td>1.37</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
with contacting prescribers to obtain first-line antidepressant prescriptions and in counseling patients about the administrative edit and therapeutic interchange.

**Conclusion**

This HMO of approximately 440,000 members implemented a step-therapy protocol for members new to antidepressant drug therapy, excluding tricyclic antidepressants, in which the use of a generic antidepressant was required prior to coverage of a brand-name antidepressant. First-year savings in 2005 were $1,880,562, equivalent to $0.36 PMPM. The generic utilization ratio for antidepressants increased from 32.5% in 2004 to 52.5% in 2005, and the average actual drug cost per day of antidepressant therapy declined by 11.7% or a relative 9.0% compared with the comparison group. Antidepressant drug utilization PMPM did not appear to be affected by the intervention.

**ACKNOWLEDGMENT**

The authors acknowledge Mark Brown, FSA, MAAA, chief actuary, SelectHealth, Intermountain Healthcare, Salt Lake City, Utah, for his guidance and assistance in statistical analyses.

**DISCLOSURES**

No outside funding supported this research. The authors disclose no potential bias or conflict of interest relating to this article. Author Jeffrey D. Dunn served as principal author of the study. Study concept and design were contributed by Dunn and author H. Eric Cannon. Data collection was the work of Dunn and author Frederic R. Curtiss, with input from Cannon; data interpretation was the work of Dunn, Cannon, Curtiss, and author Matthew P. Mitchell. Writing of the manuscript was the work of Dunn, with input from Curtiss; its revision was primarily the work of Dunn, with input from Curtiss and Mitchell.

**REFERENCES**

10. Thase ME, Haight BR, Richard N, et al. Remission rates following anti-
depressant therapy with bupropion or selective serotonin reuptake inhibi-

11. Theobald DE, Kasper M, Nick-Kresl CA, et al. Documentation of indica-
tors for antidepressant treatment and response in an HMO primary care popu-


20. Curtiss FR. Evidence-based medicine: are SSRIs more effective than placebo and what length of therapy is enough? J Manag Care Pharm. 2005;11(2):172-77.

21. U.S. Food and Drug Administration. FDA News—FDA launches a multi-
pronged strategy to strengthen safeguards for children treated with anti-


30. Amsterdam JD, Maislin G, Potter L. Fluoxetine efficacy in treatment resist-


32. Panzer PE, Regan TX, Chiao E, Sanes MW. Implications of an SSRI generic step therapy pharmacy benefit design: an economic model in anxiety disor-


Blood Pressure Goal Attainment According to JNC 7 Guidelines and Utilization of Antihypertensive Drug Therapy in MCO Patients With Type 1 or Type 2 Diabetes

VICKIE ANDROS, PharmD; ALLISON EGGER, MPH; and UMA DUA, PharmD

ABSTRACT

OBJECTIVE: Controlling hypertension (HTN) in patients with diabetes mellitus (DM) can reduce complications such as nephropathy, cerebrovascular disease, and cardiovascular disease. As part of a quality improvement project with a managed care organization (MCO), we evaluated blood pressure (BP) control relative to the type of drug therapy for patients with type 1 or type 2 DM who were identified from pharmacy claims for antihyperglycemic drug therapy.

METHODS: Pharmacy claims for antihyperglycemic drugs, including insulin, were used to identify a random sample of commercial members in an MCO comprising 30 health plans across the United States. Retrospective medical record review was conducted in October 2003 to collect data from 4,814 patient charts. BP goal attainment according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines was determined for each patient from the most recent BP reading documented in the medical chart.

RESULTS: The distribution by type of DM was 21.0% (n = 1,011) for type 1, 75.7% (n = 3,644) for type 2, and 3.3% (n = 159) for cases not documented in the medical chart. Excluding 590 charts (12.3%) without BP values, there were 1,328 of 4,224 DM patients (31.4%) at JNC 7 BP goal (<130/80 mm Hg). Of the 1,328 patients at JNC 7 BP goal, 577 (43.4%) were at JNC 7 BP goal with no drug therapy. Excluding the 577 patients who did not require drug therapy to reach JNC 7 goal, 751 (20.6%) of the remaining 3,647 patients who required antihypertensive drug therapy were at JNC 7 BP goal, and 788 (21.6%) received no antihypertensive drug therapy. For the population of 4,224 DM patients with a BP value recorded in the chart, application of the lower BP goals in the JNC 7 guidelines reduced the proportion with controlled BP to 31.4% (1,328/4,224) from 42.6% (1,799/4,224) according to the former JNC 6 guidelines (P <0.01). The proportion of DM patients with HTN was 59.6% (n = 2,870), and 28.4% (n = 814) of these patients were not taking either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB). There were 704 patients with albuminuria or nephropathy (14.6%), of which 35.4% (n = 249) were not taking either an ACEI or an ARB, preferred therapy in these patients.

CONCLUSION: In this population of MCO members with DM for whom a BP value was recorded in the medical chart, 13.7% met JNC 7 BP goal with no antihypertensive drug therapy. For the patients with DM who received antihypertensive drug therapy and had a BP value recorded in the medical chart, only 26.3% were at JNC 7 BP goal. The application of JNC 7 guidelines significantly reduced the proportion of DM patients at target BP goal from 42.6% to 31.4%.

KEYWORDS: Hypertension, Managed care, Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, Diabetes mellitus complications

J Manag Care Pharm. 2006;12(4):303-09

The JNC 7 Express: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), was initially published in the Journal of the American Medical Association in 2003 and redefined the stages of hypertension (HTN) established in the JNC 6 (Sixth Report, see Table 1). The complete JNC 7 report was published in August 2004 and is used as the standard for blood pressure (BP) control in this study despite the fact that the BP values were abstracted from medical charts in October 2003, the year prior to the release of the JNC 7 definition of appropriate BP control.

The treatment goal for individuals with HTN without other compelling conditions (i.e., diabetes mellitus [DM], heart failure, postmyocardial infarction [MI], chronic kidney disease, recurrent stroke prevention, or high coronary disease risk) is BP <140/90 mm Hg. JNC 7 guidelines set a goal of <140/90 mm Hg for the prevention and management of uncomplicated HTN to decrease morbidity and mortality by the least intrusive means possible. Although cardiovascular (CV) risk increases linearly with increases in systolic BP (SBP) >115 mm Hg, a more rapid increase in risk is noted when BP exceeds 140/90 mm Hg. In patients with HTN and DM or renal disease, the BP goal is <130/80 mm Hg. The American Diabetes Association (ADA) also recommends a BP goal <130/80 mm Hg for adults with DM. Epidemiological analyses indicate that the attainment of this BP goal is associated with a decrease in CV rates and mortality in persons with DM without compromising safety or increasing the cost of care.

Also, the rate of decline in renal function among patients with diabetic nephropathy has been reported to be a continuous function of arterial pressure down to approximately 125-130 mm Hg SBP/70-75 mm Hg diastolic BP (DBP). The
Blood Pressure Classification According to JNC 6 and JNC 7 Reports

<table>
<thead>
<tr>
<th>Blood Pressure Classification</th>
<th>JNC 6 (mm Hg)</th>
<th>JNC 7 (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120 SBP and</td>
<td>&lt;120/80</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;130 SBP and</td>
<td>≤80 DBP</td>
</tr>
<tr>
<td>High-normal</td>
<td>130-139 SBP</td>
<td>&lt;85-89 DBP</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159 SBP</td>
<td>90-99 DBP</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>160-179 SBP</td>
<td>100-109 DBP</td>
</tr>
<tr>
<td>Stage 3 Hypertension</td>
<td>≥180 SBP</td>
<td>≥110 DBP</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139 SBP</td>
<td>80-89 DBP</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159 SBP</td>
<td>90-99 DBP</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>160-179 SBP</td>
<td>100-109 DBP</td>
</tr>
<tr>
<td>Stage 3 Hypertension</td>
<td>≥180 SBP</td>
<td>≥110 DBP</td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure; JNC = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (6 = Sixth Report; 7 = Seventh Report); SBP = systolic blood pressure.

Criteria for Sample Population

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random selection of commercial members with pharmacy claims for antiyperglycemic agents</td>
<td>6,229 (100)</td>
</tr>
<tr>
<td>Exclusions:</td>
<td></td>
</tr>
<tr>
<td>Patients deceased</td>
<td>24 (0.4)</td>
</tr>
<tr>
<td>Patients no longer enrolled with MCO</td>
<td>122 (2.0)</td>
</tr>
<tr>
<td>Access to chart denied by physician or medical group</td>
<td>623 (10.0)</td>
</tr>
<tr>
<td>Charts not available for review</td>
<td>497 (8.0)</td>
</tr>
<tr>
<td>Patients without diagnosis of diabetes in medical chart</td>
<td>149 (2.4)</td>
</tr>
<tr>
<td>Final sample</td>
<td>4,814 (77.3)</td>
</tr>
</tbody>
</table>

MCO = managed care organization.

Diabetes Patients at JNC 6 and JNC 7 Blood Pressure Goals for Adults

<table>
<thead>
<tr>
<th>JNC 6 BP Goal (SBP/DBP mm Hg)</th>
<th>Classification</th>
<th>JNC 7 BP Goal (SBP/DBP mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>Prehypertension and no compelling indications</td>
<td>&lt;120/80</td>
</tr>
<tr>
<td>&lt;140/90</td>
<td>Hypertension and no compelling indications</td>
<td>≤120/80</td>
</tr>
<tr>
<td>&lt;130/85</td>
<td>Hypertension and diabetes or renal disease</td>
<td>≤80 DBP</td>
</tr>
<tr>
<td>1,799/4,814 (37.4%)</td>
<td>All study patients at BP goal*</td>
<td>1,328/4,814 (37.4%)</td>
</tr>
<tr>
<td>1,799/4,824 (42.6%)</td>
<td>Allstudy patients with BP value at BP goal†</td>
<td>1,328/4,824 (42.6%)</td>
</tr>
</tbody>
</table>

* Entire study population of 4,814 (including those with missing BP value [n=590]).
† 4,224 patients with BP value in medical chart (excluding those with missing BP value).

Hypertension Optimal Treatment (HOT) trial along with other randomized clinical trials demonstrate the benefit of targeting a DBP of ≤80 mm Hg. The updated JNC 7 guidelines emphasize SBP as the main focus of treatment since most patients with HTN (especially those older than 50 years) will reach their DBP goal once SBP is achieved. Along the same lines, the World Health Organization reports that suboptimal SBP (>115 mm Hg) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease, with little variation by gender.

Approximately 65 million Americans have high BP. A direct relationship exists between BP and risk of CV disease events; the higher the BP, the greater the chance of stroke, heart attack, heart failure, or kidney failure. In fact, HTN is second only to DM as the most common cause of end-stage renal disease (ESRD). The risk of death from heart disease and stroke begins to increase at a BP of 115/75 mm Hg and doubles for every 20 mm Hg SBP/10 mm Hg DBP increase.

Approximately 18 million Americans have DM, and 73% of patients with DM also have HTN. Studies have shown that patients with HTN and DM have approximately twice the risk of CV disease as patients with HTN but without DM. These patients are also at increased risk for diabetic nephropathy, retinopathy, and neuropathy. Controlling HTN in patients with DM has been shown to reduce the rate of progression of nephropathy and to reduce the complications of nephropathy, cerebrovascular disease, and CV disease. The U.K. Prospective Diabetes Study (UKPDS) showed a 13% reduction in microvascular complications (retinopathy or nephropathy), a 12% risk reduction for any complication related to DM, a 15% decrease in deaths related to DM, and an 11% reduction in MI with each 10 mm Hg decrease in mean SBP.

The estimated total cost of high BP in the United States in 2005 was $59.7 billion. Controlling high BP has the potential to prevent strokes and heart attacks and could result in potential savings of $463 million in avoidable costs for hospital and other costs of therapy. As noted previously, approximately three fourths of patients with DM also have HTN. The average cost per year for a patient with DM and HTN is $13,446, with hospitalizations contributing to most of the cost.

Among patients with HTN, more than 40% are not on drug therapy. Many antihypertensive drugs are available to treat HTN. To achieve BP control, the majority of patients with DM will require 2 or more antihypertensive agents from different drug classes. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, diuretics, and calcium channel blockers have demonstrated a reduction in CV events in patients with DM. In addition to lowering BP, ACEIs and ARBs have been shown to slow the development and progression of diabetic nephropathy. Multiple
clinical trials demonstrate that use of ACEIs or ARBs in patients with DM have a renoprotective effect that provides both therapeutic and cost-effective outcomes. Thus, the ADA recommends ACEIs and ARBs as first-line therapy for prevention and progression of macroalbuminuria and clinical nephropathy.

In this study, we quantified the BP goal attainment of this population according to both the JNC 6 (Sixth Report) and JNC 7 guideline (JNC 7 concurring with ADA) recommendations. We also evaluated the proportion of patients utilizing the preferred agents, ACEIs and ARBs.

### Methods

We performed a retrospective analysis of data collected from a quality improvement (QI) initiative designed to evaluate comorbid diseases and outcomes in patients with DM. The patient population for this study was identified from a computerized, random selection of 6,229 commercial members with pharmacy claims for antihyperglycemic agents (Table 2). These members were enrolled in 30 health plans that were part of a managed care organization and located in sites in the Southeast, Southwest, mid-Atlantic, Midwest, Northeast, North central, and Western United States.

Nurses who were trained in the use of standardized data abstraction methods and who had prior data abstraction experience collected the data from the patients’ medical records using a standardized data collection form. Approximately 50 nurses performed chart reviews at all sites during October 2003. The data abstracted from the patients’ medical records included patient demographics, clinical history, comorbid diseases (coronary heart disease, HTN, nephropathy, obesity), drug therapies (HTN, DM, and dyslipidemic agents), and results of clinical examinations (BP readings) and laboratory tests (glycosylated hemoglobin [A1c], low-density lipoprotein cholesterol [LDL-C], microalbuminuria) pertinent to the management of DM.

All analyses (univariate descriptive analyses and statistical tests) were carried out using SAS 8.2 software. Chi-square statistics were used to compare the difference in group proportions. A logistic regression analysis was performed to address geographic variation in the managed care population. A logistic regression analysis was performed to address geographic variation in the managed care population.

This research project compared data collected as part of a retrospective chart review from 4,814 patients with DM to guidelines set forth by JNC 7 and the ADA. The BP goals recommended by JNC 6 and JNC 7 reports based on BP classification and the existence of compelling indications are shown in Table 3. Using the data collected, we determined BP goal attainment by comparing a patient’s most recent BP reading documented in the chart (within the 2 years prior to chart review) with their BP goal according to both guidelines. Although the complete JNC 7 report was published in 2004, at the time these results were being analyzed, the JNC 7 Express guidelines had been published. And though it was expected that fewer patients would achieve BP control based on the more stringent JNC 7 BP guidelines than with JNC 6 BP guidelines, our intent in conducting the comparison was to quantify the impact of the JNC 7 standard. We also assessed the percentage of the entire population (patients with DM) and those with DM and albuminuria and/or nephropathy who were utilizing ACEIs and ARBs at the time of chart review.
Blood Pressure Goal Attainment According to JNC 7 Guidelines and Utilization of Antihypertensive Drug Therapy in MCO Patients With Type 1 or Type 2 Diabetes

**Results**

Demographics

Among the entire population, 21% (n = 1,011) were patients with type 1 DM and 75.7% (n = 3,644) were patients with type 2 diabetes, while 3.3% (n = 159) were identified as patients having diabetes but with no chart documentation of the type of diabetes (Table 4). The population consisted of 53.7% males and 46.3% females. More females had BP control (<130/80 mm Hg) than males in this population. There was racial diversity among the entire population, but the majority were white (n = 1,788, 37.1%). As corroborated in previous research, more whites had BP control (<130/80 mm Hg) than African Americans and other races (whites 29.0%, African Americans 18.3%, other races 22.9%).

The mean age for the population was 52.2 years and the median age 54.0 years. Similar BP control was seen between the Medicare population (>65 years) and the other patients (<65 years). Height and weight were available in only 30% and 50% of the entire population, respectively. The average body mass index (BMI) for females was 33.9 kg/m2 and 32.3 kg/m2 for males. The most prevalent concomitant conditions were HTN, hyperlipidemia, and obesity. Among the most prevalent conditions, obesity was the only condition that was significantly higher among patients with DM and uncontrolled BP (>130/80 mm Hg) (χ² = 22.9 and P value <0.01). Notation indicating the diagnosis of HTN (e.g. HTN, elevated BP, high BP, ↑BP) in the medical record existed in 59.6% of the entire population.

Blood Pressure Goal Attainment

The average SBP was 130.3 mm Hg, and 75% of all patients’ SBP was ≤140 mm Hg. The average DBP was 77.9 mm Hg, and 75% of all patients’ DBP was ≤84 mm Hg. Approximately 37% of the entire population met their JNC 6 BP goal, compared with 28% of the population using the JNC 7 BP goal (Table 3), resulting in a 9.8 absolute percentage difference. This correlates to a 26% relative percentage reduction in DM patients with controlled BP (P<0.01). Therefore, 1 out of 4 patients who were classified as having controlled BP according to JNC 6 guidelines are now classified as having uncontrolled BP according to JNC 7 guidelines. Approximately 12% of the entire population did not have a BP reading documented in the medical record to assess goal attainment.

A total of 4,224 patients had BP values documented in their medical charts. Among these patients, 1,328 (31.4%) were at JNC 7 BP goal (Figure 1, Table 5). Among the patients with a documented BP value (n=4,224), 68.6% (n=2,896) had uncontrolled BP (according to JNC 7 guidelines). The magnitude of BP reduction necessary to reach goal is shown in Figure 2. Only about 20% of patients with uncontrolled SBP and DBP (n = 1,566) had a SBP and DBP less than 5 mm Hg from goal.

Among patients with DM and chart-documented HTN (defined by a notation in the medical record indicating the diagnosis of HTN, n = 2,870), only 21.1% of patients had BP controlled to <130/80 mm Hg. Approximately 10% of this subpopulation did not have a BP reading documented in their medical record to assess goal attainment.

Antihypertensive Drug Utilization

Approximately 66% of the entire population was utilizing antihypertensive drug therapy. One third of all patients (n = 1,577) were on monotherapy treatment. A majority of these patients were on an ACEI, most commonly lisinopril. The average daily dose of lisinopril was 15.4 mg. Thirty-four percent of patients who discontinued ACEIs were being switched to other drugs in the same therapeutic class. Among those being treated with monotherapy, 24.9% were meeting the BP goal of <130/80 mm Hg. Two or more agents were utilized in 32.9% of all patients, and only 22.7% of these patients had controlled BP. Among the entire population, 36.8% were on ACEI, 12.1% on ARB, and 2.4% on an ACEI and ARB (Table 5).

