A Randomized Controlled Trial to Assess Pharmacist-Physician Collaborative Practice in the Management of Metabolic Syndrome in a University Medical Clinic in Jordan

Prevalence of Achievement of A1c, Blood Pressure, and Cholesterol (ABC) Goal in Veterans with Diabetes

Analysis of Drug and Administrative Costs Allowed by U.S. Private and Public Third-Party Payers for 3 Intravenous Biologic Agents for Rheumatoid Arthritis

The Case for Standardizing the Appearance of Bioequivalent Medications
RESEARCH

295 A Randomized Controlled Trial to Assess Pharmacist-Physician Collaborative Practice in the Management of Metabolic Syndrome in a University Medical Clinic in Jordan
Eman A. Hammad, MSc; Nada Yasein, MRCGP; Linda Tahaineh, PharmD, MSc; and Abla M. Albsoul-Younes, PhD

304 Prevalence of Achievement of A1c, Blood Pressure, and Cholesterol (ABC) Goal in Veterans with Diabetes
Scott Martin Vouri, PharmD; Robert F. Shaw, PharmD, MPH; Nancee V. Waterbury, PharmD; Jason A. Egge, PharmD, MS, BCPS; and Bruce Alexander, PharmD, BCPP

313 Analysis of Drug and Administrative Costs Allowed by U.S. Private and Public Third-Party Payers for 3 Intravenous Biologic Agents for Rheumatoid Arthritis
Bruce J. Wong, MBChB, FRACP; Mary A. Cifaldi, PhD, MSHA, RPh; Sanjoy Roy, MS; Dean C. Skonieczny, MBA, BSE; and Spyros Stavrakas, PhD

COMMENTARY

321 Commentary
The Case for Standardizing the Appearance of Bioequivalent Medications
Alfred B. Engelberg, JD

DEPARTMENTS

287 Cover Impressions
Two Mustangs (2008)
Jeff Ham
Sheila Macho, Cover Editor
JMCP accepts for consideration manuscripts prepared according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.1

■ Manuscript Preparation

Manuscripts should include, in this order: title page, abstract, text, references, tables, and figures (see Manuscript 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 manuscript submissions except Commentaries and Letters. The format for the abstract is Background, Objective, Methods, Results, Conclusion.

For descriptions of editorial content, see “JMCP Editorial Policy” in this Journal or at www.amcp.org (Manuscript/Supplement Submission).

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 (JMCP Peer Review Checklist and Guidelines’ tab).

• A subsection in the Discussion labeled “Limitations” is generally appropriate for all articles except Commentaries and Letters.

• Most articles 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).

• Product trade names may be used only once for the purpose of providing clarity for readers, generally at the first citation of the generic name in the article but not in the abstract.

• Many articles involve research that may pose a threat to either patient safety or privacy. It is the responsibility of the principal author to ensure that the manuscript is submitted with either the result of review by the appropriate institutional review board (IRB) or a statement of why the research is exempt from IRB review (see “Policy for Protecting Patient Safety and Privacy” at www.amcp.org), Manuscript/Supplement Submission.

■ Reference Style

References should be prepared following modified AMA style. All reference numbers in the manuscript should be superscript (e.g., 1). Each unique reference should have only one reference number. If that reference is cited more than once in the manuscript, the same number should be used. Do not use ibid or op cit for JMCP references. Please provide Web (hyperlink) addresses for all free access references. An access date should be included for every URL except links to JMCP articles. See examples 2 and 3 in the second column. Here are examples of the style format for common types of references:


■ Manuscript Submission

A complete list of documents needed for submission to JMCP appears on the Manuscript/Supplement Submission page at www.amcp.org. Prior to peer review, all manuscripts are reviewed by the editors and/or members of the Editorial Advisory Board for appropriateness of the topic for JMCP, methodological transparency, and compliance with submission requirements. See Author Guidelines for description of the “pre-review process.” Peer review generally requires 4-6 weeks but may extend as long as 12 weeks in unusual cases. Solicited manuscripts are subject to the same peer-review standards and editorial policy as unsolicited manuscripts.

Disclosures and conflicts of interest: Manuscript submissions should (a) include a statement that identifies the nature and extent of any financial interest or affiliation that any author has with any company, product, or service discussed in the manuscript and clearly indicates the source(s) of funding and financial support and (b) be accompanied by completed and signed author attestation forms for the principal author and each coauthor.

■ Manuscript Submission Checklist

Before submitting your manuscript to JMCP, please check to see that your package includes all items in the JMCP Manuscript Submission Checklist, available at www.amcp.org (JMCP/Manuscript/Supplement Submission).

REFERENCE


The Journal of Managed Care Pharmacy, including supplements, is indexed by MEDLINE/PubMed, the International Pharmaceutical Abstracts (IPA), Science Citation Index Expanded (SCIE), Current Contents/Clinical Medicine (CC/CM), and Scopus.
Have you ever looked at a painting and wondered how the artist painted it? Well, wonder no more, thanks to live painting demonstration videos posted to YouTube.com by artists such as Jeff Ham. A fun one to watch is the “Jeff Ham Live Paint Time Lapse” video which shows the artist creating a large-scale painting of his dog, Tom. It was filmed on December 11, 2010, at Lovetts Gallery in Tulsa, Oklahoma, at an exhibit titled Inside/Outside: Live Paint with Jeff Ham and Yatika Starr Fields. The link to this video is: http://tinyurl.com/3ksl5wb.