Among those patients with chart-documented HTN (n = 2,870), 90.4% were using antihypertensive agents. Approximately 48% were using 2 or more antihypertensive agents, and only 22% on monotherapy (n = 1,218) had controlled BP. However, only 50.5% were on ACEI, 17.5% on ARB, and 3.7% on an ACEI and ARB. Among those patients not achieving BP control (n = 1,975), 8% were not utilizing any antihypertensive agents, and 41% were using only 1 agent. Also, among those patients without BP control, 51.0% were on ACEI, 17.9% on ARB, and 3.9% on an ACEI and ARB.

Among the population with DM and uncontrolled BP (n = 2,896; BP ≥130/80 mm Hg), 37.6% were using 2 or more antihypertensive agents.
antihypertensive drug agents. Twenty-seven percent of patients with DM and uncontrolled BP were not taking an antihypertensive agent, and 15.2% were taking antihypertensive agents not including an ACEI and/or ARB. The top 3 drug regimens for patients with DM and controlled BP as well as those with DM and uncontrolled BP included (1) ACEIs, (2) ACEI/diuretic combinations, and (3) ARBs.

Forty-eight percent of the entire population was not using an ACEI and/or an ARB (Table 5). More specifically, among those with type 1 DM (n = 1,011), 30.1% were using an ACEI, 8.6% an ARB, and 2.5% an ACEI and an ARB. Among those with type 2 DM (n = 3,644), 38.7% were using an ACEI, 12.9% an ARB, and 2.4% an ACEI and an ARB. Albuminuria (microalbuminuria or macroalbuminuria) and/or nephropathy was classified in 14.6% (n = 704) of all patients. Within this subpopulation, 40.5% were utilizing ACEIs, 19.6% an ARB, and 4.6% an ACEI and an ARB (Table 4).

### Discussion

The present study evaluated attainment of JNC 6 and JNC 7 BP goals in patients with DM who were identified from pharmacy claims for antihyperglycemic drugs, including insulin, whether or not these patients had a diagnosis of HTN or had received antihypertensive drug therapy. In a prior study, Andros described the results of medical chart review in a population of patients with HTN (identified through medical claims for HTN) and chart-documented confirmation of both DM and HTN (n = 9,492). These data were presented as part of an HTN research and QI initiative conducted among physician practices. Approximately 28% of the entire population with DM and HTN (including those with and without documented BP values) achieved BP control (<130/80 mm Hg), compared with 27.6% of our study population of patients with DM. Among the patients in the present study with a documented BP value, 31.4% were achieving BP control (<130/80 mm Hg), 43.4% (n = 577) without drug therapy. By drug type, 55.4% were treated with an ACE inhibitor and 32.3% with an ARB in the prior study by Andros, versus 51.3% in our study. Among DM patients at JNC 7 goal who received antihypertensive drug therapy and those who were not at JNC 7 goal (n = 3,647), 61.5% (n = 2,243) were treated with an ACE inhibitor and/or an ARB.

Jackson et al. evaluated BP control and management of drug therapy for patients with concurrent heart failure and HTN in a managed care setting. Data included medical and pharmacy claims as well as results from medical chart review. The study found that, among the subpopulation with DM (n = 113), 30.1% had their BP controlled (<130/85 mm Hg) and approximately 47% were receiving ACE inhibitors or ARBs, compared with our findings of 27.6% with BP controlled (to < 130/80 mm Hg) and 51.3% on ACE inhibitors or ARBs or both. In the present study population with documented BP values (n = 4,224), 31.4% achieved BP control (<130/80 mm Hg) and 53.1% were utilizing ACE inhibitors and/or ARBs.

Despite the fact that HTN is a common comorbidity of DM and that controlling HTN in patients with DM has been shown to reduce nephropathy, cerebrovascular disease, and CV disease, 12.3% (n = 590) of the population in this study did not have a BP reading documented in the chart. It is disappointing that BP is not being monitored more closely. On the other hand, 13.7% (577/4,224) of the patients with DM who had a BP reading documented in the chart were at BP goal without drug therapy.

The ADA guidelines for BP treatment goals (<130/80 mm Hg) have not changed recently, and the JNC 7 guidelines now concur with ADA recommendations for BP control of <130/80 mm Hg for patients with DM. Our findings suggest that 27.6% of the entire population met BP goals according to the JNC 7 report and that significantly fewer patients (9.8%, n = 472) were meeting their BP goal as compared with JNC 6 recommendations. In examining the means and reduction in BP required to achieve BP control among this population with DM (Figure 2),
Blood Pressure Goal Attainment According to JNC 7 Guidelines and Utilization of Antihypertensive Drug Therapy in MCO Patients With Type 1 or Type 2 Diabetes

approximately 20% of individuals who remain hypertensive require small decreases (<5 mm Hg) in BP to achieve goal. If the patients needing minimal reduction (<5 mm Hg) in SBP and DBP readings were at goal, nearly 50% of this entire population would be achieving BP goals instead of 27.6%.

Therefore, with greater utilization of appropriate antihypertensive agents, titration of doses, and use of combination therapy, it is possible that this patient population could lower their BP values to <130/80 mm Hg.

According to JNC 7 and the ADA, the majority of patients with DM will require 2 or more antihypertensive agents from different drug classes to achieve BP control. Almost half (48%, n = 1,377) of the patients with DM and HTN (n = 2,870) in this study were using 2 or more antihypertensive agents (data not reported). Combining agents with 2 different mechanisms of action can result in an additive BP-lowering effect and may permit for lower doses of each agent to be used, possibly decreasing the potential for dose-related side effects. Forty-nine percent of the patient population with DM, HTN, and uncontrolled BP could potentially have achieved BP control if they were first dose-titrated and secondarily placed on multiple antihypertensive agents, particularly an ACEI and/or ARB.

The JNC 7 report also suggests that all patients with DM and HTN should be treated with a regimen that includes either an ACEI or ARB. The National Kidney Foundation recommends that patients with chronic kidney disease (including albuminuria and/or nephropathy) should be treated with an ACEI and/or ARB in combination with a diuretic. Underutilization of antihypertensive agents was seen among the entire population, among those with HTN, and among those with uncontrolled BP. Among the patients with DM and HTN (n=2,870), 71.7% (n=2,057) were being treated with an ACEI and/or ARB. Among those with documented albuminuria and/or nephropathy, 65% were being treated with an ACEI and/or an ARB. Considering the benefits of renal protection and control of secondary complications, ACEIs or ARBs are underutilized in this subpopulation.

For the end points of fatal coronary heart disease and non-fatal MI among patients with DM and HTN, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) found no significant difference for patients who used ACEIs or calcium channel blockers versus a thiazide diuretic. These findings suggest that thiazide diuretics should be considered first-line antihypertensive therapy in patients with DM, but the ALLHAT findings did not include the intermediate outcomes of urinary microalbuminuria, A1c levels, and other physiological tests.

In the present study, a majority of patients were on lisinopril monotherapy at an average daily dose of 15.4 mg per day. One research study showed that lisinopril monotherapy at doses of 20 to 40 mg per day produced a mean reduction in both SBP and DBP of approximately 6 mm Hg. Therefore, since our patients were receiving lower average doses, the predicted reduction in BP for these patients would most likely be something <6 mm Hg.

Limitations

As part of the quality improvement initiative, trained nurses reviewed the medical records of eligible patients in the offices of the physicians identified as the prescribers for antihyperglycemic drug therapy. Since multiple physicians may follow individual patients, all the information of interest may not have been available in the physician’s office where the chart was reviewed. Physician practices also vary in their documentation of BP and may only do so when the reading is high or low and of concern to the physician. Therefore, reliance on chart-documented information is a limitation of the present study.

Only BP readings taken by the physician or office staff and documented in the medical record were tabulated for the present study. Any BP readings reported by the patient (at home) were not included or evaluated. In excluding such readings, some patients may not have had an accurate evaluation of BP control due to phenomena such as “white coat” syndrome, which results in elevated office BP readings due to anxiety associated with the physician office visit. On the other hand, it is reasonable to expect that the patients in this study were accustomed to routine office visits as a result of their diagnosis of DM.

Another potential limitation of the study was the use of 1 BP reading to evaluate BP control. The decision to use 1 reading follows the methodology used in the Health Plan Employer Data and Information Set (HEDIS) Controlling High Blood
Pressure measure. An average of up to 3 documented BP readings was also evaluated for each patient in the study. In assessing the average of up to 3 BP readings, approximately 30% of patients had controlled BP versus 27.6% when only 1 reading was evaluated.

Lastly, the use of retrospective chart review to identify medications is unreliable since this documentation is likely to be inconsistent, incomplete, and inaccurate. Patient compliance with antihypertensive therapy is also difficult to evaluate through this method of data collection.

**Conclusion**

More than two thirds of patients with DM in this study did not have controlled BP (<130/80 mm Hg) according to JNC 7 recommendations. Approximately 14% of the patients were normotensive without antidepressant drug therapy. Approximately 60% of the DM patients had HTN, and 28% of these patients were not taking either an ACEI or an ARB. About 15% of DM patients had albuminuria or nephropathy; of these patients, 35% were not taking either an ACEI or an ARB, preferred therapy in these patients.

**DISCLOSURES**

Funding for this research was provided by Sankyo Pharma Inc. and Forest Laboratories, Inc. and was obtained by Bharat Patel, PharmD, and H. Ed Perez, PharmD, cofounders of Total Therapeutic Management, Inc. Authors Allison Egger, Uma Dua, and Vickie Andros are employed by Total Therapeutic Management, Inc., which currently has research grants from Sankyo Pharma Inc., Forest Laboratories, Inc., and numerous other pharmaceutical and health care companies.

Andros served as principal author of the study. Study concept and design were contributed by Andres and Egger, with input from Dua. Data collection and interpretation was primarily the work of Egger, with input from Andros and Dua. Drafting of the manuscript and its revision were the work of Andros and Egger, with input from Dua.

**REFERENCES**


Administrative Claims Analysis of Asthma-Related Health Care Utilization for Patients Who Received Inhaled Corticosteroids With Either Montelukast or Salmeterol as Combination Therapy

FELICIA C. ALLEN-RAMEY, PhD; DON BUKSTEIN, MD; ALLAN LUSKIN, MD; SHIVA G. SAJJAN, PhD; and LEONA E. MARKSON, ScD

ABSTRACT

OBJECTIVE: To compare asthma-related health care resource utilization among a matched cohort of asthma patients using inhaled corticosteroids (ICSs) plus either montelukast (MON) or salmeterol (SAL) as combination therapy for asthma, during a time prior to the availability of fixed-dose combinations of ICS/SAL.

METHODS: A retrospective analysis using the PHARMetrics patient-centric claims database was conducted for the period preceding the market introduction of combination fluticasone-SAL in September 2000. Patients had to meet the following criteria for inclusion in the study: they had to be between the ages of 4 and 55 years; they had to have been continuously enrolled for 2 years; they had to have initiated ICS/MON or ICS/SAL therapy between July 1, 1998, and June 30, 1999; and they had to have had either (a) a diagnosis of asthma (based on International Classification of Diseases, Ninth Revision, Clinical Modification codes of 493.xx, and oral corticosteroid (OCS) fills and short-acting beta-agonist (SABA) fills. Multivariate regression analyses were performed. Subgroup analyses, mean change in SABA fills varied by how combination therapy was initiated, with sequential addition of asthma controllers leading to a reduction in SABA fills in both groups. For patients with concurrent initiation of combination therapy, the odds of ED visits/hospitalizations were significantly lower in patients initiating ICS/MON (adjusted OR = 0.25; 95% CI, 0.08-0.79). In a 52-week trial, Bjerner et al. found that 20.1% of the patients receiving montelukast (MON) and fluticasone had an asthma exacerbation compared with 19.1% in the group receiving salmeterol (SAL) and fluticasone (relative risk [RR] = 1.05 for MON/fluticasone vs. SAL/fluticasone; 95% confidence interval [CI], 0.86-1.29).

RESULTS: A total of 1,216 patients were matched (ICS/MON = 608; ICS/SAL = 608). Decreased odds of ED visits and/or hospitalizations were observed with ICS/MON (adjusted odds ratio [OR] = 0.58; 95% confidence interval [CI], 0.35-0.98) versus ICS/SAL. The odds of postindex OCS fills were not different for ICS/MON and ICS/SAL patients (adjusted OR = 1.04; 95% CI, 0.79-1.38). Postindex pharmacy claims for SABAs were significantly higher among ICS/MON patients versus ICS/SAL patients (adjusted relative risk [RR] = 1.33; 95% CI, 1.17-1.52), and this difference remained regardless of prior use or no prior use of ICSs. In subgroup analyses, mean change in SABA fills varied by how combination therapy was initiated, with sequential addition of asthma controllers leading to a reduction in SABA fills in both groups. For patients with concurrent initiation of combination therapy, the odds of ED visits/hospitalizations were significantly lower in patients initiating ICS/MON (adjusted OR = 0.25; 95% CI, 0.08-0.79).

CONCLUSION: In this matched cohort, use of ICS/MON compared with ICS/SAL resulted in similar odds of OCS fills, decreased odds of ED visits and asthma-related hospitalizations, but higher utilization of SABA.

KEYWORDS: Asthma, Montelukast, Salmeterol, Inhaled corticosteroids, Combination therapy, Propensity scoring, Leukotriene

J Manag Care Pharm. 2006;12(4):310-21

Note: Editorials on the subject of this article appear on pages 341-42 and 343-46 of this issue.

Authors

FELICIA C. ALLEN-RAMEY, PhD, is senior manager; SHIVA G. SAJJAN, PhD, is manager, and LEONA E. MARKSON, ScD, is executive director, Outcomes Research and Management, Merck & Co., West Point, Pennsylvania; DON BUKSTEIN, MD, is assistant clinical professor of pediatrics and family practice, and ALLAN LUSKIN, MD, is clinical associate professor of medicine, University of Wisconsin, Madison.

AUTHOR CORRESPONDENCE: Felicia C. Allen-Ramey, PhD, Senior Manager, Outcomes Research and Management, Merck & Co., Sumneytown Pike, WP39-170, West Point, PA 19486-0004. Tel: (215) 652-7546; Fax: (215) 652-0860; E-mail: felicia_ramey@merck.com

Copyright © 2006, Academy of Managed Care Pharmacy. All rights reserved.
80.0% percent of patients in the MON group and 83.3% of patients in the SAL group remained attack free during the 48 weeks of treatment (RR = 1.20; 95% CI, 0.96-1.49). Trials of shorter duration showed significant differences between patients using ICS/SAL and ICS/MON. Trials with longer follow-up time (>12 weeks) reported nonsignificant differences. Among patients randomized to SAL/fluticasone combination product compared with those randomized to fluticasone plus MON, Ringdal et al. report significantly greater improvements in forced expiratory volume in 1 second (FEV₁) from baseline (mean treatment difference = 0.11 L; 95% CI, 0.06-0.16; P < 0.001) and more asthma rescue-free days (odds ratio [OR] = 1.29; 95% CI, 1.02-1.63; P = 0.03). Nelson et al. also note greater improvement in asthma control among patients treated with combination fluticasone plus SAL than those treated with fluticasone plus MON (FEV₁: + 0.34 L vs. + 0.20 L, P < 0.001; days without albuterol use: + 26.3% vs. + 19.1%, P = 0.03). Lastly, in a study of symptomatic patients adding SAL or MON to ICS therapy, Fish et al. also report greater improvement in lung function and asthma symptoms among patients adding SAL (morning peak expiratory flow: 35.0 L/min vs. 21.7 L/min; P < 0.001; symptom-free days: 24% vs. 16%; P < 0.001). Examination of patients beyond a 12-week period may more closely reflect outcomes seen with chronic use in clinical practice.
The results of retrospective studies of administrative claims data comparing outcomes for patients using these combination regimens have shown similar improvements in emergency department (ED) visits and rescue medication use for ICS/MON and ICS/SAL patients and have yielded varied results on hospitalizations.10-13 Using a 1-year predesign/postdesign, Bukstein et al. reviewed claims data for patients aged 5 to 65 years who added SAL or a leukotriene modifier to ICSs. The
analysis of administrative claims revealed similar decreases in ED visits, urgent care visits, SABA fills, and oral corticosteroid (OCS) fills across the 2 treatment groups.15 Stempel et al. also analyzed claims for patients taking an ICS alone prior to adding either MON or SAL. The investigators reported greater odds of an asthma-related hospitalization in patients taking ICS/MON compared with patients taking ICS/SAL (but the ratio was not statistically significant [OR=2.5, \( P=0.066 \)], similar odds of an ED visit (OR=1.28, \( P=0.372 \)), and greater use of a SABA (ICS/MON = 4.45 vs. ICS/SAL = 3.29, \( P<0.001 \)), as well as 25% lower costs in the ICS/SAL group.15

A third analysis of administrative claims data performed by O’Connor et al. reported a decline in ED visits and hospitalizations among patients using an ICS plus SAL or an ICS plus an LRA, with a modest increase in SABA use for the leukotriene cohort.15 Finally, Wang et al. conducted a cross-sectional examination of medical and pharmacy claims over a 6-month period for patients using combination therapy. While the authors report lower costs for combination therapy of SAL plus fluticasone and ICS plus mast cell stabilizers over other asthma combination regimens, no significant differences in ED visits between patients treated with the fluticasone plus SAL combination (22 ± 159 per 1,000) versus the ICS plus mast cell stabilizer combination (26 ± 169 per 1,000) were observed (and no \( P \) values were reported for comparisons); similar rates of hospitalizations were also observed (ICS/LRA: 8.4 ± 91.1 per 1,000 vs. ICS/SAL: 9.3 ± 96.1 per 1,000).10

To assess the relative clinical effectiveness of ICS/MON and ICS/SAL for asthma control, this analysis examined outcomes associated with asthma exacerbations in a clinical practice setting (rather than carefully controlled clinical trials). The objective of the present study was to compare asthma-related

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Baseline Characteristics for Patients Prescribed Asthma Combination Therapy Before and After Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICS+MON Before Matching</td>
</tr>
<tr>
<td>N</td>
<td>765</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>25.6 (16.8)</td>
</tr>
<tr>
<td>Propensity score, mean (SD)</td>
<td>0.41 (0.2)</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Male gender</td>
<td>47.1</td>
</tr>
<tr>
<td>Proxy for asthma severity†</td>
<td>&lt;(0.001)</td>
</tr>
<tr>
<td>Group 1</td>
<td>41.1</td>
</tr>
<tr>
<td>Group 2</td>
<td>32.8</td>
</tr>
<tr>
<td>Group 3</td>
<td>19.0</td>
</tr>
<tr>
<td>Group 4</td>
<td>7.2</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>29.0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>48.8</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>48.1</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>40.0</td>
</tr>
<tr>
<td>Acute upper respiratory conditions</td>
<td>37.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Rate per Patient-Year (SD)</th>
<th>Mean Rate per Patient-Year (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient visits</td>
<td>2.78 (4.3)</td>
</tr>
<tr>
<td>ED visits</td>
<td>0.09 (0.4)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>0.05 (0.2)</td>
</tr>
<tr>
<td>Oral corticosteroids (OCS)</td>
<td>0.54 (1.3)</td>
</tr>
<tr>
<td>Short-acting beta-agonist (SABA)</td>
<td>4.44 (5.2)</td>
</tr>
</tbody>
</table>

* \( P \) values were derived from chi-square tests for categorical variables and \( t \) tests for continuous variables.
† See footnote of Table 1 for definition. In this measure, the most severe group (Group 4) has either (a) 3 or more OCS fills or (b) 2 OCS fills and >6 SABA fills. Group 3 has either (a) 2 OCS fills or (b) >6 SABA fills or (c) 1 OCS fill and >6 SABA fills. Group 1 has either no OCS fills and ≤1 SABA fill. All other combinations of SABA and OCS are in Group 2.
Methods

Data Source/Study Population

The PHARMetrics patient-centric database was used as the data resource for this analysis. At the time of this analysis, the database contained enrollment data and medical, facility, and pharmacy claims for approximately 17 million privately insured members enrolled in U.S. health plans. Enrolled members are geographically dispersed across the United States, with enrollment in plans in 35 states.