Another interesting live painting video can be found on the homepage of his website, www.jeffham.net (click on the “see Jeff in action” link). It reveals the step-by-step creation of his 2009 Tipi painting. Although Ham was a bit apprehensive about doing his first live painting demonstration 3 years ago, he has grown to enjoy interacting with an audience. “My goal is to capture spontaneity,” he says. “I do my best to translate emotion and feelings into color and communicate my individual interpretation of each subject.” All of Ham’s paintings explode with raw, bright, color whether they are landscapes, portraits, or pictures of animals. To see more of his spectacular semi-abstract expressionist work, simply visit his website.

Ham was born and raised in Cincinnati, Ohio. His father is an illustrator, so he had the advantage of growing up surrounded by art. He recalled his early life in an article that appeared in the April 2008 issue of Total Health magazine: “…as a child, I would stand on a chair, peer over [my father’s] shoulder and watch him work. Oils, acrylics, fixatives, markers, and pencils were the aromas of my childhood and to this day give me a sense of comfort and home. Those early years with my father and illustration gave me a solid base in the fundamentals of drawing and painting. Over the years, I have expanded on these basic elements and am learning how to express myself more with my heart and less with my head.”

Because numerous readers had inquired about the marvelous illustrations and artwork in Total Health, the article was written as a tribute to Ham, the magazine’s art director since 2004. “We felt it [was] time to give our readers a peek into the man and his art,” wrote editor Lyle Hurd. “We are proud to be affiliated [with him].” A photograph of the artist in his studio and numerous images of his colorful paintings accompanied the text.

After attending the Central Academy of Commercial Art in Cincinnati, Ohio, during the early 1980s, Ham pursued a career in commercial art. His illustrations for Don Johnston Publishing graced many of its children’s books, including Black Beauty, Frankenstein, Anne of Green Gables, The Legend of Sleepy Hollow, and 20,000 Leagues Under the Sea. He soon began working for advertising agencies and moved to Chicago. Companies such as Disney, McDonald’s, Frito-Lay, Keebler, and Hanes have used his artwork in their advertisements.

Ham now lives and works in Ivins, Utah, located in the southwest corner of the state. His decision to relocate was influenced by the fond memories of a trip he took to the Southwest and southern Utah when he was 18 years old. Sites such as Zion National Park, Bryce Canyon, and the south rim of the Grand Canyon had a profound influence on Ham and his art.

Many distinguished art galleries represent Ham’s work. In addition to Lovetts Gallery, the list includes Mountain Trails Gallery, Jackson Hole, Wyoming; Beartooth Gallery, Red Lodge, Montana; District Gallery, Park City, Utah; Michael Henington Fine Art gallery, Santa Fe, New Mexico; Rive Gauche Art Galleries, Scottsdale, Arizona; and El Prado Gallery, Sedona, Arizona. Ham’s artist profile page on the El Prado Gallery website (www.elpradogalleries.com) has an astute description of his artistic style: “Jeff Ham’s paintings dismiss all rules. Yet they greet you with an open heart and open arms…. The viewer becomes an eyewitness to Jeff’s creative energy from the fierce and dense tracks of his brush, [and] the dripping paint…”

Ham’s work also seems to capture energy—he often outlines part of a figure or animal, as if he is painting their aura. This technique is evident in his vibrant Two Mustangs painting. A soft yellow outline begins above the first horse’s head and flows into the sea of bright yellow that caresses both horses. The lone bird in flight above the Mustangs appears to be flying from one dimension to another, represented by the change of hue from orange to yellow. This flight into the yellow zone may symbolize the bird’s connection with the horses as well as other living things. Meanwhile, a number of other birds sit peacefully atop the horses. Ham has depicted the birds in such a way that their bodies are barely distinguishable from the horses’ manes, thus reinforcing the “connectedness” theme. As Native American Indian Chief Seattle (1780-1866) once said, “Humankind has not woven the web of life. We are but one thread within it. Whatever we do to the web, we do to ourselves. All things are bound together. All things connect.”

Sheila Macho
Cover Editor

SOURCES
Interview with the artist.
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

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 STAFF

Editor-in-Chief
Frederic R. Curtiss, PhD, RPh, CEBS
830.935.4319, fcurtiss@amcp.org

Associate Editor, Kathleen A. Fairman, MA
602.867.1343, kfairman@amcp.org

Cover Editor, Sheila Macho, 952.431.5993, jmcpcoverart@amcp.org

Copy Editor, Carol Blumentritt

Peer Review Administrator, Jennifer A. Booker
703.317.0725, jmcpreview@amcp.org

Graphic Designer, Margie Hunter, 703.297.9319, mhunter@amcp.org

Publisher
Judith A. Cahill, CEBS, Chief Executive Officer, Academy of Managed Care Pharmacy

EDITORIAL ADVISORY BOARD

The JMCP Editorial Advisory Board is chaired by Marvin D. Shepherd, PhD, Center for Pharmacoeconomic Studies, College of Pharmacy, University of Texas at Austin, Thomas Delate, PhD, Kaiser Permanente of Colorado, Aurora, serves as vice chair. They and the other advisers review manuscripts and assist in the determination of the value and accuracy of information provided to readers of JMCP.