Inpatient, outpatient, and pharmacy claims were included in the dataset, which covered the years 1997 to 2000. To be considered for the analysis, patients had to meet the following criteria: they had to be between the ages of 4 and 55 years; they had to have received a diagnosis of asthma (based on International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes of 493.xx) at 2 outpatient visits, 1 or more ED visits, or during 1 or more hospitalizations within 1 year, or they had to have pharmacy claim records that contained a National Drug Code for an antiasthma medication (a beta-agonist, theophylline, an ICS, cromolyn, or a leukotriene) 2 or more times within 1 year; and they had to be continuously enrolled for 2 years. Patients were excluded if they had a medical claim with a diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, cystic fibrosis, or bronchopulmonary dysplasia, or if they had pharmacy claims for ipratropium bromide (Atrovent) or ipratropium bromide and albuterol (Combivent).

Study Design

Among patients identified with asthma, those initiating use of combination therapy were examined for changes in asthma-related resource utilization. Use of combination therapy was defined as use of an ICS only in the 6 months preceding the addition of a second asthma therapy (SAL or MON) or initiation of an ICS and SAL or MON on the same day, between July 1, 1998, and June 30, 1999 (index event). Patients had to be continuously enrolled in a health plan with pharmacy benefits for the 12-month period prior to the index prescription (referred to as the preindex period) and for 12 months following the index prescription (referred to as the postindex period) (Figure 1). Patients were excluded if their pharmacy records indicated use of an asthma controller other than an ICS in the 6 months preceding the index event or use of a third asthma controller within 30 days after the addition of MON or SAL. Continued use of both medications was confirmed by identification of another claim for an ICS within 60 days following the addition of MON or SAL.

Propensity Score Analysis

The propensity score methodology was used to obtain comparable groups of patients treated with ICS/MON and ICS/SAL based on patient and provider characteristics that may influence treatment selection. The propensity score is the probability of receiving MON versus SAL treatment concomitant with ICS for a given patient. For each patient, the propensity

### TABLE 3 Baseline Characteristics of Study Population

<table>
<thead>
<tr>
<th>Prior ICS Use (N = 813)</th>
<th>No Prior ICS Use (N = 401)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>29.3 (16.4)</td>
<td>25.7 (15.7)</td>
</tr>
<tr>
<td>Propensity score, mean (SD)</td>
<td>0.40 (0.2)</td>
<td>0.24 (0.2)</td>
</tr>
<tr>
<td>ICS/MON</td>
<td>0.40 (0.18)</td>
<td>0.25 (0.15)</td>
</tr>
<tr>
<td>ICS/SAL</td>
<td>0.39 (0.18)</td>
<td>0.24 (0.15)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>54.4</td>
<td>57.9</td>
</tr>
<tr>
<td>Preindex medication use (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCS fills</td>
<td>0.59 (1.2)</td>
<td>0.35 (1.2)</td>
</tr>
<tr>
<td>SABA fills</td>
<td>5.04 (5.5)</td>
<td>2.47 (4.1)</td>
</tr>
<tr>
<td>Antibiotic fills</td>
<td>1.11 (1.7)</td>
<td>0.99 (1.9)</td>
</tr>
<tr>
<td>Preindex medical visits (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED visits</td>
<td>0.09 (0.4)</td>
<td>0.06 (0.3)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>0.05 (0.3)</td>
<td>0.05 (0.2)</td>
</tr>
<tr>
<td>ED visits and/or hospitalizations</td>
<td></td>
<td>0.15 (0.6)</td>
</tr>
<tr>
<td>Comorbid conditions (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>47.0</td>
<td>48.6</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>26.6</td>
<td>24.9</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>4.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>49.1</td>
<td>38.4</td>
</tr>
<tr>
<td>Acute URI</td>
<td>34.5</td>
<td>33.7</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>4.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Chronic otitis media</td>
<td>17.4</td>
<td>14.2</td>
</tr>
<tr>
<td>Nasal polyposis</td>
<td>2.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*P values were derived from chi-square tests for categorical variables and t tests for continuous variables.

ED = emergency department; ICS = inhaled corticosteroids; MON = montelukast; OCS = oral corticosteroid; SABA = short-acting beta-agonist; SAL = salmeterol; URI = upper respiratory infection.
score was estimated using a logistic regression model. The variables included in the propensity score model were age, sex, provider specialty of the physician writing the index prescription, season in which combination therapy was prescribed, asthma health care resource use in the year prior to the index prescription (including prior outpatient visits, prior hospitalizations, prior ED visits, prior acute/rescue medication use, and prior antibiotic use), concomitant respiratory conditions, direct pharmacy costs, proxy for asthma severity (see footnote in Table 1), and significant interaction terms determined through forward selection procedure. The result of the propensity model was a single score between 0 and 1 for each patient that summarized the patient’s baseline characteristics. The derived propensity score and age groups (4-14 years and 15-55 years) were used to match patients 1 to 1 across treatment groups (using the Greedy matching technique). The results of the propensity score model are presented in Table 1; since 23.5% of the pharmacy claims had an unknown prescriber specialty, a covariate representing these data were included in the propensity score model.

**Outcomes**

Asthma-related health resource utilization outcomes included hospitalizations, ED visits, and prescription fills for OCSs and SABAs. The mean change in rates per patient-year from the preindex period to the postindex period was determined for each outcome. Tests of difference in mean change across treatment groups were performed using bootstrap methods with 50,000 iterations. The bootstrapping method was applied because of the skewed distribution of the outcome variables. Logistic regression models were used to obtain the adjusted odds of postindex ED visits and hospitalizations and postindex fills for OCS. ED visits and hospitalizations were combined into a single composite measure because of the low number of events. Poisson regression was used to obtain an adjusted RR for SABA fills because of the distribution of the number of SABA claims. Model covariates included treatment regimen, gender, age, preindex comorbid conditions, preindex medication use (antibiotics, SABA, LABA, OCS), and preindex resource use.

Additional exploratory analyses were performed to more fully understand the population being examined. Asthma-related outcomes were examined separately for patients using an ICS in the preindex period and adding MON or SAL versus those initiating combination therapy on the same day. A descriptive analysis of baseline (preindex) characteristics for patients who experienced an ED visit and/or hospitalization following the initiation of combination therapy was also conducted. Lastly, because symptoms associated with asthma overlap with symptoms for which antibiotics are often prescribed (i.e., chronic productive cough), change in the number of prescriptions filled for antibiotics during the study period was analyzed.

**Results**

**Patient Characteristics**

Of 12,251 asthma patients identified in the PHARMetrics database with combination therapy, a total of 3,171 met the inclusion criteria (ICS/MON: N = 765; ICS/SAL: N = 2,406). The patient selection process is presented in Figure 1. Before propensity score matching, the treatment groups differed on a number of baseline characteristics. On average, patients in the ICS/MON cohort were younger (mean age: 25.6 years) versus ICS/SAL (mean age: 33.2 years), had more males (47.1% ICS/MON vs. 39.9% ICS/SAL), and had a significantly greater number of outpatient and ED visits per year. In addition, the MON cohort required more rescue medication (in the form of OCSs and/or SABAs) prior to initiating combination therapy and experienced more comorbid respiratory conditions (such as sinusitis, rhinorrhea, pharyngitis, allergic rhinitis, and acute upper respiratory conditions). After being matched on propensity score and age, each treatment group contained 608 patients with similar baseline characteristics, as confirmed by statistical tests. Baseline characteristics of the study population before and after matching are presented in Table 2.

Within the study cohort, 815 patients used an ICS in the 6 months prior to adding MON (N = 401) or SAL (N = 414), and

---

**Table 4**

<table>
<thead>
<tr>
<th></th>
<th>ICS/MON (N = 608) Mean Rate Per Patient-Year (SD)</th>
<th>ICS/SAL (N = 608) Mean Rate Per Patient-Year (SD)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preindex</td>
<td>Postindex</td>
<td>Change</td>
</tr>
<tr>
<td>SABA fills</td>
<td>4.34 (5.5)</td>
<td>4.36 (5.9)</td>
<td>0.02 (4.9)</td>
</tr>
<tr>
<td>OCS fills</td>
<td>0.53 (1.3)</td>
<td>0.47 (1.2)</td>
<td>-0.06 (1.2)</td>
</tr>
<tr>
<td>ED visits</td>
<td>0.08 (0.4)</td>
<td>0.03 (0.2)</td>
<td>-0.05 (0.4)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>0.05 (0.2)</td>
<td>0.03 (0.2)</td>
<td>-0.02 (0.3)</td>
</tr>
</tbody>
</table>

* P value represents test of difference in the change for ICS/MON patients versus ICS/SAL patients using bootstrap method with 50,000 iterations.

ED = emergency department; ICS = inhaled corticosteroid; MON = montelukast; OCS = oral corticosteroid; SABA = short-acting beta-agonist; SAL = salmeterol.
401 patients initiated combination therapy on the same day (MON = 207; SAL = 194). Compared with those without prior ICS use, patients with prior ICS use had a significantly greater number of pharmacy claims in the preindex period for OCS (0.59 vs. 0.35 claims, \( P = 0.002 \)) and SABA (5.04 vs. 2.47 claims, \( P < 0.001 \)). Examination of the mean (SD) propensity score among patients with prior ICS use (SAL=0.39 [0.18], MON = 0.40 [0.18]) and those initiating combination therapy on the same day (SAL=0.24 [0.15], MON = 0.25 [0.15]) indicated that patients were adequately matched.

### Change in Asthma-Related Resource Utilization

An analysis of the mean change in annual asthma-related utilization rates was conducted for patients from the preindex to the postindex period for each cohort (Table 4). Hospitalizations declined by the same magnitude in both the ICS/MON group (mean change: -0.02 claims [SD=0.3]) and the ICS/SAL group (mean change: -0.02 claims [SD=0.3]) from preindex to postindex period. Likewise, the mean number of ED visits declined by 0.04 claims (SD=0.4) and 0.03 claims (SD=0.5) for the ICS/MON and ICS/SAL groups \((P = 0.46)\), respectively. Prescriptions for OCSs also declined in nearly identical fashion for those patients using ICS/MON, (mean change: -0.06 claims [SD=1.2]) as compared with ICS/SAL patients (mean change: -0.06 claims [SD=1.2]).

Mean change in SABA fills varied by how controller therapy was initiated. For the total population, SABA fills were essentially unchanged for patients using ICS/MON but decreased for ICS/SAL patients (mean change: -0.06 claims [SD=3.4]) as compared with ICS/SAL patients (mean change: -0.06 claims [SD=1.2]).

![Figure 2: Results of Multivariate Regression Analyses for Patients Initiating Asthma Combination Therapy (N = 1,216)](image-url)

<table>
<thead>
<tr>
<th>Model and Covariates*</th>
<th>Coefficient</th>
<th>Adjusted OR†</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postindex OCS fills</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS/MON treatment</td>
<td>0.04</td>
<td>1.04</td>
<td>(0.79, 1.38)</td>
<td>0.76</td>
</tr>
<tr>
<td>ICS/SAL treatment</td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>0.68</td>
<td>1.98</td>
<td>(1.12, 3.52)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior OCS fills (ref.: ≥2 claims)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 claims</td>
<td>-1.04</td>
<td>0.17</td>
<td>(0.11, 0.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 claim</td>
<td>0.32</td>
<td>0.67</td>
<td>(0.43, 1.05)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Postindex ED/hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS/MON treatment</td>
<td>-0.54</td>
<td>0.58</td>
<td>(0.35, 0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>ICS/SAL treatment</td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior ED/hospital</td>
<td>0.79</td>
<td>2.20</td>
<td>(1.14, 4.26)</td>
<td>0.02</td>
</tr>
<tr>
<td>Chronic otitis media</td>
<td>0.61</td>
<td>1.83</td>
<td>(1.01, 3.34)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Postindex SABA fills</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS/MON treatment</td>
<td>0.29</td>
<td>1.33</td>
<td>(1.17, 1.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICS/SAL treatment</td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior SABA fills (ref.: ≥8 claims)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 claims</td>
<td>-1.61</td>
<td>0.20</td>
<td>(0.16, 0.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-2 claims</td>
<td>-1.56</td>
<td>0.21</td>
<td>(0.17, 0.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3-7 claims</td>
<td>-0.88</td>
<td>0.42</td>
<td>(0.36, 0.49)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Only statistically significant variables for each model are shown. Additional covariates for each model included treatment group, gender, age, preindex comorbid conditions, preindex medication use (antibiotics, SABA, LABA, OCS).

† Odds ratio (OR) was estimated from logistic regression model.

‡ Relative risk (RR) was estimated from Poisson regression model.

CI= confidence interval; ED= emergency department; ICS= inhaled corticosteroid; LABA= long-acting beta-agonist; MON= montelukast; OCS= oral corticosteroid; OR= odds ratio; ref= reference; RR= relative risk; SABA= short-acting beta-agonist; SAL= salmeterol.
Administrative Claims Analysis of Asthma-Related Health Care Utilization for Patients Who Received Inhaled Corticosteroids With Either Montelukast or Salmeterol as Combination Therapy

ICS/MON groups (mean change: 0.85 claims [SD = 6.5]); this difference was not significant (P=0.12). These data are not shown. Regardless of history of ICS use, lower rates of ED visits, Hospitalizations, and OCS fills were observed for both the ICS/MON and ICS/SAL groups in the postindex period compared with the preindex period.

A total of 62 ED visits and 39 hospitalizations occurred in the postindex period, experienced by 74 patients. Compared with those without a postindex ED visit and/or hospitalization, patients with a postindex ED visit and/or hospitalization had a significantly greater number of pharmacy claims for OCS (0.93 vs. 0.48 claims, P = 0.02) and SABA (7.02 vs. 4.01 claims, P <0.01) in the preindex period. Patients with an ED visit/hospitalization in the postindex period had a significantly greater number of ED visits (0.53 vs. 0.06, P <0.01) and/or hospitalizations (0.19 vs. 0.04, P = 0.01) in the preindex period compared with those who did not have an ED visit/hospitalization after initiating combination therapy.

While studies of patients using a single controller therapy have noted significantly less antibiotic use for MON patients,20-21 no difference in the mean change in antibiotic prescriptions was observed in this study for the ICS/MON (-0.09 claims) vs. ICS/SAL (-0.08 claims).

Multivariate Regression Analyses

Logistic regression models of resource use in the postindex period were constructed. For modeling purposes, ED visits and hospitalizations were combined into a single outcome variable indicating the occurrence of an ED visit and/or hospitalization. Results of the models revealed significantly decreased odds of ED visits and/or hospitalizations with ICS/MON (adjusted OR: 0.58; 95% CI, 0.35-0.98; P = 0.04) versus ICS/SAL. There were similar odds of postindex use of OCSs for patients using ICS/MON (OR 1.04; 95% CI, 0.79-1.38; P = 0.76) versus ICS/SAL. For the total population, SABA fills were significantly greater among patients who took ICS/MON versus ICS/SAL (adjusted RR: 1.33; 95% CI, 1.17-1.52; P <0.001). These data are summarized in Figure 2.

<table>
<thead>
<tr>
<th>Model and Covariates*</th>
<th>Coefficient</th>
<th>Adjusted OR†</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postindex OCS fills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS/MON treatment</td>
<td>-0.34</td>
<td>0.71</td>
<td>0.42-1.20</td>
<td>0.20</td>
</tr>
<tr>
<td>ICS/SAL treatment</td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at index</td>
<td>0.02</td>
<td>1.02</td>
<td>1.00-1.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior OCS fills (ref.: 0 claims)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 claim</td>
<td>1.06</td>
<td>2.89</td>
<td>1.47-5.70</td>
<td>0.002</td>
</tr>
<tr>
<td>≥2 claims</td>
<td>2.33</td>
<td>10.24</td>
<td>4.03-26.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Postindex ED/hospital |             |              |        |         |
| ICS/MON treatment     | -1.39       | 0.25         | 0.08-0.79 | 0.02    |
| ICS/SAL treatment     |             | 1.0          |        |         |
| Prior ED/hospital     | 1.26        | 3.54         | 1.01-12.47 | 0.05    |
| Prior OCS fills (ref.: 0 claims) |    |              |        |         |
| 1 claim               | 1.21        | 3.36         | 1.01-11.18 | 0.05    |
| ≥2 claims             | 1.90        | 6.68         | 1.84-24.25 | 0.004   |

| Postindex SABA fills  |             |              |        |         |
| ICS/MON treatment     | 0.34        | 1.40         | 1.03-1.92 | 0.03    |
| ICS/SAL treatment     |             | 1.0          |        |         |
| Prior SABA fills (ref.: ≥8 claims) |    |              |        |         |
| 0 claims              | -1.42       | 0.24         | 0.16-0.37 | <0.001  |
| 1-2 claims            | -1.72       | 0.18         | 0.11-0.29 | <0.001  |
| 3-7 claims            | -0.96       | 0.38         | 0.25-0.60 | <0.001  |

* Only statistically significant variables for each model are shown. Additional covariates for each model included treatment group, gender, age, preindex comorbid conditions, preindex medication use (antibiotics, SABA, LABA, OCS).
† Odds ratio (OR) was estimated from logistic regression model.
‡ Relative risk (RR) was estimated from Poisson regression model.
CI= confidence interval; ED= emergency department; ICS=inhaled corticosteroid; LABA= long-acting beta-agonist; MON= montelukast; OCS= oral corticosteroid; OR= odds ratio; ref= reference; RR= relative risk; SABA= short-acting beta-agonist; SAL= salmeterol.
In general, models examining patient outcomes by history of prior ICS use agreed with those of the total population. For patients initiating combination therapy on the same day (Figure 3), ICS/MON use resulted in significantly lower odds of postindex ED visits/hospitalizations (OR = 0.25; 95% CI, 0.08-0.79) and greater risk of SABA fills (RR = 1.40; 95% CI, 1.03-1.92); no difference in OCS fills by treatment was observed. For patients adding MON or SAL to ICS (Figure 4), there was no difference in postindex ED visits/hospitalizations or OCS fills across treatment groups; greater risk of SABA fills for ICS/MON patients was observed (RR = 1.3; 95% CI, 1.17-1.48) as compared with ICS/SAL patients.

In summary, treatment with ICS/SAL was associated with significantly fewer claims for SABA for the total population and for subgroups analyzed by history of ICS use. Patients initiating ICS/MON experienced significantly fewer claims for ED visits/hospitalizations as seen in the total population and among patients with concurrent initiation of controller therapy. These results were observed in both bivariate and multivariate analyses (Table 5).

Discussion

This retrospective claims-based analysis compared asthma-related health care resource utilization among a matched patient cohort initiating use of either ICS plus MON or ICS plus SAL as combination therapy for asthma. Multivariate regression analyses of the total population revealed significantly decreased odds of ED visits and/or hospitalizations and no significant difference in OCS fills among users of ICSs and MON compared with users of ICSs and SAL.

The need for rescue medication in the form of a SABA has often been used as a measure of asthma control and was therefore included in this analysis. Regression analyses of the matched cohort indicated a significantly greater decrease in SABA for patients on ICS/SAL—a decrease of 1 canister per patient-year. Analyses of change in SABA varied according to when combination therapy was initiated (sequentially vs. concurrently) and may reflect the patients'...
Administrative Claims Analysis of Asthma-Related Health Care Utilization for Patients Who Received Inhaled Corticosteroids With Either Montelukast or Salmeterol as Combination Therapy

health status at that time. Based on emergent care and rescue-medication-use patterns in the preindex period, those adding a second controller sequentially to an ICS required additional intervention to better manage their asthma. The addition of MON or SAL to their ICS regimen decreased SABA, OCS, ED visits, and hospital admissions. In contrast, patients beginning ICS/MON or ICS/SAL on the same day did not experience improvements in SABA fills. Similarly, in a review of asthma combination therapy as first-line therapy, Ni Chroinin et al.22 concluded that the initiation of combination therapy does not significantly reduce SABA use as compared with ICS alone. It is possible that beginning asthma treatment with a single controller therapy and periodically reassessing patients’ asthma control may allow providers to more accurately determine and respond to the needs of their patients.

Chronic LABA use presents a challenge in the measurement and interpretation of SABA use. The asthma treatment guidelines continue to emphasize minimal use of SABA as a goal of therapy, but it is unclear how SABA use should be interpreted in patients using a LABA daily compared with those who are not. A decreased need for a SABA in patients using a LABA daily may simply reflect the replacement of one bronchodilator for another. In clinical practice, it may be reasonable to establish acceptable levels of SABA use by medication regimen. It is unknown whether total beta-agonist consumption (a measure of SABA + LABA) is important or whether providers should simply continue to make distinctions between demand use and regular use of beta-agonists. Additional research is needed to more fully understand how chronic LABA use impacts the use of SABA, for both clinical management and research purposes.

The findings of this analysis are in agreement with long-term comparative trials reporting equivalent asthma control for patients treated with fluticasone plus MON or fluticasone plus SAL. Our study sought to strengthen this body of evidence by using the propensity score methodology to correct for baseline differences in groups, thereby examining the relative effectiveness of ICS/MON and ICS/SAL in comparable patient groups. It should be noted that this study purposely predates the introduction of the fluticasone propionate/SAL fixed-dose combination product (Advair). This fixed-dose combination product is recommended for patients not adequately controlled on other asthma controller medications or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Fixed-dose combination products may offer an advantage for patients who need the simplicity and convenience of 2 therapies in 1 device and do not require tapering of the individual medications. The use of 2 separate medications, such as MON with ICSs, allows greater flexibility in dosing than fixed doses. The ability to taper ICS dosage when used concomitantly with MON has been demonstrated.23 Flexibility in dosing allows for convenient step-up in ICS dose, as recommended in the guidelines; this is more difficult with the fixed-dose combination typically used when SAL is chosen as the add-on therapy. The ability to make incremental changes in asthma medication reg-

| TABLE 5 | Summary of Results of Primary Outcomes Measures for the Overall Study Population and Subgroups Using Different Analytic (Bivariate and Multivariate) Methods |
|-----------------------------------|-----|-----|-----|-----|-----|
| Total Population (N = 1,216)     | Prior ICS Use (N = 815) | No Prior ICS Use (N = 401) |
|-----------------------------------|-----|-----|-----|-----|-----|
| Bivariate analyses of postindex characteristics* |
|-----------------------------------|-----|-----|-----|-----|-----|
| ICS/MON (N = 608)                 | ICS/SAL (N = 608) | ICS/MON (N = 401) | ICS/SAL (N = 414) | ICS/MON (N = 207) | ICS/SAL (N = 194) |
| SABA*                            | 4.36 (5.88) | 3.16 (4.08) | 4.78 (5.42) | 3.57 (4.32) | 3.53 (6.60) | 2.28 (3.35) |
| OCS                              | 0.47 (1.22) | 0.42 (1.11) | 0.56 (1.37) | 0.47 (1.23) | 0.30 (0.80) | 0.33 (0.76) |
| ED visits†                       | 0.03 (0.20) | 0.07 (0.34) | 0.04 (0.20) | 0.08 (0.37) | 0.02 (0.18) | 0.05 (0.24) |
| Hospital visits                  | 0.03 (0.19) | 0.04 (0.27) | 0.02 (0.14) | 0.04 (0.30) | 0.03 (0.27) | 0.03 (0.17) |
| Multivariate models‡             |
|-----------------------------------|-----|-----|-----|-----|-----|
| SABA                              | 1.33 | <0.001 | 1.31 | <0.001 | 1.40 | 0.03 |
| OCS                               | 1.04 | 0.76 | 1.26 | 0.18 | 0.71 | 0.20 |
| ED/hospital visits                | 0.58 | 0.04 | 0.80 | 0.47 | 0.25 | 0.02 |

* Significantly greater number of pharmacy claims for SABA in ICS/MON compared with ICS/SAL patients for each comparison: total population, P <0.001; prior ICS use, P = 0.01; no prior ICS use, P = 0.03.
† Significantly fewer ED/hospital visits for ICS/MON vs. ICS/SAL for the total population comparison, P = 0.04.
‡ ICS/SAL served as the reference group for all models; relative risk was estimated using Poisson regression for model of SABA fills and odds ratio was estimated using logistic regression for models of OCS fills and ED/hospital.
ED = emergency department; ICS = inhaled corticosteroid; MON = montelukast; OCS = oral corticosteroid; SABA = short-acting beta-agonist; SAL = salmeterol.
imens allows both physicians and patients to titrate medications as needed to achieve asthma control.

**Limitations**

This analysis was performed using medical and pharmacy claims to examine resource utilization for asthma. Detailed information about the patients’ asthma symptoms, lung function, or treatment preferences that might affect the combination therapy prescribed are generally not available in claims databases and could not be accounted for in this analysis. In addition, the presence of a pharmacy claim does not guarantee patient use of the medication or indicate how the physician instructed the patient to use the medication. Secondly, while the propensity score technique was used to identify comparable patient groups for comparison, this method accounts only for variables that have been observed or measured; for instance, we could not adjust for ethnicity since these data were not available.

In addition, we did not study financial measures associated with asthma-related resource utilization as an outcome since these data are difficult to interpret in claims. Cost data in claims are subject to wide variability in amounts charged and paid for any particular service, given contractual differences that can exist across employer-sponsored health plans and the lack of sufficient information to adjust for these differences.

### Conclusion

In this matched cohort, use of ICS/MON compared with ICS/SAL resulted in similar odds of OCS fills, decreased odds of ED visits and asthma-related hospitalizations, but higher utilization of SABAs.

### ACKNOWLEDGMENTS

The authors would like to acknowledge Phong Duong, PharmD, Merck & Co., Inc., West Point, PA, for his contributions to the conception and design of analysis; David Anstatt, MBA, for his management, presentation, and interpretation of data (he was an employee of Merck at the time of this study); Data Virtuoso, Inc., Schwenksville, PA, for its programming assistance; and Judith Grief, Griffin Communications, East Brunswick, NJ, for writing assistance.

### DISCLOSURES

Funding for this research was provided by Merck & Co., Inc., which also provided scientific and technical input; it was obtained by authors Felicia C. Allen-Ramey, Leona E. Markson, and Shiva G. Sajan, who are employed by Merck. Authors Don Bukstein and Allan Luskin disclose no potential bias or conflict of interest relating to this article.

Allen-Ramey served as principal author of the study. Study concept and design were contributed by Allen-Ramey, Sajan, and Markson, with input from Bukstein and Luskin. Data collection was primarily the work of Allen-Ramey and Markson, with input from the coauthors; data interpretation was primarily the work Bukstein and Luskin, with input from the coauthors. Drafting of the manuscript and its revision were primarily the work of Allen-Ramey and Markson, with input from the coauthors.

### REFERENCES


Administrative Claims Analysis of Asthma-Related Health Care Utilization for Patients Who Received Inhaled Corticosteroids With Either Montelukast or Salmeterol as Combination Therapy


The Cost-effectiveness of Lamotrigine in the Maintenance Treatment of Adults With Bipolar I Disorder

NEILL W. CALVERT, PhD; STEVEN P. BURCH, PhD; ALEX Z. FU, PhD; PENNY REEVES; and THOMAS R. THOMPSON, MD

ABSTRACT

OBJECTIVE: To present an economic model and cost-effectiveness estimates for lamotrigine in maintenance treatment of bipolar I disorder (BD-I) using outcomes from the pivotal lamotrigine trials. The main comparator treatments in the pivotal trials were lithium and “no maintenance” (acute-only) treatment. A comparison with olanzapine was included as an indirect analysis following publication of data during the course of our research.

METHODS: A Markov model was built around the 3 health states of euthymia, mania, and depression. The base-case model simulates a cohort of 1,000 patients with BD-I who have recently stabilized after resolution of a bipolar manic episode. The cohort was modeled for a period of 18 months. Resource-use estimates were derived from best available published data, treatment guidelines, a physician survey, and published unit cost data. Outputs were measured in terms of costs per acute mood episode avoided, costs per euthymic day gained, and costs per quality-adjusted life-years (QALYs). Direct health care payer costs are used in the analyses.

RESULTS: The base-case model for patients with a recent manic episode indicated that lamotrigine is the most effective treatment for avoiding both acute depression episodes and all types of acute episodes (depression and mania). It is also the most effective treatment in terms of number of euthymic days achieved (309 days per patient per year). Olanzapine is most effective for avoiding acute mania episodes. Total direct costs of treatment are lowest for the lithium treatment arm ($8,710 per patient for the 18-month period). All maintenance therapies were cost effective compared with the no-maintenance (acute-only treatment) arm. In the base case, lamotrigine had incremental cost-effectiveness ratios of $30 per euthymic day and $2,400 per acute episode avoided compared with lithium. A QALY analysis indicated that lamotrigine is cost effective in patients with a recent manic episode at $26,000 per QALY. The base-case model indicated that lamotrigine dominates olanzapine, (that is, lamotrigine costs less and is more effective than olanzapine) in patients with a recent manic episode. In a sensitivity analysis using outcomes from the pivotal trial of recently depressed patients, lamotrigine, in comparison with lithium, was not shown to be as cost effective as in the recently manic patients, but it was still cost effective compared with no maintenance treatment.

CONCLUSIONS: For a defined cohort of patients with BD-I, the pharmacoeconomic model indicated that prevention of mood episodes with lithium and lamotrigine is cost effective in patients with a recent manic, mixed, or hypomanic episode. The conclusions with respect to the indirect comparison with olanzapine should be validated if and when direct trial data become available. Cost-effectiveness of maintenance treatments for patients with BD-I (recently depressed as well as recently manic) are likely to improve in models with a broader costing perspective and that take a longer time frame. Further research into the outcome implications of health-related quality of life and other BD subgroups are recommended.

KEYWORDS: Modeling, Cost-effectiveness, Bipolar, Maintenance treatment

J Manag Care Pharm. 2006;12(4):322-30

Bipolar disorder (BD) is a psychiatric disorder characterized by recurrent mood episodes. In the most common manifestation of the disease, bipolar I disorder (BD-I), the patient’s mood alternates between periods of euphoria, restlessness, poor judgment, and risk-taking behavior (manic episodes); periods of depression, anxiety, and hopelessness (depressive episodes); and periods of euthymia (normal mood).

Management of BD usually involves a combination of drug treatment, psychotherapy, and social support. For patients experiencing an acute mood event, the goal of treatment is to normalize the patient’s mood and help the patient resume normal functioning, while minimizing risk to the patient. The goal of medication therapy of patients in the euthymic state is to maintain euthymia for as long as possible and to reduce the patient’s risk of experiencing another acute mood episode. In maintenance treatment, lithium has been generally accepted as a first-line therapy; although the evidence base for its effectiveness has until recently been incomplete. There is increasing evidence that newer agents, in particular anticonvulsants and atypical antipsychotics, have a potentially important role to play in the management of BD.2,4

The U.S. prevalence of BD has been estimated at 2%, affecting both men and women equally.5 Relatively new epidemiologic data expand the concept of BD to include subthreshold expressions of mania, hypomania, brief hypomania, and cyclothymia. These studies suggest a higher prevalence of up to 5% of BD.5,6 The burden of illness for BD in the United States has been estimated at $45 billion,11 with a more recent estimate of $24 billion for the lifetime costs for bipolar patients.12

Given the considerable resource burden of BD, it was surprising that, at the time our work started, there was no
The Cost-effectiveness of Lamotrigine in the Maintenance Treatment of Adults With Bipolar I Disorder

Evidence regarding the cost-effectiveness of bipolar maintenance treatments. This article reports the results of a modeling exercise designed primarily to derive estimates of the cost-effectiveness of lamotrigine and lithium. The research was commissioned by the manufacturers of lamotrigine, who wanted to explore the cost-effectiveness of their product using outcomes results of their pivotal trials.13,14

These double-blind, placebo-controlled trials were conducted to meet the requirements of the U.S. Food and Drug Administration for approval of lamotrigine (Lamictal) as maintenance treatment in BD-I. The studies were conducted to assess the efficacy and tolerability of lamotrigine and lithium compared with placebo for the prevention of relapse or recurrence of mood episodes in recently (within 60 days of screening) manic or hypomanic patients (Bowden et al.13), and in currently or recently depressed (Calabrese et al.14) patients, respectively. The primary outcome measure was time from randomization to intervention (addition of pharmacotherapy or ECT) for any current or emerging mood episode (depressive, manic, hypomanic, or mixed).

Although the original objective of this research was to assess the cost-effectiveness of lamotrigine pivotal trial drugs alone, new data regarding the effectiveness of olanzapine became available during the course of our research.15 This research has recently been published.16 The olanzapine study used similar patients and outcome measures to the Bowden trial (bipolar patients with a recent manic episode). A summary of the trial designs, patient inclusion criteria, and primary outcome measures used in the 3 trials are summarized in Table 1. In light of this development, we refocused the economic appraisal on to the recently manic subpopulation from Bowden's trial, which is appended with an analysis using an indirect comparison with olanzapine. In a sensitivity analysis, we investigated the effects of substituting the outcomes data from Bowden's trial of recently manic bipolar patients with those from Calabrese's trial of recently depressed patients.

Methods

The 3 treatment options originally included in our model were those from the pivotal trials for lamotrigine, namely
1. lamotrigine monotherapy,
2. lithium monotherapy, and
3. acute treatment only (placebo) therapy.

As discussed above, a supplementary economic evaluation of olanzapine monotherapy (using an average dose of 12.5 mg

| TABLE 1 Schematic Representation of the Quarterly Model Structure |
|-----------------|-----------------|-----------------|
| Randomized      | Bowden13         | Calabrese14     | Tohen15,16 |
| Blinded         | Yes             | Yes             | Yes |
| Placebo-controlled | Double-blinded | Double-blinded | Double-blinded |
| Patient inclusion criteria | Bipolar I patients aged ≥18 years had a diagnosis of bipolar I disorder, most recent episode manic or hypomanic as determined by DSM-IV, or had a manic/hypomanic episode either currently or within 60 days prior to screening, and had at least 1 manic/hypomanic episode and 1 depression episode within the previous 3 years | Bipolar I patients aged ≥18 years had a diagnosis of bipolar I disorder, most recent episode depressed, as defined by DSM-IV criteria, either currently or within 60 days prior to the screening visit, and had at least 1 manic or hypomanic episode and 1 depression episode within the previous 3 years | Bipolar I patients aged ≥18 years Index manic or mixed as determined by DSM-IV and a Young mania rating Score ≥20 and at least 2 manic or mixed episodes in previous 6 years |
| Primary outcome measure | Time to intervention (addition of pharmacotherapy or ECT) for any mood episode | Time to intervention (addition of pharmacotherapy or ECT) for any mood episode | Time to symptomatic relapse to, or hospitalization for, any mood episode |
| Study follow-up | Up to 18 months | Up to 18 months | Up to 48 weeks |

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ECT = electro-convulsive therapy.
The Cost-effectiveness of Lamotrigine in the Maintenance Treatment of Adults With Bipolar I Disorder

Model Structure
A schematic representation of the model structure is given in Figure 1. Patients enter the model once their illness has been stabilized and they are initially assigned to the euthymic health state.

In subsequent time periods, the model assumes that patients either remain euthymic or transition either to acute depression or mania health states. Patients entering the acute health states remain in that state for a period of time determined by the average length of the acute episode.

Unlike the pivotal trials, where patients were usually withdrawn once they had experienced an acute bipolar episode, our model retains the patient in the health care system as per the real world. One modeling simplification that we made was to assume that patients experiencing an acute bipolar episode transition back to the euthymic state before they experience a second or subsequent acute episode. The trial data indicated that some patients autonomously discontinue maintenance treatment. Discontinuation is facilitated in the model structure by allowing patients to switch from the maintenance treatment arm into a "no-maintenance" (placebo) arm.