J. Daniel Allen, PharmD, RegenceRx, Portland, OR
John P. Barbuto, MD, Modify Motion, LLC, Salt Lake City, UT
Mitchell J. Barnett, PharmD, MS, Touro University College of Pharmacy, Vallejo, CA
Christopher F. Bell, MS, Global Health Outcomes, GlaxoSmithKline Research & Development, Research Triangle Park, NC
Joshua Benner, PharmD, ScD, Brookings Institution, Washington, DC
Scott A. Bull, PharmD, ALZA Corporation, Mt. View, CA
Douglas S. Burgoyne, PharmD, RPh, VRx Pharmacy Services, Salt Lake City, UT
Norman V. Carroll, PhD, School of Pharmacy, Virginia Commonwealth University, Richmond, VA
Mark Conklin, PharmD, MS, Highmark Blue Cross Blue Shield, Pittsburgh, PA
Eric J. Culley, PharmD, MBA, Highmark Blue Cross Blue Shield, Pittsburgh, PA
Timothy Cutler, PharmD, School of Pharmacy, University of California, Sacramento, CA
Gregory W. Daniel, RPh, MPH, PhD, HealthCore, Inc., Wilmington, DE
Thomas Delate, MS, PhD, Kaiser Permanente of Colorado, Aurora, CO
Melissa S. Denno, PharmD candidate, Mercer University College of Pharmacy, Atlanta, GA
Patrick P. Gleason, PharmD, BCPS, Prime Therapeutics, LLC, Eagan, MN
Mark Jackson, BScPhm, BComm, RPh, Green Shield Canada, Windsor, Ontario
Richard A. Kipp, MAAA, Milliman USA, Wayne, PA
Stephen J. Kogut, PhD, MBA, College of Pharmacy, University of Rhode Island, Kingston, RI
Charnelda Gray Lewis, PharmD, BCPS, Kaiser Permanente, Atlanta, GA
Bradley C. Martin, PharmD, PhD, College of Pharmacy, University of Arkansas, Little Rock, AK
Brenda R. Mothaler, RPh, MBA, PhD, University of Kentucky College of Pharmacy, Lexington, KY
Robert P. Navarro, PharmD, University of Florida College of Pharmacy, Gainesville, FL
Robert L. Ohnsfeldt, PhD, School of Rural Public Health, Texas A&M Health Science Center, College Station, TX
Mary Jo V. Pugh, RN, PhD, South Texas Veterans Healthcare System, San Antonio, TX
Brian J. Quilliam, PhD, RPh, College of Pharmacy, University of Rhode Island, Kingston, RI
Marsha Raebel, PharmD, Kaiser Permanente of Colorado, Denver, CO
Elan Rubinstein, PharmD, MPH, EB Rubinstein Associates, Oak Park, CA
Jeremy A. Schafer, PharmD, MBA, Prime Therapeutics, LLC, Eagan, MN
Jordana Schmier, MA, Exponent, Alexandria, VA
Marvin D. Shepherd, PhD, College of Pharmacy, University of Texas, Austin, TX
Joshua J. Spooner, PharmD, MS, School of Pharmacy, Western New England College, Springfield, MA
Linda M. Spooner, PharmD, BCPS, Massachusetts College of Pharmacy, Worcester, MA
Marilyn Stebbins, PharmD, CHW Medical Foundation, University of California, Sacramento, CA
Karen Stockl, PharmD, Prescription Solutions, Irvine, CA
Burgunda V. Sweet, PharmD, FASHP, University of Michigan Health System, Ann Arbor, MI
Connie A. Valdez, PharmD, MSeD, BCPS, School of Pharmacy, Aurora, CO
Peter Whittaker, PhD, School of Medicine, Wayne State University, Detroit, MI
Vincent Willey, PharmD, University of the Sciences in Philadelphia, Philadelphia, PA
Karen Worley, PhD, Competitive Health Analytics, Humana Inc., Louisville, KY
Andrew Yu, PhD, Analysis Group, Boston, MA

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, 703.683.8418; 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.
**JMCP Mission Statement and Editorial Policy**

**Editorial Content and Peer Review**

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

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

All manuscript submissions except Commentaries and Letters should include an abstract and 1-3 takeaway bullet points in each of 2 sections that immediately follow the abstract for “what is already known about this subject” and “what this study adds.”

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. The Methods section in the abstract and in the body of the manuscript should make clear to the reader the source of the material used in the review, including the specific criteria used for inclusion and exclusion of information and the number of articles included and excluded by each criterion. Narrative reviews, defined as noncomprehensive reviews that cover only a portion of the literature on a topic, are not considered for publication by JMCP. However, articles of this type may be considered as Commentary.

**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 generally include description and interpretation of clinical evidence and comparative cost information.

**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 hypothesis or hypotheses that guided the research, the principal methods, and results.

**Brief Communications**

The results of a small study or a descriptive analysis that does not fit in other JMCP departments may be submitted as a Brief Communication. Brief Communications may warrant an Abstract with the typical JMCP categories (Background, Objective, Methods, Results, Conclusion).

**Commentary**

These submissions should be relevant to managed care pharmacy and address a topic of contemporary interest: they do not require an abstract but should include references to support statements.

**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 and Disclosure Policies**

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, and advertising is not accepted for placement opposite or near subject-related editorial content.

The Academy of Managed Care Pharmacy (AMCP) endorses the Uniform Requirements for Manuscript Submissions to Biomedical Journals, available at: http://www.icmje.org/ including editorial freedom and management of conflicts of interest. Financial disclosure, conflict-of-interest statements, and author attestations are required when manuscripts are submitted, and these disclosures accompany the article in abstracted form if the article is published. See JMCP Author Guidelines in this issue or online including complete description of disclosure policies and requirements for author attestations at www.amcp.org.

See JMCP advertising opportunities at: www.amcp.org. Contact the Advertising Sales Office to receive a Media Kit.

**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.
A Randomized Controlled Trial to Assess Pharmacist-Physician Collaborative Practice in the Management of Metabolic Syndrome in a University Medical Clinic in Jordan

Eman A. Hammad, MSc; Nada Yasein, MRCGP; Linda Tahaineh, PharmD, MSc; and Abla M. Albsoul-Younes, PhD

ABSTRACT
BACKGROUND: The prevalence of metabolic syndrome is increasing worldwide, and patients with metabolic syndrome have increased risk of developing cardiovascular disease and type 2 diabetes. Although specific criteria vary, the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria (2002) defined metabolic syndrome as the presence of 3 or more of the following 5 components: waist circumference more than 102 centimeters (cm) for men or more than 88 cm for women; triglycerides 150 milligrams per deciliter (mg per dL) or more; high-density lipoprotein cholesterol (HDL-C) less than 40 mg per dL for men or less than 50 mg per dL for women; blood pressure (BP) 130/85 millimeters mercury (mm Hg) or more; and fasting blood glucose 110 mg per dL or more.

OBJECTIVE: To evaluate the effect of a pharmacist-physician collaborative practice compared with usual care in the management of patients with metabolic syndrome as defined by the NCEP/ATP III criteria.

METHODS: A prospective, randomized controlled trial conducted in family medicine outpatient clinics in Jordan enrolled 199 patients who met the NCEP/ATP III criteria for metabolic syndrome during an enrollment period from March 15, 2009, through May 10, 2009. Patients were randomized into 2 groups, with 110 in the intervention group (pharmacist-physician collaborative practice) and 89 in usual care (physician only). The patients in the intervention group were provided with pharmacist recommendations and pharmaceutical care counseling. Outcome measures included metabolic syndrome status (binomial) and changes in mean values for each metabolic syndrome component (waist circumference, triglycerides, HDL-C, fasting blood glucose, and systolic and diastolic BP) and for body weight. A 2 × 2 contingency table with a Pearson chi-square test was used to assess by-group differences in metabolic syndrome status after 6 months of follow-up. In difference-in-difference analyses, t-tests (Mann-Whitney U tests when appropriate) were used to assess by-group differences in changes in the individual metabolic syndrome components and body weight.

RESULTS: From baseline to follow-up, 39.1% (n = 43) of intervention group patients versus 24.7% (n = 22) of usual care patients were successfully shifted from a status of metabolic syndrome to no metabolic syndrome (P = 0.032). Three of 7 outcome measures were improved more in the intervention group compared with the usual care group. Mean (SD) triglyceride (mg per dL) declined by 30.9 (54.4) from 189.3 (79.6) to 158.4 (89.0) in the intervention group (P = 0.029). For the intervention and usual care groups, mean baseline systolic BPs were 134.7 (16.2) mm Hg and 134.6 (12.2) mm Hg, respectively, declining after 6 months follow-up by 12.1 (20.1) mm Hg in the intervention group versus 6.9 (14.6) mm Hg in the usual care group (P = 0.018). Mean baseline diastolic BPs were 83.6 (10.7) mm Hg and 83.6 (7.9) mm Hg, respectively, declining by 7.2 (12.6) mm Hg in the intervention group versus 4.9 (8.1) mm Hg in the usual care group (P = 0.049).

CONCLUSIONS: Compared with usual care provided by physicians only, pharmacist involvement in the clinical management of patients with metabolic syndrome increased the proportion of patients who no longer met criteria for the syndrome after 6 months follow-up and improved control of BP and triglycerides.

J Manag Care Pharm. 2011;17(4):295-303
Copyright © 2011, Academy of Managed Care Pharmacy. All rights reserved.

What is already known about this subject
- Metabolic syndrome is a secondary target of risk reduction in patients with coronary heart disease after the primary targets of low-density lipoprotein cholesterol and blood pressure (BP). In addition, metabolic syndrome predicts the development of type 2 diabetes mellitus and cardiovascular disease (CVD).
- Clinical pharmacist interventions have been studied for several chronic diseases, such as hypertension, diabetes, and dyslipidemia. A randomized controlled trial by Carter et al. (2009), conducted in a sample of patients with uncontrolled hypertension treated in community medical practices, found BP control rates of 63.9% in patients receiving collaborative pharmacist-physician care versus 29.9% in a control group receiving usual care. In a pooled analysis of 2 randomized controlled trials conducted in outpatients with CVD, Murray et al. (2009) found that the risk of adverse drug events and medication errors was reduced by approximately 34% in patients who received monitoring and instruction from pharmacists compared with those receiving routine dispensing alone.
- The role of pharmacists in managing metabolic syndrome has not been evaluated extensively. Two cross-sectional studies have studied the benefits of pharmacist care on metabolic syndrome screening in community pharmacy patrons and in patients receiving antipsychotics in an outpatient psychiatry clinic.