Markov models are frequently used to evaluate clinical scenarios where patients can transition between defined health states during any of the defined transition periods. The Markov structure makes the assumption that the transition probabilities remain constant for each of the transition periods. We thus adopted a Markov model structure with a time span of 18 months, determined by the length of the lamotrigine trials, but divided into 6 quarterly transition periods.

Populating the Model
We populated the base-case model with a theoretical cohort of 1,000 patients deemed to have stabilized following a mixed/manic BD-I episode. That is, our base-case patients are similar to the patients included in the Bowden trial.13

Transitional Probabilities
The trials recorded the time to intervention for the first event per day, derived from using outcome data from results presented by Tohen15,16), was added during the course of our research.

### Table 2: Quarterly Transitional Probability Estimates

<table>
<thead>
<tr>
<th>Quarterly Transitional Probability</th>
<th>No Maintenance Treatment</th>
<th>Lithium</th>
<th>Lamotrigine</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (manic in a given quarter)</td>
<td>0.592</td>
<td>0.111</td>
<td>0.215</td>
<td>0.116</td>
</tr>
<tr>
<td>P (depressed in a given quarter)</td>
<td>0.408</td>
<td>0.143</td>
<td>0.071</td>
<td>0.168</td>
</tr>
<tr>
<td>P (remain euthymic)</td>
<td>0</td>
<td>0.561</td>
<td>0.655</td>
<td>0.617</td>
</tr>
<tr>
<td>P (adverse event or withdrew consent)</td>
<td>–</td>
<td>0.185</td>
<td>0.059</td>
<td>0.099</td>
</tr>
</tbody>
</table>

*Sources: Bowden et al.13 and Tohen et al.15,16.*
(manic, hypomanic, mixed, or depressive episode) and the number of patients completing the 18 months free of intervention for an actual or emerging mood episode (completers). These event probabilities were used to derive the quarterly transitional probabilities used in the model. The placebo outcomes were used as a proxy for the no-maintenance treatment group in our model. Data from patients who withdrew from the study due to an adverse event or consent withdrawal were used to represent patients who stop maintenance therapy and transition to the no-maintenance therapy state.

In line with Markov modeling principles, the transitional probabilities were assumed to be equal over the 6 quarterly time periods of the model. For example, for a given treatment option, if X% of patients completed after 18 months, then the quarterly probability of being event free in a given quarter was estimated as X(1/6) The residual probability was then assigned across the other events in proportion to the size of the 18-month event risks.

We derived transitional probabilities for olanzapine using Tohen’s15 reported outcomes and anchoring to Bowden outcomes using the placebo results from these 2 trials. In brief, we estimated the risks ratios of modeled events for patients receiving olanzapine compared with the placebo group. In an attempt to allow for differences in patient populations in the 2 trials, these risk ratios were then multiplied by the absolute placebo rates from Bowden. Because the placebo rate for completers was zero in Bowden, we arbitrarily assumed that there was 1 completer to enable us to estimate a completer rate for olanzapine. The resulting risk probabilities for olanzapine were then converted to constant Markov quarterly transitional probabilities in the same way as for lithium and lamotrigine. The resulting modeled transitional probabilities are given in Table 2.

**Resource-Use Estimates**

The model takes a direct-payer costing perspective (year 2004 US$). Modeled resource-use items include drug costs for maintenance treatment, drug and hospitalization costs for the treatment of acute manic and depressive episodes, and costs of associated contacts with health care professionals for monitoring and pathology tests. In brief, patients experiencing an acute episode were assumed to remain on maintenance treatment in addition to any newly added acute treatments (valproate for mania and paroxetine for depression). A proportion of these patients are assumed to require inpatient care.

All the resource-use assumptions, unit costs, and data sources are presented in Table 3. Unit costs were obtained from common sources such as drug prices from the Red Book. The length of acute episodes, the proportion of patients hospitalized, and physician monitoring time were estimated using responses from a physician survey. The objective of the survey was to assess BD knowledge, attitudes, and practice patterns of psychiatrists and primary care providers from a large, vertically integrated health system in the Midwest. In order to fill in some of the data gaps for populating our model, we appended some targeted questions to the psychiatrist survey. Other results from the original survey are to be published shortly.17 All of these resource-use assumptions are tested in sensitivity analyses.

**Health-State Utilities**

Health-state utility values were estimated using a standard algorithm,14 and the 36-item short form (SF-36) values were collated as part of the lamotrigine pivotal trials and supplemented with values from published literature.17 Consequently, our analysis assumed utility values of 0.8, 0.7, and 0.4 for euthymic, manic, and depressive mood states, respectively. Key outcomes estimated by the model for each treatment arm included the number of acute episodes, the number of euthymic days, direct health care costs, and QALYs.

**Results**

Table 4 presents the results of modeling the 3 baseline treatment options and olanzapine monotherapy using effectiveness data from pivotal trials including patients with a recent episode of mania or hypomania. Over the 18-month period analyzed, and for the 1,000 patient cohort, the model indicated that treatment with lithium monotherapy was the least-costly treatment option in terms of total direct costs. The no-maintenance treatment option was the highest direct-cost option, due to more hospitalizations. In common with previously published burden of disease analyses,20-22 our model indicated that the majority of BD
The Cost-effectiveness of Lamotrigine in the Maintenance Treatment of Adults With Bipolar I Disorder

Direct costs are hospitalization costs. For patients with recent manic episodes, the model indicated that lamotrigine may save hospital resources compared with lithium, through reduced admissions for depressive episodes.

Lamotrigine monotherapy resulted in the fewest depressive episodes, achieved the most euthymic days, and gained the most QALYs of all 4 treatment options. Olanzapine avoided the most acute manic episodes in the model. All of the active treatment regimes dominated the no-maintenance treatment option for all 3 measures of effectiveness (Figure 2). That is, maintenance treatments were less costly and more effective.

Lamotrigine also dominated olanzapine for all 3 measures of effectiveness using this model. The incremental cost-effectiveness of lamotrigine compared with lithium was $2,400 per episode avoided, $30 per euthymic day gained, and $26,000 per QALY. Compared with lithium, we estimated olanzapine incremental cost-effectiveness ratios (ICERs) of $200 per euthymic day gained, $7,000 per acute episode avoided, and $374,500 per QALY.

Sensitivity Analysis

In order to test the sensitivity of our model outputs to the input assumptions, we undertook a comprehensive set of sensitivity analyses, including 1- and 2-way sensitivity analyses, threshold, and scenario analyses.

Table 5 presents the proportional change in euthymic day and cost outcome variables for lamotrigine as well as the incremental cost per euthymic day (lamotrigine compared with lithium), which results from having changed lamotrigine input variables by 10%.

The model outputs were most responsive to the transitional risk probabilities. A 10% increase in the lamotrigine mania quarterly transitional probability produced a 66% increase ($30.30 to $50.00) in the value of the euthymic day ICER. Although changing the price of lamotrigine itself had a relatively small impact on direct cost outcomes, it had a proportionate effect on the ICER. Other variables that had a greater relative influence on direct costs (e.g., inpatient costs for mania) had a relatively small effect on the ICER because lithium patients experiencing mania also incurred these increased costs.

One-way sensitivity analyses to assess the sensitivity of the lithium-lamotrigine QALY ICER to a 10% change (increase) in the 3 health-state utility values, were also undertaken. The results showed a relatively sensitive (16%) improvement in the ICER from changing the euthymic utility in contrast to a relatively insensitive (1.5%) improvement resulting from changing the mania utility. There was a proportionate change in the ICER resulting from the 10% change in the depression utility.

A threshold analysis that sought out a dominant solution for lamotrigine over lithium required large changes in input assumptions. For some variables, including those associated with the use of a mania-related hospitalization resource, a dominant solution was not possible. The most responsive variable was the mania risk transitional probability for lamotrigine. Lamotrigine dominated lithium if the value of the mania risk transitional probability changed to a value of 0.172 from the base-case value of 0.215.

Our base-case model used effectiveness data from the Bowden trial (bipolar patients with a recent bipolar mania episode). We undertook a sensitivity analysis in which we replaced the effectiveness data with that from the Calabrese trial (bipolar patients with a recent depressive episode). Olanzapine was excluded from this subanalysis because there

QALY = quality-adjusted life-year.
was no direct or indirect data available with which to make an appropriate comparison.

Over the 18-month period modeled in this sensitivity analysis, treatment with lithium monotherapy was the least-costly treatment option, at $2.7 million per annum, followed by the no-maintenance treatment option ($3.8 million), and lamotrigine monotherapy ($4.4 million). Lamotrigine monotherapy resulted in the fewest depressive episodes (732) compared with 803 and 1,087 for lithium and no-maintenance treatment, respectively. The modeled number of manic episodes was 174 for lithium, 288 for lamotrigine, and 364 for no-maintenance treatment. Lamotrigine monotherapy achieved the most QALYs (1,142) compared with 1,137 and 1,113 for lithium and no-maintenance treatment, respectively.

Thus, Lamotrigine saves 0.24 depression episodes per patient per year (33% reduction) compared with no-maintenance treatment, and 0.05 (9%) episodes per patient compared with lithium. Lamotrigine gains 18 (6%) euthymic days per patient per year compared with no-maintenance treatment and 1.04 (0.32%) days compared with lithium. Lamotrigine is still cost effective versus the no-maintenance treatment option with ICERs of $20 per euthymic day, $1,300 per acute episode avoided, and $19,400 per QALY. Compared with lithium, the incremental cost-effectiveness in term of cost per euthymic day gained is $1,043. Because lamotrigine is modeled only to gain 5 additional QALYs compared with lithium over the 18-month period modeled, the incremental cost per QALY is $360,000. Likely explanations for this less-optimistic cost-effectiveness result for lamotrigine in the depression subpopulation analysis are included in the discussion below.

**Discussion**

A model, by definition, is a simplification of the real world. By describing BD-I as 3 discrete and mutually exclusive states (euthymia, mania, and depression), our model deliberately simplifies what is a complex disease process. We did this in the foreknowledge that limited data were available to populate the model and in order to maintain transparency. Interviewed clinicians broadly endorsed this simplified view as having relevance in the description of some patients with BD. Analysis of U.K. prescription data as part of a European modeling project found a large number of prescriptions consistent with this simplified structure: long periods of mood stabilizer use with short duration for antipsychotic and antidepressive drugs. The model has been reviewed and validated by clinicians and by 2 senior academic health economic modelers. We have undertaken both internal and external validation of our model.

Our base-case model assumptions used transitional probabilities generated from pivotal trial data in patients with a recent bipolar manic episode. The modeled ICERs for lamotrigine compared with lithium were estimated at $30 per euthymic day gained and $2,400 per acute episode avoided. In a recent National Institute for Health and Clinical Excellence (NICE) appraisal in the United Kingdom, an ICER for valproate compared with olanzapine was estimated at between £300 and £500 (approximately $500-$900) per remission day gained. Likewise, a base-case analysis for olanzapine compared with haloperidol estimated an ICER of £7,200 (approximately $12,500) per treatment responder. Although not directly comparable, our lamotrigine cost-effectiveness estimates look relatively favorable in comparison. On the basis of the above U.K. results, NICE gave positive guidance by recommending that both olanzapine and valproate be prescribed to NHS patients.

The assertion that lamotrigine is cost effective in patients with a recent bipolar manic episode, as inferred by our model, is also supported by the QALY analysis. In the United Kingdom, willingness-to-pay thresholds of £20,000 to £30,000 per QALY are used by NICE and the Scottish Medicines Consortium (SMC). Our modeled estimate of $26,000 per QALY for lamotrigine compared with lithium is a value therefore likely to be acceptable to U.S. payers.

While our model indicates that olanzapine is cost effective compared with no-maintenance treatment and lithium in patients with a recent manic episode, it also indicates that

---

**Table 5: Sensitivity Analyses: 1-Way and 2-Way**

<table>
<thead>
<tr>
<th>Sensitivity Variable</th>
<th>% Change in Direct Costs</th>
<th>% Change in Euthymic Days</th>
<th>Incremental Cost per Euthymic Day ($)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>30.30</td>
</tr>
<tr>
<td>Daily cost of lamotrigine</td>
<td>+1.4</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>P (depressed in any quarter)§</td>
<td>+0.11</td>
<td>-0.44</td>
<td>33</td>
</tr>
<tr>
<td>Average days of depressive episode</td>
<td>+0.2</td>
<td>-0.76</td>
<td>27</td>
</tr>
<tr>
<td>Antidepressant costs</td>
<td>+0.12</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>% depression hospitalized</td>
<td>+0.57</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Inpatient LOS, depression</td>
<td>+0.57</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Inpatient daily cost, depression</td>
<td>+0.57</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>P (manic in any quarter)¶</td>
<td>+5.36</td>
<td>-0.68</td>
<td>50</td>
</tr>
<tr>
<td>Average days of manic episode</td>
<td>+0.44</td>
<td>-0.92</td>
<td>31</td>
</tr>
<tr>
<td>Antimanic drug costs</td>
<td>+0.14</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>% mania hospitalized</td>
<td>+6.75</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>Inpatient LOS, mania</td>
<td>+6.75</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>Inpatient paid cost, mania</td>
<td>+6.75</td>
<td></td>
<td>32</td>
</tr>
</tbody>
</table>

* Input variable changed by 10%. † Incremental cost per euthymic day for lamotrigine relative to lithium. § To compensate for the increased likelihood of patients becoming depressed, a compensatory reduction in the probability of remaining euthymic was assumed. ¶ To compensate for the increased likelihood of patients becoming manic, a compensatory reduction in the probability of remaining euthymic was assumed. LOS=length of stay.
The Cost-effectiveness of Lamotrigine in the Maintenance Treatment of Adults With Bipolar I Disorder

Lamotrigine costs less and is more effective than olanzapine. These findings are the result of an indirect comparison using outcomes from the Bowden\textsuperscript{13} and the Tohen\textsuperscript{15,16} trials. In the absence of head-to-head trial data, it is legitimate practice in economic evaluations to use modeling techniques to make indirect comparisons (as frequently demonstrated by NICE and the SMC in the United Kingdom). However, the validity of our findings is dependent on the validity of our indirect comparison. We believe that the similarity of the Bowden and the Tohen study designs, and their patient inclusion criteria (Table 1), support our decision to add olanzapine to our base case analysis.

Sensitivity analyses indicated that key results were insensitive to variables that can be described as having a right-skewed distribution, including length of acute episode and length of hospital stay. The modeled ICERS were, however, sensitive to input variables that independently affect outcomes for individual treatment options such as the cost of maintenance treatments. The ICERS were most sensitive to inputs that increased the numerator (incremental costs) and simultaneously decreased the denominator (incremental effectiveness), or vice versa. As such, the ICERS were relatively sensitive to changes in transitional probability values.

With this in mind, it should be noted that the Markov transitional probabilities for lamotrigine, lithium, and the no-maintenance treatment arms were estimated using the 18-month event rates in the 2 lamotrigine pivotal trials. The event rates were assumed to decline exponentially from time zero to 18 months. In fact, the Kaplan-Meier curves indicate that avoidance of events was relatively good up to 12 months but declined between 12 and 18 months. As such, our exponential decline assumption may underestimate the 12-month survival rates for lithium and lamotrigine, and particularly so for the no-maintenance treatment arm in the base-case model, since no placebo patients in the Bowden trial survived to 18 months. Furthermore, the olanzapine trial only had a 12-month follow-up period, so the transitional probabilities for olanzapine were estimated from the 12-month “survival” data reported by Tohen et al. It may be that our analysis is therefore biased against lamotrigine and lithium.

Replacing the effectiveness data from the Bowden trial (recently manic patients) with that from the Calabrese trial (recently depressed patients)\textsuperscript{18} produced less-optimistic economic messages for lamotrigine. This may seem counterintuitive, given lamotrigine’s efficacy against bipolar depression, but it can be explained by the following:

- patients with a recent manic episode have a greater tendency to relapse to the manic pole, while patients recently depressed tend to relapse to the depressive pole\textsuperscript{25,26};
- the pivotal trial data also indicate that patients in the recently manic trial experienced more acute episodes than patients in the recently depressed trial;
- the average cost of a manic episode is greater than that of a depressive episode primarily because a greater proportion of patients are hospitalized during a manic episode; and
- manic episodes are, on average, shorter than depression episodes.

The combined effect of the above in our 18-month model is that there is reduced opportunity for avoidance of acute events in patients with a recent depression episode, with poorer health and cost consequences for this patient subgroup compared with that available to patients with recent mania as presented in the base-case model.

In order to undertake a QALY analysis, we needed to make assumptions about the health utility values for patients experiencing euthymic, depression, and mania health states. Because of the potential difficulties of eliciting utility values for patients experiencing mania,\textsuperscript{27} further research in this area of health-state valuation would be helpful to inform future cost-utility (QALY) analysis.\textsuperscript{28}

Limitations

The limitations of our study are determined largely by the simplifying assumptions that were made in constructing and populating the model. The validity of model results is restricted to the subgroup of patients with BD included in the pivotal clinical trials. The results should not be interpreted as being relevant to patients excluded from the trials, for example, rapid cyclers.

We believe the indirect comparison with olanzapine is a valid one both methodologically and because of the similarities between the Bowden and the Tohen trials. Having said this, we acknowledge that the ideal would be a well-designed randomized head-to-head trial of competing maintenance treatments. The outcomes of such a trial could then be used to derive transitional probabilities, which could be fed into our model in order to test the robustness of our current findings. Until such time, we argue that our model outcomes can be supported as currently best available evidence.

The 18-month time frame of our model was driven by the 18-month time frame of the pivotal clinical trials. However, BD is a chronic disease with a relatively young age of onset. We alluded to the fact that a longer time frame model may be necessary in order to demonstrate the economic advantages of maintenance treatments in patients with a recent bipolar depression episode. Also, the current model does not consider the disutility and costs of long-term adverse medication events. The well-tolerated side-effect profile of maintenance treatments, such as lamotrigine, may well mean that inclusion of such events in a longer time frame model will favor some maintenance treatments in comparison to lithium.

As discussed above, our model takes a direct-payer costing perspective. Broadening the costing perspective to include patient and caregiver costs, indirect costs to the economy through time lost from work, and the cost implications for the
The Cost-effectiveness of Lamotrigine in the Maintenance Treatment of Adults With Bipolar I Disorder

criminal justice system and substance abuse services is likely further to improve the pharmacoeconomics of maintenance therapies that avoid acute episodes of bipolar depression and mania.

Conclusions

ICERs are an appropriate outcome variable for efficiency decision making in health economic evaluation. To date, few economic studies in BD have presented ICERs. In light of this, we constructed an economic model that generated ICERs for lamotrigine, lithium, and no-maintenance treatment using pivotal trial data, and have made an indirect comparison with olanzapine. Our model indicates that lithium and lamotrigine are cost effective in patients with a recent episode of mania.