What this study adds
- The current study is the first randomized controlled trial to evaluate physician-pharmacist collaborative practice in clinical management of metabolic syndrome by combining lifestyle changes and drug therapy.
- Compared with usual physician care, pharmacist-physician collaboration resulted in greater improvements in metabolic syndrome status: 39.1% in the intervention group versus 24.7% in usual care (P = 0.032).
- Pharmacist-physician collaboration resulted in improvements in BP and triglycerides but did not have a significant effect on body weight, waist circumference, high-density lipoprotein cholesterol, or fasting blood sugar.
Many patients have a constellation of lifestyle risk factors that constitute a condition known as metabolic syndrome, also called insulin resistance or syndrome X. Various definitions for metabolic syndrome have been proposed. The World Health Organization (WHO) first defined metabolic syndrome in 1998 based on impaired glucose tolerance, diabetes, or insulin resistance combined with 2 or more of the following: obesity, dyslipidemia, hypertension, and microalbuminuria. In 1999, the European Group for the Study of Insulin Resistance (EGIR) proposed several modifications to the WHO definition, including deletion of microalbuminuria as a criterion, and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) revised the definition in 2002. A definition closely based on that of the NCEP/ATP III was adopted by the American Heart Association (AHA) and the National Heart Lung and Blood Institute (NHLBI) in 2005. In 2005, the International Diabetes Foundation (IDF) published new criteria for metabolic syndrome in an attempt to reduce “confusion” caused by “contrasting views on pathogenic mechanisms and the need for clinical usefulness”; however, that definition relied in part on ethnicity-specific waist circumference criteria for obesity.

The present study adopted the NCEP/ATP III (2002) definition of metabolic syndrome because it (a) incorporates the key features of hyperglycemia/insulin resistance, visceral obesity, atherogenic dyslipidemia, and hypertension and (b) uses measurements and laboratory results that are readily available to physicians or other health providers. NCEP/ATP III defined metabolic syndrome as the presence of 3 or more of the following 5 components: waist circumference more than 102 centimeters (cm) for men or more than 88 cm for women; triglycerides 150 milligrams per deciliter (mg per dL) or more; high-density lipoprotein cholesterol (HDL-C) less than 40 mg per dL for men or less than 50 mg per dL for women; blood pressure (BP) 130/85 millimeters mercury (mm Hg) or more; and fasting blood glucose 110 mg per dL or more. The NCEP/ATP III definition differs slightly from that of the AHA/NHLBI, in which the fasting blood glucose criterion is 100 mg per dL or more.

The National Health and Nutrition Examination Survey (NHANES) 2003-2006 found that approximately one-third of adults in the United States met the NCEP/ATP III diagnostic criteria for metabolic syndrome. The prevalence increased with age and body mass index (BMI), and varied by race or ethnicity and gender. In a study from Jordan (2005), the prevalence of metabolic syndrome was 36.3% overall, 28.7% among men and 40.9% among women, and increased significantly with age in both men and women. Similar prevalences were found in other countries in the Middle East.

Metabolic syndrome is recognized as a secondary target of coronary heart disease (CHD) risk reduction therapy after the primary target of low-density lipoprotein cholesterol (LDL-C) reduction is achieved. It is well established that metabolic syndrome predicts the development of type 2 diabetes mellitus and cardiovascular disease (CVD). Although each individual component of the metabolic syndrome increases the risk of CVD, this risk is even more pronounced when the components are combined in metabolic syndrome. Additionally, increases in the number of metabolic syndrome components presented by a patient are associated with a higher cardiovascular mortality rate.

The role of clinical pharmacists in improving treatment outcomes; achieving therapeutic goals; lowering adverse reactions or undesirable effects; and reducing medication costs in many chronic medical conditions, such as hypertension, diabetes mellitus, heart failure, and dyslipidemia, has been demonstrated by many studies using different designs.

In the present study, a pharmaceutical care program was developed, allowing 1 clinical pharmacist to work at a physician’s practice site to assess and manage the components of metabolic syndrome. The pharmaceutical care program included interventions and patient counseling to address medication, diet, and physical activity. The aim of the present study was to describe the clinical benefits of a physician-clinical pharmacist collaboration in achieving better glycemic control and better lipid and BP measurements in patients with metabolic syndrome as defined by NCEP/ATP III guidelines.

### Methods

#### Patient Enrollment

This randomized controlled clinical trial was conducted over 9 months in 6 family medicine clinics involving 13 physicians at Jordan University Hospital (JUH), a major teaching hospital in Amman, Jordan. Family medicine clinics at JUH serve approximately 100 patients daily. Of those, approximately one-third are followed up on a monthly basis for management of hypertension, diabetes, dyslipidemia, and other chronic diseases.

This study was approved by the Institutional Review Board (IRB) at JUH. Study enrollment took place during an 8-week time period from March 15, 2009, through May 10, 2009. The pharmacist reviewed paper medical records prior to each visit to identify patients with suspected metabolic syndrome. Patients were asked to participate in the study if they met the NCEP/ATP III criteria for the diagnosis of metabolic syndrome at the time of enrollment. Patients with any of the following conditions documented in the medical record were excluded: pregnancy, renal or hepatic diseases, and dementia or cognitive impairment. Patients who were unable to provide informed written consent were also excluded. Written informed consent...
was obtained from all study participants in both study arms. During the process of obtaining patient consent, the patients were informed that they would be assigned to either the intervention group (physician-pharmacist collaborative practice) or control (usual care) group (physician-only team). At the time of recruitment, patients were randomized into the intervention arm \( (n=112) \) and the control arm \( (n=90) \) using a coin-toss method.

Patients remained in the same randomized study arm throughout the duration of the study period. Both study groups were followed for 6 months by the same physician team, which consisted of 2 fellows (post-residency specialists), 6 fourth-year residents, 3 third-year residents, 3 second-year residents, and 1 consultant (at least 2 years in residency subspecialty). The pharmacist team consisted of a master’s degree pharmacy student (Hammad) and a faculty pharmacist (Albsoul-Younes).

Data Collection

All patients who agreed to take part in the study were interviewed to collect demographics and clinical values for fasting blood glucose, total cholesterol, triglycerides, HDL-C, and LDL-C. All laboratory measurements were performed in the laboratory of the teaching hospital. Tests were reported as baseline values if they were performed within the last 3 months prior to or on the date of study enrollment (i.e., no baseline values were used that were older than 3 months prior to the date of enrollment). Follow-up testing was performed during the course of the study to assess clinical progress. The last follow-up measurements were collected from both study arms at the sixth scheduled visit and compared with baseline values. The data collection period extended for 9 months (March through November 2009) to ensure at least 6 months of data for all enrolled patients.

Data on age, gender, weight, height, BMI, abdominal circumference, family history of cardiovascular disease and diabetes mellitus, smoking, alcohol consumption, dietary habits, and physical activity were also collected. Physical activity was defined as regular practice of any type of activity 3 to 4 times per week for duration of 30 minutes or more, such as brisk walking, jogging, cycling, or swimming. A current smoker was defined as one who smoked 1 or more cigarettes per day. Waist circumference was measured using a steel measuring tape, with the measurement made halfway between the lower border of the rib and the iliac crest in a horizontal plane. Two independent measurements of waist circumference to the nearest 0.5 cm were recorded at the time of enrollment, 1 by a pharmacist and the other by a physician; the mean of the 2 measurements was recorded and reported as the baseline value.

BP levels were measured monthly by assistant nurses who were blinded to the patient’s study arm assignment and recorded the BP measures in the patients’ medical records. Patients were instructed to abstain from smoking or caffeine consumption within 30 minutes of the measurement. BP measurements were taken in the right arm with a standard mercury sphygmomanometer after the patient had been seated quietly for at least 5 minutes.

Description of the Intervention Versus Usual Care

Prior to randomization, the pharmacist initially interviewed patients in both study groups to collect information about medications, medical conditions, and lifestyle (e.g., diet, smoking). At each monthly visit, patients in the intervention group met with a clinical pharmacist for 30 minutes before seeing the physician. In the intervention group, metabolic components were assessed and managed collaboratively by focused care plans designed by the clinical pharmacist and approved by the physician. Pharmacists provided medication counseling, answered questions asked by patients or physicians, encouraged compliance, offered instructions on self-monitoring BP, and advised patients on healthy lifestyle choices (e.g., tobacco cessation and adhering to a healthy diet). Educational materials were also distributed to patients in the intervention group, including brochures on metabolic syndrome, increased risk of cardiovascular disease, and type 2 diabetes mellitus. Pamphlets were provided to patients with information on the recommended dietary approaches to stop hypertension (DASH), dyslipidemia, and diabetes mellitus, which were translated into Arabic and tailored to the food habits and recipes of the Jordanian community. Patients in the intervention group were counseled on the components of metabolic syndrome, including cut-off points and goals. An emphasis was put on optimizing adherence to pharmacological and nonpharmacological therapy to reduce the risk for cardiovascular and renal disease and to prevent the development of type 2 diabetes mellitus and the risks associated with individual components of metabolic syndrome.

The pharmacist emphasized lifestyle changes, particularly weight loss and physical activity, as a first-line therapy for at least 3 months. Patients were started on drug therapy as recommended by clinical guidelines. The pharmacists’ interventions and proposed patient care plans were discussed with the physicians, who specified whether to accept or reject them as part of each patient’s individualized treatment plan.

In the control group, patients received usual care provided by physician teams. For the usual care group, the clinical pharmacist did not provide any recommendations and did not offer educational materials or counseling.

For patients in both study arms, Framingham scores were calculated, and 10-year CHD risk was determined. Based on the CHD risk category, therapeutic choices (low-dose aspirin, therapeutic life changes, lipid-lowering therapy) were recommended by the pharmacist to the treating physician in the intervention arm only.
Patient Follow-Up

Patients in both study arms provided valid phone numbers, which the clinical pharmacist used to call patients and set up appointments during their regular, monthly follow-up visits to the clinic. The pharmacist contacted patients 1 week and 1 day prior to each upcoming appointment to remind and confirm the scheduled visit.

Outcome Measurements

The primary outcomes measured the improvement in metabolic syndrome status over the course of the study period and absolute mean improvement in individual metabolic syndrome components. At baseline and follow-up, metabolic syndrome status was assessed according to the NCEP/ATP III definition (at least 3 of 5 components: abdominal obesity measured by waist circumference, elevated triglycerides, low HDL-C, elevated BP, elevated fasting blood glucose). Patients with 2 or fewer components at the 6-month follow-up were defined as improved (i.e., change from metabolic syndrome to no metabolic syndrome). The intervention pharmacist reviewed the medical records to transfer baseline and 6-month values for each patient into a data collection form. In addition to the 5 metabolic syndrome components, body weight was assessed as an outcome measure.

Data Management and Analysis

Contingency tables with Pearson chi-square tests and t-tests were used to evaluate the baseline differences between the arms at the beginning of the study. To make a by-group comparison of the percentage of patients whose metabolic status improved during the study, a 2×2 contingency table (metabolic syndrome vs. no metabolic syndrome for intervention vs. control at 6-month follow-up) with statistical testing by the Pearson chi-square test was used. To make by-group comparisons of the changes (improvements) in the individual metabolic syndrome components and body weight from

---

**FIGURE 1** Patient Selection Flowchart

820 patients visited the family medicine clinic during the enrollment period and met NCEP/ATP III criteria for metabolic syndrome.