We have presented the assumptions that were used to structure and populate our model and have indicated where the outputs are sensitive to such assumptions. We also highlighted potential limitations of our approach and acknowledge their significance. Despite the limitations, we feel this study has resulted in useful and informative economic data in an under-researched area.

We believe that our economic model of maintenance treatments for BD-I provides a good baseline on which future models can be developed. We recommend that future models should consider inclusion of a longer time perspective and a broader costing perspective. We believe that such models are likely to provide even more optimistic cost-effectiveness outputs for maintenance treatments in BD.

DISCLOSURES

Funding for this research was provided by GlaxoSmithKline (GSK) and was obtained by author Neill W. Calvert. Authors Steven P. Burch, Alex Z. Fu, and Thomas R. Thompson are current or former employees of GSK. Calvert and author Penny Reeves were commissioned by GSK specifically for this research. Calvert served as principal author of the study. Study concept and design were contributed by Calvert and Burch, with input from the coauthors. Data collection was the work of Calvert, Fu, and Reeves, with input from Burch; data interpretation was the work of Calvert, Burch, and Fu, with input from Thompson. Drafting of the manuscript and its revision were primarily the work of Calvert, Burch, and Thompson, with input from the coauthors.

REFERENCES


Drug and Medical Cost Effects of a Drug Formulary Change With Therapeutic Interchange for Statin Drugs in a Multistate Managed Medicaid Organization

BRIAN MEISSNER, PharmD, PhD; MICHAEL DICKSON, PhD; JUDY SHINOGLE, PhD, MSc; C.E. REEDER, PhD; DEA BELAZI, PharmD, MPH, PAHM; and VIRAN SENEVIRANTE, PharmD

ABSTRACT

OBJECTIVE: Therapeutic interchange (TI) interventions are commonly used to manage pharmacy benefit costs. While several studies have considered the effect that TI interventions have on drug costs, most have not considered the effect they have on medical management costs. The purpose of the present study was to assess drug cost and drug therapy management costs of a TI intervention following a change in the drug formulary for 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) drugs, including the conversion of atorvastatin from formulary to nonformulary status.

METHODS: A retrospective, quasi-experimental within-subjects design was used in this study. Administrative claims data were obtained from a select northeastern segment of a multistate Medicaid managed care organization (MCO). To be included in the study, patients had to meet the following criteria: (1) they must have had a minimum of 3 atorvastatin prescriptions during a 6-month enrollment phase, (2) they must have been continuously enrolled throughout the 900-day study period, and (3) they must have switched from atorvastatin to another statin between April 1, 2003, and July 31, 2003. The day of the switch from atorvastatin marked for each patient the end of the 12-month pre-TI period and the beginning of the 12-month post-TI period. Two separate dependent variables were developed: (1) statin drug costs (statin cost + dispensing fee) and (2) the costs paid by the MCO for the medical management of statin therapy, including office visit costs and the medical laboratory costs of measuring lipids and creatine kinase, and of checking liver functions. To estimate expenditures over 24 months, a panel analytic technique was used that allows each patient to serve as his or her own control. Multivariate models were used to assess the effects of the TI policy while controlling for age, gender, adjunctive dyslipidemia therapy, comorbidity, presence of a prior coronary artery event, statin compliance, cardiologist management, and disease severity.

RESULTS: Of the 3,636 patients who met the study inclusion criteria and were converted from atorvastatin to an alternate statin drug, 129 patients (3.5%) switched back to atorvastatin following the TI. The average statin cost per claim in the 12-month post-TI period was $70.93, 9.5% less than the average cost in the 12-month pre-TI period ($78.40). The average cost per patient per year (PPPY) for statin laboratory tests (lipid panels, creatine kinase tests, and liver function tests) increased by 31.5% to $16.15 in the post-TI period compared with $12.28 PPPY in the pre-TI period, and medical office visit costs increased by 44.9% to $20.70 PPPY in the post-TI period compared with $14.29 PPPY in the preperiod. These increased costs related to the medical management of statin therapy were overwhelmed by an 11.7% reduction in statin drug costs, from $793.69 PPPY in the pre-TI period to $701.01 PPPY in the post-TI period, resulting in a net 10.0% reduction for combined statin costs and related medical costs, from $820.27 PPPY in the pre-TI period to $737.87 in the post-TI period. After limiting the analysis to patients who did not convert from atorvastatin to pravastatin (which cost more than atorvastatin before the rebate) and controlling for the influence of potential confounders, statin expenditure decreased by 33% (P < 0.001). Multivariate models indicated no statistically significant differences in the costs related to the medical management of statin therapy after the TI compared with before the TI.

CONCLUSIONS: Total costs for medical management of dyslipidemia with statin therapy decreased following implementation of the TI intervention for atorvastatin

KEYWORDS: HMG-CoA reductase inhibitors (statins), Therapeutic interchange, Pharmacy expenditure, Ambulatory expenditure, Panel estimation

J Manag Care Pharm. 2006;12(4):331-40

Authors

BRIAN MEISSNER, PharmD, PhD, is an assistant professor, University of Montana, College of Health Professions and Biomedical Sciences, Missoula; MICHAEL DICKSON, PhD, and C.E. REEDER, PhD, are professors, University of South Carolina, College of Pharmacy, Columbia; JUDY SHINOGLE, PhD, MSc, is a health scientist, RTI International, Washington, D.C.; DEA BELAZI, PharmD, MPH, PAHM, is associate vice president, clinical programs, PerformRx, Philadelphia, Pennsylvania; VIRAN SENEVIRANTE, PharmD, is senior clinical pharmacist, Amerihealth Mercy/PerformRx, Philadelphia, Pennsylvania.

AUTHOR CORRESPONDENCE: Brian Meissner, PharmD, PhD, Assistant Professor, University of Montana, College of Health Professions and Biomedical Sciences, 32 Campus Dr., SB 320, Missoula, MT 59812-1522. Tel: (406) 243-4555; Fax: (406) 243-4353; E-mail: brian.meissner@umontana.edu

Copyright© 2006, Academy of Managed Care Pharmacy. All rights reserved.
using a pretest/posttest study design. They found that drug acquisition costs decreased by 21% ($56,875 versus $71,693) and that serum lipid levels did not change following the TI. Similarly, Patel et al. found a 21.9% decrease in drug acquisition costs during a 2-month period and no differences in the ability to achieve National Cholesterol Education Program goals following a TI from pravastatin to lovastatin. Fugit and Resch used a similar patient population and study design but limited the evaluation to individuals already at the low-density lipoprotein cholesterol (LDL-C) goal prior to the TI (simvastatin to lovastatin). In the study by Fugit and Resch, a pharmacist-managed hyperlipidemia clinic was utilized during the study period, making the percentage change in TI expenditure results difficult to interpret.

Ito et al. used a prospective pretest/posttest study design within a VA population to examine patients converted from pravastatin to simvastatin with a focus on achieving individual lipid goals. After considering costs directly related to the TI program (laboratory and personnel time, including physician, nursing, pharmacist, and technician time) and drug acquisition, TI costs totaled $40,644 for the first year because of program implementation costs. This resulted in an increase of $39.12 per patient per year (PPPY) following the TI although the actual drug cost decreased by $0.23 per person. Furthermore, the TI program caused an additional 25% (P<0.001) of patients to achieve LDL-C goal following the TI. Moisan et al. examined the influence of a TI from lovastatin or pravastatin to simvastatin or fluvastatin using a pretest/posttest study design. Based on health care service expenditure (laboratory and physician visits) and drug acquisition costs, the TI resulted in an average monthly savings of $18.30 per patient. Moisan et al. also found that the proportion of patients meeting LDL-C goal increased by 18.2%.

Hilleman et al. used a pretest/posttest study design to assess the influence of a TI from pravastatin or simvastatin to atorvastatin in patients with coronary artery disease. This study was conducted in a university-affiliated hospital and outpatient clinics and limited its economic analysis to drug acquisition costs. Conversion to atorvastatin resulted in a savings of $558 PPPY. Billups et al. examined both the clinical and economic outcomes associated with a pharmacy-intensive conversion program in which patients were switched from doses of simvastatin up to 40 mg per day to equipotent doses of lovastatin within a group-model health maintenance organization (HMO). They found that the proportion of patients at LDL-C goal increased from 75.9 to 79.1% (P<0.001), and the mean alanine aminotransferase (ALT) levels, a measure of safety, were 26.9 IU/L before and 26.4 IU/L after the conversion (P=0.134). After considering drug costs and appropriate monitoring costs, they found that the total cost for statin therapy decreased by $1.6 million, or $4.14 per member per year (PMPY), across the entire HMO membership of nearly 400,000.

Cheetham et al. also documented the clinical effectiveness of converting patients from simvastatin to lovastatin using equipotent doses. Their results indicated a statistically significant reduction in LDL-C: 110.9 mg/dl during the preconversion phase compared with 108.4 mg/dl during the postconversion phase (P<0.001).

Taylor et al. and Grace et al. used decision analysis models to examine the influence of a TI from atorvastatin, fluvastatin, or pravastatin to either cerivastatin or simvastatin in a patient group from the Walter Reed Army Medical Center. Both of these studies used the same decision analytic model to determine the potential cost savings associated with TI. Interestingly, these were the only 2 of a few studies to consider additional costs related to TI, such as additional medical visits and laboratory tests. Model uncertainties included adverse events (minor and serious), physical complaints, and medication tolerance. The authors assumed that any physical complaints/adverse events would generate 1 to 2 physician visits and laboratory-related costs. All probabilities and costs (drug, laboratory, and physician) were calculated from the study population. After considering the conversion cost, including medication, laboratory monitoring, adverse events, and personnel costs, the researchers found a $115 per-patient savings in the first year following the TI.

Although numerous studies have examined the economic influence of a statin TI, a few limitations compromise the usefulness of the results of prior studies. All of the studies employed a simple pretest/posttest study design without a control group. Additionally, no multivariate statistical analyses were used to address potential confounding variables such as disease severity, which is often predictive of the intensity of health resource utilization and costs. Lastly, only a few studies included additional resource utilization costs associated with the statin TI; yet even these did not control for confounding variables. Given the limitations in previous work, this study will examine the economic outcomes, including statin acquisition costs and select health care utilization costs, induced by a statin TI. Furthermore, this study enhances the methodological and statistical robustness of prior studies by utilizing a panel analytic technique allowing the individual to serve as his or her own control and permitting consideration of an explicit time component during the study period. The present study was conducted from the perspective of a third-party Medicaid payer.

**Methods**

This study was conducted using data from the northeastern market segment of a Medicaid MCO with approximately 330,000 beneficiaries. This study was reviewed and approved by the University of South Carolina Institutional Review Board.

**Description of the TI Intervention**

Significant rebate incentives contributed to the decision by the...
Drugs and Medical Cost Effects of a Drug Formulary Change With Therapeutic Interchange for Statin Drugs in a Multistate Managed Medicaid Organization

Pharmacy and therapeutics committee of the Medicaid MCO to change the formulary status of atorvastatin from preferred drug to nonformulary and to implement a TI intervention to convert atorvastatin patients to other statins. The confidentiality of rebate contract prices preclude the presentation of cost data specific to these contracts; therefore, the cost data presented in this study understates the actual value (after rebate revenues) to the MCO of this TI intervention.

Implementation of the drug formulary change occurred in multiple phases. Beginning in April 2003, all physicians under contract with the managed Medicaid provider were notified by letter that atorvastatin would become a nonformulary drug on July 1, 2003, and that all patients on atorvastatin would need to be converted to an alternate formulary statin (simvastatin, lovastatin, pravastatin, or fluvastatin) since the health plan would no longer reimburse for atorvastatin. No treatment guidelines were developed to encourage use of a specific statin as a therapeutic alternative to atorvastatin or to ensure equipotent doses of the alternative statin. Thus, the choice and dose of the alternate statin were determined entirely by each patient’s prescriber.

In May 2003, physicians prescribing and pharmacies dispensing atorvastatin to health plan beneficiaries were sent a letter reminding them of the formulary change with the specific names of patients who were taking atorvastatin. In collaboration with the state’s regulatory agency, patients were also sent letters explaining that they would be converted to another statin in the upcoming months.

On July 1, 2003, the health plan modified the drug claim adjudication system so that when a patient presented with either a new prescription or refill request for atorvastatin, the claim would be rejected with a nonformulary message to the pharmacist. As a consequence of this rejection, pharmacists were required to contact the prescribing physician to change the prescription to a formulary statin. For a patient to remain on atorvastatin and have his or her prescription reimbursed by the health plan, the prescribing physician was required to submit a prior authorization request explaining the rationale for keeping the patient on atorvastatin. For a patient to remain on atorvastatin after implementation of the drug formulary conversion, 2 conditions were necessary: (1) the physician was required to indicate that the patient was previously not successful using any of the multiple formulary statins, and (2) the PBM could document prior statin use. There were no other statin formulary changes during the time of this study.

A quasi-experimental design was used to evaluate the medical management costs and pharmacy costs following a statin TI. Since the TI process used by the Medicaid MCO did not permit identification of a control group, a panel estimation technique was used, which is a more robust methodology than a traditional pretest/posttest cohort because the panel estimation method allows each patient to serve as his or her own control; thus, the design has a within-subjects control group. Furthermore, the panel estimation method explicitly considers multiple measurements of both the dependent variable and confounders throughout the study’s time frame.16 (See Statistical Methods section.)

Patients were followed for a total of 900 days, which included a 180-day enrollment preperiod, a 360-day pre-TI period, and a 360-day post-TI period. Within the two 360-day measurement periods, 4 quarterly panels (3 months each) were created for a total of 8 quarterly panels for the entire study period. Based on the clinical literature and prior statin TI studies, the 2-year study period is appropriate to examine the economic expenditures related to the TI.

This study evaluated administrative claims to determine patients who switched from atorvastatin during a 4-month (April 1, 2003, to July 31, 2003) time frame. Since not all patients converted on the same calendar day, the TI date determined the study time frame for each subject. The 360-day pre-TI period (panels 1-4) began 360 days before the TI conversion date and ended the day before the conversion date. Likewise, the 360-day post-TI period (panels 5-8) began the day of the TI and ended 360 days thereafter. Thus, the date of the first nonatorvastatin statin claim was defined as day 1 of panel 5 and day 1 of the 360-day post-TI period. The day prior to the first nonatorvastatin claim was defined as day 180 of panel 4 and day 360 of the pre-TI period.

To be included in the study, a minimum of 3 atorvastatin claims per patient was required during the 180-day enrollment period. This criterion was intended to ensure that only patients stabilized on statin therapy were included in the study. New statin users were excluded as they had the potential to artificially inflate the pre-TI expenditure, given the laboratory monitoring associated with initial prescribing and monitoring. To ensure that patients who went through the TI had a minimum of 1 year of data following the TI and were continuously enrolled throughout the study period, the switch from atorvastatin to another statin must have occurred between April 1, 2004, and July 31, 2004.

The 3 main dependent variables were statin drug cost, statin therapy medical management cost, and combined statin drug and medical management cost. To ensure an even comparison of costs across the 2-year study time frame, post-TI costs were discounted by 5% to account for price inflation. Statin drug costs comprised the statin ingredient cost plus a dispensing fee. These costs were summed every 3 months. Statin rebate information was not available; thus, statin cost estimates in the present study overstate actual MCO statin drug costs after consideration of rebate revenues. As a result, several 1-way sensitivity analyses were performed using an upper-bound rebate percentage of 40% and a lower-bound of 15% for the statins. Since the actual rebate percentages are unknown, these lower- and upper-bound estimates are an educated guess of a reasonable range of
Figure 1 Presentations and Sample Size—Medicaid MCO

Patients With at Least 1 Statin Pharmacy Claim During the Enrollment Period (From April 1, 2003, to July 31, 2003) 6,992 (2.1% of Eligible Members)

Patients With at Least 1 Atorvastatin Pharmacy Claim During the Enrollment Period (180-Day Period Prior to the 12-Month Preperiod) 5,473 (78.3% of Statin Users)

Patients With 3 or More Atorvastatin Pharmacy Claims During the Enrollment Period 4,801 (87.7% of Atorvastatin Users)

Patients With a TI Between April 1, 2003, and July 31, 2003 3,690 (76.9% of Atorvastatin Users With at Least 3 Pharmacy Claims)

Continuously Enrolled Patients During the 180-Day Enrollment and 2-Year Study Period 3,636 (75.7% of Atorvastatin Users With at Least 3 Pharmacy Claims)

MCO = managed care organization; TI = therapeutic interchange (of atorvastatin to another statin drug).

The multivariate models addressed potential confounding through the use of several independent variables. Age and gender were controlled, but race was unavailable. Level of comorbidity was measured using the latest version of the chronic disease score. To determine the level of coronary artery disease burden, a disease staging procedure based on work by the Medstat Group was used. The scale ranges from 0 to 4, where 0 indicates no complications and stage 4 indicates death. To address patients’ medication-taking behavior, the maximum gap in statin therapy was computed and used as a proxy to predict an individual’s compliance behavior, such as scheduling and meeting appointments. The maximum gap in therapy captures the largest theoretical period of time an individual is without a therapy. A dichotomous variable was used to indicate individuals who had visited cardiologists since these individuals may require more intensive management than those managed by primary care physicians. Furthermore, a variable to indicate patients on certain medications that may influence the intensity of ambulatory services was included in the model. For example, concomitant multiple lipid-lowering agents and medications that interact with statins or increase serum lipid levels may be associated with greater overall resource use. A dichotomous variable was included to indicate unstable patients who switched statin therapy before or after TI since switching statin therapy may result in additional physician visits. As cardiac events may substantially increase expenditure, a dichotomous variable was created using ICD-9-CM and CPT codes to capture major cardiac events such as acute myocardial infarction, other acute and subacute forms of ischemic heart disease, angioplasty, coronary artery bypass graft, or placement of a coronary stent.

Statistical Methods

Basic descriptive statistics were used to describe the study population. Paired t tests were conducted to determine if significant differences in expenditure existed between the pre-TI and post-TI periods. Panel estimation regression modeling was used to control for potential confounding and to permit each patient to serve as his or her own control. A unique advantage of panel estimation is that it permits estimation of unobserved characteristics (e.g., smoking status, family medical history) not captured in the data.