618 patients excluded:
- 611 patients did not meet inclusion criteria
- 7 patients declined to participate:
  - 4 patients for personal reasons
  - 1 patient for traveling plan
  - 2 patients for other reasons

112 patients randomized to intervention arm
- Physician-pharmacist collaboration

90 patients randomized to control arm
- Usual care (physician only)

110 patients followed for 6 monthly visits

90 patients followed for 6 monthly visits

Dropouts:
- 2 patients were lost to follow-up due to invalid contact numbers
- 1 patient was lost to follow-up due to traveling

---

*NCEP/ATP III criterion for metabolic syndrome: at least 3 of the following 5 criteria:
1. Abdominal circumference more than 102 centimeters for males or more than 88 centimeters for females.
2. HDL-C less than 40 mg per dL for males or less than 50 mg per dL for females.
3. Triglycerides 150 mg per dL or more.
4. Blood pressure 130/85 mm Hg or more, or receiving hypertension treatment.
5. Fasting blood glucose 110 mg per dL or more.

611 patients were excluded for the following reasons: pregnancy, renal or hepatic disease, and dementia or cognitive impairment.

HDL-C = high-density lipoprotein cholesterol; mg per dL = milligrams per deciliter; mm Hg = millimeters mercury; NCEP/ATP = National Cholesterol Education Program/Adult Treatment Panel.
baseline to 6-month follow-up, a difference-in-difference analysis, which is a commonly used analytic technique for designs with pre-intervention versus post-intervention measures and a control or comparison group, was used. First, baseline values were subtracted from 6-month follow-up values to calculate change amounts. Then, the statistical significance levels of by-group differences in the change amounts were calculated using Student’s t-tests for variables with normal distributions and Mann-Whitney U tests when normality and equality of variance assumptions were not met.

Normality of mean reduction of systolic and diastolic BP, absolute changes in individual components of metabolic syndrome, and other clinical values or demographics were determined visually by probability plots, quantile-quantile plots, and Kolmogrov-Smirnov-Lilliefors tests. Equality of variances was tested using Levene’s test. All data were processed using SPSS version 16 (SPSS Inc., Chicago, IL) and an a priori alpha level of 0.05.

### Results

Of the 202 patients who were initially recruited, 199 were randomized into the intervention arm (n = 110) and usual care arm

---

### TABLE 1 Baseline Characteristics of Patients with Metabolic Syndrome

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Intervention n = 110</th>
<th>Usual Care n = 89</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean [SD]</td>
<td>56.0 [9.6]</td>
<td>57.4 [11.5]</td>
<td>0.385</td>
</tr>
<tr>
<td>Demographic and clinical categories</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>66 (60.0)</td>
<td>57 (64.0)</td>
<td>0.559</td>
</tr>
<tr>
<td>BMI categoryb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>68 (61.8)</td>
<td>52 (58.4)</td>
<td>0.695</td>
</tr>
<tr>
<td>Obese</td>
<td>38 (34.5)</td>
<td>34 (38.2)</td>
<td></td>
</tr>
<tr>
<td>Morbid obesity</td>
<td>4 (3.6)</td>
<td>3 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>46 (41.8)</td>
<td>50 (56.2)</td>
<td>0.232</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>64 (58.2)</td>
<td>39 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Sedentary lifestylec</td>
<td>less than 30 min of moderate exercise 4 times per week</td>
<td>106 (96.4)</td>
<td>83 (93.3)</td>
</tr>
<tr>
<td>Past medical historyd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension and diabetes</td>
<td>39 (35.5)</td>
<td>25 (28.1)</td>
<td>0.642</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (20.9)</td>
<td>18 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia and diabetes</td>
<td>12 (10.9)</td>
<td>15 (16.9)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, diabetes, and dyslipidemia</td>
<td>27 (24.5)</td>
<td>23 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism and diabetes</td>
<td>2 (1.8)</td>
<td>4 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7 (6.4)</td>
<td>4 (4.5)</td>
<td></td>
</tr>
</tbody>
</table>

a P value for Pearson chi-square tests for categorical variables and Student’s t test for continuous variables.
b BMI categories (kg per m²): overweight = 25-29.9; obese = 30-39.9; morbid obesity = 40 or more.
c Defined as a past illness treated by family medicine physicians and recorded in patient medical record; past medical history was verified with the patients. P value represents Pearson chi-square test for a 6 × 2 table.
d BMI = body mass index; kg per m² = kilograms per square meter; SD = standard deviation.

### TABLE 2 Number of Metabolic Syndrome Components at Baseline and 6 Months

<table>
<thead>
<tr>
<th>Metabolic Syndrome Components</th>
<th>Intervention After 6 months</th>
<th>Usual Care After 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention n = 110</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>5</td>
<td>10 (10.0)</td>
<td>7 (7.9)</td>
</tr>
<tr>
<td>4</td>
<td>44 (40.4)</td>
<td>36 (40.4)</td>
</tr>
<tr>
<td>3</td>
<td>55 (50.0)</td>
<td>46 (51.7)</td>
</tr>
<tr>
<td>2 or fewer</td>
<td>0 (0.0)</td>
<td>43 (39.1)</td>
</tr>
</tbody>
</table>

b denotes a patient who did not meet criteria for metabolic syndrome. P value of Pearson chi-square test was 0.032.

HDL-C = high-density lipoprotein cholesterol, mg per dL = milligrams per deciliter, mm Hg = millimeters mercury; NCEP/ATP = National Cholesterol Education Program/Adult Treatment Panel.