A basic panel analytic model uses the following equation:

\[ Y_{it} = \alpha_i + \beta_i X_{it} + \epsilon + u_i \]

where \( i \) is the subject; \( t \) is the time component; \( Y \) is the dependent variable; and \( Y_{it} \) is a linear function of the intercept \( \alpha_i \), the parameter estimates \( \beta_i \), the independent variables \( X_{it} \) (some of which may be time-varying while others may be time-invariant), the time-invariant individual specific unobserved error term \( \epsilon \) (also called the unobserved effect), and the time-variant error component \( u_i \). More specifically, \( \epsilon \) is an unobserved patient effect that represents all factors influencing expenditure that do not change over time, such as family history.
Both error terms (\(e_i\) and \(u_i\)) are assumed to be independent and normally distributed with 0 mean and constant variance. All multivariate models were examined for multicollinearity. Both SAS version 8.2 and Stata version 8 were utilized for descriptive and multivariate statistics. An \(\alpha\) level of 0.05 was used for all multivariate models.

Results

The final study population consisted of 3,636 patients who were continuously enrolled throughout the entire study (pre-TI and post-TI period (Figure 1). Of the 3,636 atorvastatin patients involved in the TI intervention, 3.5\% (129) converted back to atorvastatin during the 12-month post-TI period. The majority of study participants were female, 67.4\% (2,454), with an average age of 63 (SD, 12.7). Interestingly, 97.5\% of the final study population had experienced a major cardiac event. As a result of the TI, 78.4\% (2,851) of the study population converted to either lovastatin or pravastatin (Table 1).

The mean cost per claim for a statin lab increased from $6.94 (SD, 16.8) to $8.06 (SD, 11.5), while the average office visit claim (related to statin therapy) increased from $40.29 (SD, 602.80) to $42.21 (SD, 618.7). A combination of an increase in ambulatory service utilization and an average cost per claim (unadjusted) contributed to a 38.6\% increase in statin therapy medical management cost per person ($26.58 Pppy vs. $36.86 Pppy; \(P < 0.001\)), a 31.5\% increase in statin therapeutic and adverse-event laboratory monitoring costs per person ($12.28 Pppy vs. $16.15 Pppy; \(P < 0.001\)), and a 44.9\% increase in statin office visit expenditure per person ($14.29 PPPY vs. $20.70 PPPY; \(P < 0.001\)) (Table 2). These increased expenditures are primarily the result of an increase in the average cost/claim. When limited to expenditures related to the medical management of statin therapy, the multivariate models did not indicate an increase in expenditure after controlling for potential confounding variables (Table 3).

The total number of statin prescriptions dispensed for these 3,636 patients was 2.3\% less in the post-TI intervention period than in the pre-TI period (35,935 vs. 36,807 statin claims), 0.82 claims Pppm (SD, 0.31) in the post-TI period versus 0.84 claims PPPm (SD, 0.24) in the pre-TI period. This result is consistent with the maximum-gap-in-therapy compliance measure, which increased from 30.4 days (SD, 44.2) to 63.1 days (SD, 86.2) following the TI program.

Among statin claims, atorvastatin claims accounted for 99.8\% (36,748) of all statins dispensed in the pre-TI period (Table 4). In the post-TI period, atorvastatin claims accounted for only 1.4\% (509) of all statin claims. The prior authorization process permitted individuals to switch back to atorvastatin if they reportedly were not successful using any of the other statins, thus explaining the 509 atorvastatin claims during the post-TI period. The mean statin cost per claim declined by 9.5\%, from $78.40 to $70.93 (\(P < 0.001\)), and resulted in a 11.5\% decrease, from $66.14 PPPM (SD, 20.12) in the pre-TI period to $58.41 PPPM (SD, 35.68) after the TI (Table 4).

Pravastatin had the largest percentage (38.3\%) of statin claims in the post-TI period even though pravastatin was more than 3 times more expensive than generic lovastatin, the cheapest statin, and 40\% more expensive, before rebate, than atorvastatin (Table 4). The absence of rebate contract information makes this switch from atorvastatin to pravastatin appear to be irrational for this Medicaid MCO. As a consequence of the high utilization and high price of pravastatin following the TI relative to the price of atorvastatin during the pre-TI period, no cost differences were found between the 2 periods after controlling for confounders (Table 3). The calculated average cost per claim for pravastatin does not reflect the discount resulting from the contract rebates, so pravastatin patients were excluded from the multivariate analysis. When the model was limited to patients who were not converted to pravastatin, the statin costs decreased by 33\% (\(P < 0.001\)) after controlling for explanatory variables (Table 4). Discussions with the pharmacy benefit administrators revealed that, in fact, the cost for pravastatin was significantly less than atorvastatin after rebates were considered.

Total statin expenditure (unadjusted for potential confounders) but discounted at a 5\% rate decreased by 10.0\%, from $820.27 PPPY in the pre-TI period to $737.87 PPPY in the post-TI period (\(P < 0.001\), Table 2). This change is driven primarily by an 11.7\% decrease in statin expenditure per person, which underscores the high drug cost of statins as compared with the medical costs for office visits and laboratory tests necessary to ensure safe and effective use of statin pharmacotherapy. Similar to the statin expenditure multivariate models, the total statin expenditure multivariate models did not indicate a statistically significant difference following the TI (Table 3). However, when the models were limited to those individuals who did not convert to pravastatin, TI resulted in a 33\% (\(P < 0.001\)) decrease in total expenditure, which is consistent
with the statin expenditure models.

Sensitivity Analysis

Based on the total statin expenditure related to the TI before (medical management expenditure, $96,646; statin drug cost, $2,885,860) and after (medical management expenditure, $134,026; statin drug cost, $2,548,898), statin costs would only need to decrease by 1.2% in order to account for the additional costs related to the medical management of statin therapy following the TI. When a 15% discount rate was applied to the post-TI statins, the multivariate models (including pravastatin patients) resulted in an 18% (P < 0.001) decrease in total expenditure. When a discount rate of 40% was applied, the estimated total expenditure decrease (when pravachol patients were included) increased to 50% (P < 0.001).

Discussion

Results of this study show that total medical management and statin drug costs decreased following a statin TI intervention. The decrease in total statin cost was driven primarily by the estimated 11.7% reduction in statin drug acquisition cost (unadjusted for potential confounders), which represented 97% of the total expenditure (medical management and statin cost) in the pre-TI period and 97% in the post-TI period. These findings were validated using multivariate models after adjusting for study design artifacts (including the exclusion of patients converting to pravachol) and sensitivity analyses. These results highlight the high acquisition cost of statins relative to the reimbursement claims for laboratory costs and physician encounters necessary for the appropriate management of patients on statin therapy.

Preliminary analyses produced varying estimates due to the distribution of statins to which patients were converted. First, it was determined that almost 40% of the study population was converted to a statin that was 40% more expensive (pravastatin) than atorvastatin. This pharmacy cost was offset by the other 60% of the patient population who were converted to statins that were between 12.1% (fluvastatin) and 57% (lovastatin) less expensive than atorvastatin. As a result, the multivariate models differed when the population was limited to those converted to pravastatin and those converted to another less-expensive statin. The multivariate model including all statin users indicated no difference in statin expenditure after the TI. This finding can be attributed directly to the higher drug cost of pravastatin relative to atorvastatin. In contrast, the multivariate model limited to nonpravastatin patients found that statin expenditure decreased by 33% following the conversion, which can be attributed to a lower drug cost relative to atorvastatin. This decrease in statin expenditure is driven primarily by the lower cost per statin claim resulting from the statin TI and secondarily by a 2.3% decrease in the number of statin claims following the TI.

As stated in the Methods section, statin rebates were not considered, which resulted in an overestimate of the actual cost paid by the MCO. Due to the confidentiality of rebate contracts, it is difficult to assess the true cost difference or magnitude of
Drug and Medical Cost Effects of a Drug Formulary Change With Therapeutic Interchange for Statin Drugs in a Multistate Managed Medicaid Organization

change among the different statin drugs in the post-TI period as compared with the pre-TI period. This situation is further confounded by the fact that almost 40% of the patients were converted to pravastatin, which was about 40% more expensive than atorvastatin in direct drug cost before rebates. However, the break-even analysis shows that even a minimal reduction in statin acquisition costs of 1.2% or more would result in total expenditure savings. These expenditure reductions are consistent with other published studies, which have shown a statin expenditure reduction of between 10% and 58%.6,8,14,15

This was the first study to explicitly assess the medical management expenditure associated with statin therapy following a TI intervention. However, findings from other related studies are consistent with these estimates. Moisan et al. separated ambulatory costs from the total costs associated with the TI and found that the average cost for a medical encounter related to cholesterol management was $16.46 (1997 Canadian estimates).10 This figure is much lower than the average ambulatory cost per statin management claim ($36.20 and $37.40 per claim in 2004) found in the present study. A couple of factors besides medical inflation between 1997 and 2004 may explain the difference. The Moisan et al. study was conducted in Ontario.
and thus may not be representative of a managed Medicaid study population in the United States. Furthermore, the patient population and associated costs were derived from the Canadian armed forces.

Except for the Billups et al. study, external validation of these study results is difficult since no previous statin TI study has adequately assessed both related medical costs and pharmacy costs of a drug formulary change for statins and the associated TI intervention.\textsuperscript{12} Billups et al. found an overall PMPY decrease in antihyperlipidemic drug costs and a slight increase in additional laboratory costs resulting from the statin TI, although no statistical tests were conducted. Despite study limitations, Moisan et al. was one of the few papers that considered physician, laboratory, and drug expenditure.\textsuperscript{10} They found that the average monthly cost savings were $6.56 per patient. In contrast, the present study estimated $6.86 (based on descriptive statistics) in cost savings per statin patient per month, which is remarkably similar to that found in Moisan et al. Taylor et al. and Grace et al. used decision analysis to estimate the cost associated with converting patients at the Walter Reed Army Medical Center from atorvastatin, fluvastatin, or pravastatin to either cerivastatin or simvastatin to either cerivastatin or simvastatin.\textsuperscript{14,15}

Similar to the present study, the studies of Grace et al. and Taylor et al. included ambulatory expenditure (both laboratory and general statin management cost), pharmacy cost, and personnel cost. After the first year, savings of $115 per patient were realized. This is consistent with the findings of the present study in which the unadjusted data show a mean statin cost savings of $92.68 PPPY following the TI intervention, which became net savings of $82.40 PPPY after the addition of medical management costs associated with statin drug therapy. This cost difference of $82.40 versus $115 may be attributed to

### Table 4: Mean Statin Expenditure* Per Claim During Pre-TI and Post-TI Periods

<table>
<thead>
<tr>
<th>Statin Formulary Status</th>
<th>No. of Claims (%)</th>
<th>Mean Cost Per Claim ($) [SD]</th>
<th>Formulary Status</th>
<th>No. of Claims (%)</th>
<th>Mean Cost Per Claim ($) [SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin† (Altocor)</td>
<td>NF</td>
<td>3 (0)</td>
<td>50.60 [4.68]</td>
<td>F</td>
<td>685 (1.9)</td>
</tr>
<tr>
<td>Lovastatin plus niacin (Advicor)†</td>
<td>NF</td>
<td>0 (0)</td>
<td>–</td>
<td>F</td>
<td>4,115 (11.4)</td>
</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>NF</td>
<td>0 (0)</td>
<td>–</td>
<td>F</td>
<td>6 (0)</td>
</tr>
<tr>
<td>Fluvastatin (Lescol)</td>
<td>NF</td>
<td>1 (0)</td>
<td>28.10 [-]</td>
<td>F</td>
<td>3,005 (8.3)</td>
</tr>
<tr>
<td>Fluvastatin (Lescol XL)</td>
<td>NF</td>
<td>9 (0.02)</td>
<td>58.75 [11.37]</td>
<td>F</td>
<td>4,167 (11.5)</td>
</tr>
<tr>
<td>Atorvastatin (Lipitor)</td>
<td>F</td>
<td>36,748 (99.8)</td>
<td>73.40 [17.88]</td>
<td>NF</td>
<td>509§ (1.4)</td>
</tr>
<tr>
<td>Lovastatin (generic)</td>
<td>NF</td>
<td>2 (0)</td>
<td>23.19 [23.71]</td>
<td>F</td>
<td>9,630 (26.7)</td>
</tr>
<tr>
<td>Pravastatin (Pravachol)</td>
<td>NF</td>
<td>34 (0.09)</td>
<td>91.14 [28.66]</td>
<td>F</td>
<td>13,770 (38.3)</td>
</tr>
<tr>
<td>Simvastatin (Zocor)</td>
<td>NF</td>
<td>10 (0.02)</td>
<td>15.50 [3.79]</td>
<td>F</td>
<td>48 (0.13)</td>
</tr>
<tr>
<td>Rxs PPPM</td>
<td>F</td>
<td>–</td>
<td>0.84 [0.24]</td>
<td>F</td>
<td>0.82 [0.31]</td>
</tr>
<tr>
<td>Total/average</td>
<td>–</td>
<td>36,807</td>
<td>$78.40 [19.09]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* All costs were discounted at a 5% rate.
† The pre-TI period commenced 12-months before the switch, and the 12-month post-TI period commenced the day of conversion to a non-atorvastatin prescription between April 1, 2003, and July 31, 2003.
‡ Branded generic.
§ The prior authorization process permits individuals to switch back to atorvastatin if they were not successful using any of the other statins, thus explaining the 509 atorvastatin claims during the post-TI period.
|| P <0.001; analysis was limited to the mean total statin expenditure pre-TI period versus post-TI period and not the individual statins.
F=formulary; NF=nonformulary; PPPM=per patient per month; TI=therapeutic interchange.
a greater reduction in drug acquisition cost by Grace et al. and Taylor et al. as compared with the 11.7% reduction found in the present study.

**Limitations**

Foremost among the several limitations of this study was the selective method of determining the administrative claim records to include in the study. Patients had to have demonstrated continued use of atorvastatin. Therefore, the effects of this TI policy on all affected Medicaid recipients or the overall statin budget for this multistate Medicaid MCO are not evaluated.

Second, the pharmacy claims database only captured pharmacy claims that were adjudicated by the PBM. Thus, prescription claims that were either paid in full by the patient or paid under dual pharmacy benefits coverage were not captured. No data are available to determine the frequency of these events. However, unlike patients within private employer-sponsored health plans, these Medicaid patients are required to meet household income levels that would limit their ability and willingness to pay out of pocket for their prescription medication.

Third, the confidentiality of manufacturer rebate contracts precludes assessment of total actual MCO cost savings associated with drug TI interventions. As observed in the present study, the higher cost of pravastatin compared with atorvastatin seems counterproductive to MCO cost management in the absence of information about drug manufacturer rebate revenues.

Fourth, this study did not measure humanistic service outcomes. While no adverse patient effects, including dissatisfaction, were anticipated from this TI intervention, this category of outcome should be measured in future studies.

Fifth, the enrollment criteria restricted the patient population to a group of patients who were demonstrated atorvastatin users, thus limiting external validity. Additional research is needed to identify the influence of a statin TI intervention on individuals not stabilized on statin therapy. As a result, the conclusions of this study are conditional on a select patient population.

Sixth, the personnel time and administrative costs associated with the implementation of the TI intervention were not assessed since few administrative resources were required. However, there was an unknown cost for the plan administrator for contracting with a third party to generate and send letters to the pharmacies, physicians, and patients. On the other hand, the cost of pharmacy personnel at the managed Medicaid plan for reviewing prior authorizations is primarily a fixed cost and would not be expected to add to the administrative cost of this TI intervention; this may not be a relatively fixed cost for other MCOs. Finally, the personnel and administrative costs incurred by community pharmacies in calling physicians to convert patients from atorvastatin to other statins were also not measured. There were, of course, community pharmacy costs and some PBM and health plan administrative costs incurred that would reduce the total system costs savings associated with this TI intervention.

**Conclusions**

Total expenditures for drug costs and the costs of medical management of hyperlipidemia with statin drug therapy decreased by 10% before consideration of rebate revenues, following the implementation of a TI intervention to convert atorvastatin patients to other statin therapy. The savings in drug costs overwhelmed the increase in medical management costs related to statin therapy. Total costs after consideration of rebate revenues would exceed the 10% cost savings found with this TI intervention in a managed Medicaid MCO. Future research on TI interventions might include clinical effectiveness, safety, and humanistic service outcomes in addition to the drug and medical management costs assessed in the present study.

**DISCLOSURES**

No outside funding supported this study. Author Brian Meissner served as principal author of the study. Study concept and design were contributed by Meissner and authors Michael Dickson, Judy Shincole, C.E. Reeder, and Viran Senevirante. Data collection was the work of Senevirante and author Dea Belazi; data interpretation was primarily the work of Meissner and Shincole, with input from the coauthors. Writing of the manuscript was primarily the work of Meissner and Dickson, with input from Reeder and Senevirante; its revision was primarily the work of Meissner, with input from Reeder, Dickson, and Belazi. The authors disclose no potential bias or conflict of interest relating to this article.

**REFERENCES**


When skimming through the piles of journals that arrive in your mailbox every month, do you have a quick method to bookmark high-quality studies for later review? Can you read the abstract and essentially “judge a book by its cover?” A model was recently published to do exactly that.

Starting with the traditional evidence-based medicine “PICO” model of framing a clinical question, the author expanded the idea into “PP-ICONS” and applied it to evaluation of clinical literature (Table 1).

Given the large number of potential studies we can read each month, it is critical to spend our time on those that are most relevant and valid; therefore, if the abstract fails to meet the PP-ICONS criteria, our time may be better spent elsewhere. Obviously, no tool is perfect in every situation, and PP-ICONS is no exception. While being better suited to treatment and prevention studies, it can also be used in diagnostic and screening studies.

If we desire to test-drive our new tool and look at the asthma health care utilization study by Allen-Ramey et al. in this issue of JMCP2 how does the abstract perform? The problem presented is one faced by almost any large managed care organization or solo physician practice—asthma. The patients were aged 4 to 55 years and pulled from a proprietary administrative claims database. They were required to have an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for asthma on a medical or facility claim, or at least 2 pharmacy claims for an asthma medication. Since the study was retrospective, it was difficult to control for all relevant patient characteristics, such as disease severity. In order to account for different characteristics (covariates), a propensity model was created to match patients evenly into both treatment groups.

The intervention tested was inhaled corticosteroids (ICSSs) and montelukast (MON), while the active comparator was ICSSs and salmeterol (SAL). Of immediate concern is the time period selected by the authors: 1998-1999. During this time, the combination product Advair (fluticasone/salmeterol) was not well chosen. When reviewing the outcome results, a significant discrepancy is immediately noted. The SABA fill rate was significantly higher among ICS/MON patients than ICS/SAL (adjusted OR = 0.25; 95% CI, 0.08-0.79) that it caused the total hospitalizations, if ICS/MON required more SABA use and was not recommended based on the preponderance of guideline evidence? The abstract did not provide more details, but, if the results do not fit expectations, either the reference NHBLI guidelines may be flawed or the propensity model created for the study may need correction. Upon further reading, 2 key points in the tables are found that may partially explain the contradiction.

First, Table 1 illustrates that there was no difference in the ED/hospital rate for the 815 patients who had been treated with ICS previously. Only in the smaller group of 401 patients without prior ICS use was a significant decrease in ED/hospital rates found for the ICS/MON group. The difference was so profound (adjusted OR = 0.25; 95% CI, 0.08-0.79) that it caused the total study population to show a difference on this key patient-
oriented outcome. The distinction that ICS/MON had lower ED/hospital rates in patients without prior ICS use is potentially explained by treatment bias; patients who received MON were likely considered to have less-severe disease based on NHLBI disease classification tables and were therefore less likely to later require emergent care.

The second key point to potentially explain lower ED/hospital rates in the ICS/MON group is the failure to properly categorize disease severity when building the propensity model. Originally buried in the footnotes of Table 1 was the notation that the disease severity covariate was factored into the model as a binary variable: patients were either considered mild intermittent or persistent (mild, moderate, and severe). Overlapping all forms of persistent disease into a single category when they have different treatment regimens and risk for ED/hospital makes the ICS/MON results questionable.

During the editing process, the authors attempted a post hoc classification of disease severity, based on a nonvalidated model from an abstract presented at a conference but otherwise unpublished. (The proxy 4-group classification scheme was not used to construct the propensity model.) Since the model has never been tested against the NHLBI guidelines, the 4 “severity groups” are only estimates of true disease severity. If the estimates are assumed to reflect NHLBI categorization, then only 25% of the study patients should have been included; only patients in class 3 (moderate persistent asthma) or higher generally need add-on therapy with MON or SAL. So, do the 75% of patients included with mild asthma not requiring add-on medications skew the study results showing that ICS/MON lowers the odds of ED/hospital visits? The model design does not measure severity in a way that allows such questions to be answered.

Finally, the number of patients and statistics chosen must be assessed. Including 1,216 patients would typically be considered a large study, but the authors did not discuss why they chose the number 1,216 or if a prestudy power calculation was performed. Using ORs with 95% CIs is standard practice and appropriate for this type of retrospective study.

In conclusion, PP-ICONS has been introduced as a tool for skimming abstracts and selecting relevant studies for further reading. When applied to the study by Allen-Ramey et al., issues of concern were found for the comparator design (ICS/SAL) as well as the outcome put forth by the authors that ICS/MON lowered ED and hospitalization rates. Unidentified treatment bias and failure to adequately classify disease severity may have skewed the results favoring montelukast.

**DISCLOSURE**

The author is a board-certified family physician assigned to Eglin AFB Florida, where he serves as Family Medicine Residency program director, HQ Air Armament Center. The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of any organization, including the U.S. Air Force medical department or the U.S. Air Force. He discloses no potential bias or conflict of interest relating to this editorial.

**REFERENCES**


**Letters to the Editor**

*JMCP* welcomes letters that serve to clarify subjects published in previous issues of the Journal or regarding subject matter of interest to managed care pharmacists. Letters in *JMCP* are not peer reviewed but are subjected to editorial review. Letters should be prepared in a word processing program, preferably Microsoft Word, and submitted electronically at jmcp.msubmit.net. See www.amcp.org for details.
More Evolution of the Evidence in Asthma Disease Management—SMART Versus GOAL Clinical Trials Debate the Cost-Benefit of LABA While the Value of Leukotriene Modifiers, Particularly Montelukast, Is Uncertain

In a previous issue of JMCP, Heaton et al. challenged the value of leukotriene modifiers (LMs) in disease management of asthma. Based on the 3 clinical outcomes—emergency department (ED) visits, hospitalizations for asthma, and the use of oral prednisone ("steroid burst") to indicate exacerbation of asthma—these authors concluded that LM use was not more effective than nonuse. Worse than no improvement in these 3 clinical outcomes, LM users appeared to have more ED visits, a higher rate of hospitalization, and a higher rate of use of oral prednisone bursts. Heaton et al. calculated that LM use added $1.63 per patient per month (PPPM) in costs (in 2002 dollars) for these 3 clinical outcomes compared with LM nonusers diagnosed with asthma.

Coincident to publication of the article by Heaton et al. in JMCP, Martinez suggested, in a commentary published in the New England Journal of Medicine on asthma disease management, that LMs or theophylline might be better alternatives to long-acting beta-agonists (LABAs) in patients not controlled adequately on inhaled corticosteroids (ICSs) alone. While the motivation for this recommendation was primarily concern regarding the safety risk associated with the LABAs, Mintz, in a follow-up letter, decried overstatement of the risk of LABAs and called this “irresponsible,” possibly contributing to suboptimal pharmacotherapy or patient nonadherence.

In advocating the use of LABAs over LMs in asthma patients not controlled on ICSs alone, Mintz attempted to dismiss the product label warning and U.S. Food and Drug Administration (FDA) Public Health Advisory for the LABAs regarding the increased chance of a severe asthma episode in LABA users. Mintz argued that the label warning of risk in the use of LABAs is contradicted by results from the Salmeterol Multicenter Asthma Research Trial (SMART). The FDA analysis of the SMART study concluded that there was a “small increase in the risk of asthma-related deaths with salmeterol use in the SMART study.” The FDA proposed label changes for all salmeterol-containing products in a letter sent by fax to the manufacturer on September 10, 2004. The present prescribing information in the labels for salmeterol and fluticasone with salmeterol, updated March 2, 2006, includes the following language in the black-box warning, “Long-acting beta-agonists such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related deaths. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose ICSs) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.”

Interwoven in the asthma disease management literature and clinical trials is the opportunity for higher rates of improved patient outcomes through more attention to clinical monitoring of titrated dosing of ICSs. The clinical preference for more attention to adequate dosing of ICSs is supported by the GOAL (Gaining Optimal Asthma Control) trial. The focus of this study was to establish the proportion of patients with asthma who could achieve the target level of control with optimal prevention therapy. The study showed that 59% of patients with previously uncontrolled asthma were well-controlled at 1 year with higher doses of fluticasone alone, while 71% of patients were well-controlled with higher doses of fluticasone plus LABA.

While the GOAL trial results showed that LABA might have a role as add-on therapy to ICS in asthmatic patients uncontrolled with ICS alone, the role of LM as add-on therapy to ICS is less certain. A review of 336 citations in the Cochrane Database, including 11 randomized controlled trials (RCTs) performed by Ducharme in 2001 (CD003133), concluded that the addition of an LM to ICS therapy may improve lung function slightly, but this strategy is inferior to increased dosing of ICS. An update in 2004 from a review of 587 Cochrane Database citations, including 16 RCTs, found the accumulated data from the RCTs insufficient to support the use of LM as a substitute for increased dosing of ICS, and there was no overall value of LM in patients undergoing dose tapering of ICS.

The current asthma management guidelines from the National Asthma Education and Prevention Program (NAEPP) Expert Panel of the National Institutes of Health (National Heart, Lung, and Blood Institute), last updated in 2002, classify asthma into 4 distinct categories. “Step 1” for mild intermittent asthma cases involves no daily medication. The “Step 2” category for mild persistent cases involves low-dose monotherapy for prevention. It may require revision subsequent to research published last year. Boushey et al. found the group of patients with mild persistent asthma randomized to no controller (ICS) therapy did not have significantly poorer lung function and experienced no greater frequency of asthma exacerbation than those who received regular treatment. Daily budesonide (ICS) was superior to intermittent budesonide therapy and to daily zafirlukast (LM) therapy in most clinical measures including asthma control and symptom-free days in patients with mild persistent asthma, but daily zafirlukast therapy was not superior to intermittent zafirlukast therapy in any outcome. Based on these and other findings, Boushey et al. estimated that patients...
with mild persistent asthma may require as little as 1 course of inhaled budesonide, on average, every 2 years or oral corticosteroids, on average, once every 8 years. This symptom-driven treatment of mild-to-moderate exacerbations is a radical departure from current guidelines for treatment of mild persistent asthma. The cost savings from a change in treatment of mild persistent asthma from daily medication use to symptom-driven corticosteroid therapy could be large since up to 75% of asthma is mild disease.

The 2002 NAEPP asthma management guidelines might also be updated regarding the recommendations for use of LABAs, based on the Cochrane Database review of 18 RCTs performed by Chroinin et al. and first published in October 2004. The more recent data support the conclusions that (a) combination therapy with ICS and LABA does not increase protection against exacerbations but does improve lung function and asthma symptoms and (b) there is not sufficient evidence to support the initial use of a combination of ICS and LABA over ICS alone. This latter conclusion argues against first-line use of the popular combination of salmeterol and fluticasone (Advair) and provides support for a step-therapy edit imposed by managed care organizations (MCOs).

The clear placement of combination ICS and LABA in only “Step 3” (moderate persistent) and “Step 4” (severe persistent asthma) of the NAEPP guidelines and the Cochrane Database review by Chroinin appear to be at odds with the popularity and sales of Advair. Advair sales in community pharmacies increased by 21.8% in 2005 to $2.83 billion, making it the fifth-highest-sales drug in the United States. For the first 3 months of 2006, Advair was the fourth-highest-expenditure drug in one PBM database, with an average allowed cost of $5.25 per day or $157 per 30-day supply. Worldwide sales of Advair were $3.6 billion in 2005, up 19%, making it the fourth-highest-selling drug in the world. Advair is also one of the most heavily advertised drugs, with $137 million in advertising, and Wall Street analysts have suggested that the sales figures prove that the drug is no longer used in the narrow population of severe asthma patients.

While the LABAs appear to have a minor role in asthma disease management, based on the clinical evidence of cost versus benefit, the LM agents should play an even smaller role and be used as only second-line treatment in asthma disease management. The current (2002) version of the NAEPP asthma management guidelines clearly puts LMs in a minor role. The use of LMs is recommended only for one category of patients, those in “Step 3” with moderate persistent asthma and then only as “alternative treatment” to the “preferred treatment” consisting of low-to-medium-dose ICS + LABA. These asthma treatment guidelines also do not give preference to (a) the use of either theophylline or LM with low-to-medium-dose ICS or (b) an increase in ICS monotherapy into the medium-dose range.

In a crossover study of 20 adults with persistent asthma requiring at least 400 mcg per day of an inhaled steroid, Wilson et al. showed that pulmonary function tests were improved similarly with montelukast or salmeterol. However, salmeterol was superior to montelukast because it required less use of SABA rescue therapy and had better asthma symptom scores. Fish et al., in a study of 948 asthma patients not controlled with ICS, found that salmeterol 50 mcg twice daily was superior to oral montelukast 10 mg daily. For only 1 outcome measure, likelihood of an asthma exacerbation, were the 2 drugs similar over 3 months of therapy. For the 6 other clinical outcome measures—daytime symptoms, percentage of symptom-free days, percentage of rescue-free days, albuterol use, nighttime awakenings, and patient dissatisfaction with how well and how fast the 2 drugs worked—salmeterol was superior to montelukast.

Critecos et al. found potential risk in the use of the LM zafirlukast in older adults in a retrospective analysis of 5 randomized, double-blind, double-dummy studies 4 to 12 weeks in duration of 1,742 patients younger than 50 years and 243 patients aged 50 years or older. Their analyses indicate that inhaled fluticasone controls inflammation effectively in older patients, but zafirlukast did not provide either adequate bronchodilation or the anti-inflammatory activity necessary to achieve effective asthma control in asthma patients older than 50 years. Critecos et al. suggested that the LM may mask inflammation.

In this issue of JMCP, Allen-Ramey et al. conducted an analysis of administrative claims incurred prior to the market introduction of combination salmeterol-fluticasone in an effort to show that dual therapy with montelukast + ICS was similar or better in utilization and cost outcomes compared with dual therapy with salmeterol + ICS. In an accompanying commentary, Crownover points out some of the methodological shortcomings in the analyses by Allen-Ramey et al., including the failure to use the 4-level disease proxy to construct their propensity score (matching) model, which, if used, might have excluded 75% of the cases in that study since only those patients in Step 3 (moderate persistent asthma) or higher generally should be considered for add-on therapy with montelukast or salmeterol.

Allen-Ramey et al. found comparable utilization of rescue medication (oral corticosteroids) for users of combination ICS + montelukast and users of combination ICS + salmeterol and slightly lower odds of ED visits or hospitalization for ICS + montelukast (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.35-0.98). Of perhaps more clinical significance was the higher rate of use of SABAs such as albuterol among the ICS + montelukast patients (RR [relative risk] compared with ICS + salmeterol, 1.33, 95% CI, 1.17-1.52). Previously, Stempel et al. claimed that experimental clinical studies demonstrate that the addition of salmeterol to ICS is superior to the addition of montelukast to ICS and found in their administrative claims analysis that patients in the ICS + salmeterol group had 35% fewer SABA claims compared with patients in the ICS + montelukast group. This higher use of SABAs among ICS + montelukast patients is very similar to the 38% higher use...
of SABAs found among ICS + montelukast patients in the study by Allen-Ramey et al. (Table 3, page 314), an average of 4.36 pharmacy claims for SABAs in the postindex period for ICS + montelukast versus 3.16 for ICS + salmeterol.

It is also noteworthy that Stempel et al. found 63% higher total adjusted asthma costs for patients who received ICS + montelukast (compared with ICS + salmeterol), which is consistent with the finding of Heaton et al. of an additional $1.63 PPPM in costs (in 2002 dollars) for LM users diagnosed with asthma compared with nonusers of LMs diagnosed with asthma.1

Montelukast is on the radar screen of every managed care pharmacist with responsibility for drug benefit costs and determining the value of alternate drug therapy.24 Montelukast had community pharmacy sales of $1.85 billion in 2004, placing it at rank number 14 by expenditure among all brand-name drugs.25 Community pharmacy sales increased by 13% in 2005 to $2.09 billion, making montelukast the ninth-highest-ranked drug in total prescription drug sales.26 Monelukast was used by 50 times more patients than zafirlukast (Accolate), the other LM, and had a discounted allowed charge per day of $3.09 before copayment, or $93 per 30-day supply in the first 3 months of 2006.16 Some of this spending on montelukast is for allergic rhinitis, and Lakomski and Chitre found, in a previous issue of JMCP, that even years prior to the FDA-approved indication for allergic rhinitis, 25% of LM utilization in 2001-2002 was not for asthma.27 Even at 75% of current spending on montelukast, the drug ranks in the top 10 drugs in the United States, second only to combination fluticasone-salmeterol (Advair, rank #5) among the high-expenditure drugs used in treating asthma.

The return on investment for this tremendous spending on montelukast should be of great interest. The Chronic Asthma Protocol 049 in the original FDA drug application for montelukast showed a 4.65% improvement in forced expiratory volume in 1 second (FEV1): 8.71% for montelukast vs. 4.16% for placebo) over 8 weeks of treatment with montelukast in 198 patients versus 133 patients who received placebo.27 A more interesting finding was that for patients who received placebo, the mean percentage of days over the 8 weeks with an asthma exacerbation was 25.67% versus 20.58% for montelukast (P = 0.049). Headache determined to be drug-related occurred more often in the montelukast group, 3.5% vs. 0.7% for placebo.

A meta-analysis of 1 pediatric and 12 adult clinical trials for the primary outcome of the number of exacerbations requiring systemic glucocorticoids found that patients treated with LMs were 60% more likely to require systemic glucocorticoid as a result of exacerbation of asthma symptoms compared with patients on monotherapy with an ICS.28 LMs were also more likely to be withdrawn as a result of inadequate asthma control (RR, 2.5). The study concluded that 400 mcg of beclometasone or 200 mcg of fluticasone is more effective than 10 mcg per day of montelukast or 20 mg of zafirlukast twice daily.

The hope for some potential value of montelukast in a subset of asthma patients with allergic rhinitis was undercut by The Medical Letter consultants who concluded in October 2005 that comparative studies with oral antihistamines and intranasal steroids are necessary, particularly since these 2 categories of therapeutic alternatives cost (much) less than montelukast.29 The current guidelines for the step-wise approach to pharmacotherapy for seasonal allergic rhinitis from the American Academy of Allergy, Asthma & Immunology do not mention LM.30

The evidence of the value of montelukast in patients with a history of both allergic rhinitis and asthma is confined to a single randomized, crossover, placebo-controlled study in 52 patients with symptoms provoked by exposure to cats.31 In a large study of nearly 900 patients, montelukast 10 mg was found to be inferior to fluticasone nasal spray 200 mcg per day in controlling symptoms of allergic rhinitis in patients with persistent asthma.32 Fluticasone nasal spray became available by generic name in the first week in April 2006,33 and the MCO cost will soon be $1.00 or less per day of therapy. So, where is the value of montelukast in the treatment of either a small subset of asthma patients or in perhaps an even smaller subset of allergy patients when fluticasone nasal spray is more effective and will soon cost less than one third the price of montelukast, and the cost of loratadine over-the-counter (OTC, Claritin) is less than $1.00 per day of therapy?

Perhaps elsewhere are some data to justify the direct drug cost of more than $3 per day for montelukast for the treatment of perennial allergic rhinitis, the second indication for this drug approved by the FDA in July 2005.34 The most recent study on this subject found that 10 mg per day of montelukast was no more effective than 240 mg per day of OTC pseudoephedrine in adult patients with ragweed allergic rhinitis documented by (a) positive skin test to ragweed and (b) history of symptoms during previous ragweed seasons. There was no difference in the outcome measures of nasal peak inspiratory flow and diurnal and nocturnal rhinoconjunctivitis quality-of-life scores.35 Not only was there no difference between these 2 drugs in measures of effectiveness, pseudoephedrine was superior to montelukast in the symptoms of nasal congestion, and no difference was found between the 2 drugs in tolerability.

The major difference, of course, between montelukast and OTC pseudoephedrine or OTC loratadine is its much higher cost.36 It is possible to use OTC pseudoephedrine or OTC loratadine to treat the symptoms of allergic rhinitis, more effectively, in 4 patients for the same cost as treating one patient with montelukast, before consideration of the cost of physician office visits to obtain the prescription drug montelukast. This creates a terrific opportunity for the use of a step-therapy protocol for either indication for montelukast, asthma or allergy, particularly since montelukast was the eleventh-highest-volume brand-name prescription drug in dispensed units in 200537 and the
ninth-highest-expense drug in total community pharmacy sales in 2005.

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

REFERENCES


16. Data search performed April 6, 2006, of the data warehouse of a national pharmacy benefits manager representing approximately 500,000 beneficiaries of small employer drug benefit plans for pharmacy claims with dates of service from January 1, 2006, through March 31, 2006.


29. Montelukast (Singulair) for perennial allergic rhinitis. BMJ. 2001;323:164-72.


34. Available at: www.drugstore.com for montelukast (Singulair) 10 mg oral tablet and pseudoephedrine 240 mg (Sudafed 24 Hour). Accessed April 28, 2006.