---

### FIGURE 2 Percentage of Patients Achieving the Recommended Values of Metabolic Syndrome Criteria in the Intervention Group at Baseline and After 6 Months

Body weight was included as an outcome measure, although it is not a component of metabolic syndrome as defined by NCEP/ATP III. DBP = diastolic blood pressure; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; NCEP/ATP = National Cholesterol Education Program/Adult Treatment Panel; SBP = systolic blood pressure; TG = triglycerides; WC = waist circumference.

(n = 89; Figure 1). Baseline levels and different demographic characteristics for study samples are shown in Table 1. There were no significant between-group differences in baseline demographics or medical history measures.
A Randomized Controlled Trial to Assess Pharmacist-Physician Collaborative Practice in the Management of Metabolic Syndrome in a University Medical Clinic in Jordan

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n = 110)</th>
<th>Usual Care (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 6 Months of Follow-Up</td>
</tr>
<tr>
<td>Body weight (kg)*</td>
<td>86.7 [12.8]</td>
<td>86.0 [12.8]</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>103.4 [8.9]</td>
<td>103.3 [8.3]</td>
</tr>
<tr>
<td>Triglycerides (mg per dL)</td>
<td>189.3 [79.6]</td>
<td>158.4 [77.3]</td>
</tr>
<tr>
<td>FBG (mg per dL)</td>
<td>120.1 [47.6]</td>
<td>106.8 [47.5]</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>83.6 [10.7]</td>
<td>76.6 [10.7]</td>
</tr>
</tbody>
</table>

*A: Baseline values were collected at the initial enrollment visit; the enrollment period was from March 15, 2009, through May 10, 2009. The values for the 6-month follow-up were collected at the last patient visit (i.e., the sixth monthly visit); the follow-up was from March 15, 2009, through November 12, 2009.

**P** values for the between-group comparisons of the baseline-to-follow-up change amounts. For waist circumference, HDL-C, and FBG, Student's t-tests were used, for body weight, systolic BP, and diastolic BP, Mann-Whitney tests were used.

At baseline, 55 (50.0%) patients in the intervention group had 3 components of metabolic syndrome according to NCEP/ATP III; 44 (40.0%) had 4 components; and 11 (10.0%) had all 5 components (Table 2). The baseline distribution was similar in the control arm: 46 (51.7%) had 3 components; 36 (40.5%) had 4 components; and 7 (7.9%) had 5 components. After 6 months, 43 (39.1%) patients were successfully shifted from metabolic syndrome status to nonmetabolic syndrome status in the intervention arm, compared with 22 (24.7%) patients in the control arm (P = 0.032).

From baseline to follow-up, statistically significant differences between the intervention and control arms were observed for triglycerides, systolic BP (SBP), and diastolic BP (DBP; Table 3, Figure 2). Rates of achievement of goals for SBP and DBP at the 6-month follow-up were 70.0% and 84.5%, respectively. This improvement in metabolic status did not appear to be significantly associated with gender (P = 0.632), age (P = 0.651), or weight (P = 0.923, data not shown).

A total of 308 pharmacist interventions were provided during the course of the study, with a mean of 2.8 interventions per patient. Of these, 182 interventions were provided to the physicians, and 126 were provided to the patients, including patient education and adherence counseling (Table 4). Physicians agreed to and implemented 128 (70.3%) of the pharmacist recommendations. For 90 patients, a recommendation to initiate 1 or more new drug therapies was made, including angiotensin-converting enzyme (ACE) inhibitors (n = 23), angiotensin II receptor blockers (ARBs, n = 6), simvastatin (n = 32), atorvastatin (n = 8), gemfibrozil (n = 12), low-dose aspirin (n = 22), and omeprazole (n = 27). Thirteen interventions were recommended to increase doses, and 27 interventions suggested that patients were at high risk of developing adverse drug reactions and required monitoring or prophylactic therapy. Laboratory monitoring was recommended in 24 interventions, including 9 recommendations for liver enzyme testing (e.g., for patients on statins, particularly in combination with fibrates); 4 for kidney function testing (e.g., for patients on ACE inhibitor and/or planned titration to combination antihypertensive); 5 for thyroid function testing (to exclude secondary causes of high triglycerides); 2 for potassium-level testing; and 4 for testing of creatinine phosphokinase (CPK) levels. Cost-effective interchange was recommended in 19 interventions; drug discontinuation due to adverse reactions or side effects was suggested in 6 interventions; and drug-drug interactions were identified in 3 interventions. We counseled patients on adherence in 13 interventions and on lifestyle modifications in 113 interventions.

### Discussion

In family medicine clinics affiliated with a teaching hospital, pharmacist-physician collaboration resulted in a greater rate of success in shifting patients with metabolic syndrome status to nonmetabolic syndrome status compared with usual care, 39.1% versus 24.7%, respectively. Although this study failed to demonstrate significant between-group differences in weight and waist circumference reductions or HDL-C increases, triglycerides were significantly improved in the intervention arm compared with the control arm. Furthermore, both SBP and DBP improved more in the pharmacist care collaborative practice arm than in usual care, and rates of goal achievement in the intervention arm for SBP (less than 85 mm Hg) and DBP (less than 130 mm Hg) at the 6-month follow-up were 70% and 85%, respectively.

The greater success of physician-pharmacist collaboration compared with usual care may have occurred because diagnosis and management of metabolic syndrome are typically not integrated into standard health care protocols. Procedures for metabolic syndrome identification and for making a
Furthermore, implementing clinical pharmacist services in evaluating metabolic syndrome components, monitoring, and well-established diagnosis in real clinical settings are critical. Furthermore, implementing clinical pharmacist services in evaluating metabolic syndrome components, monitoring, and educating patients might provide an effective and applicable tool to identify patients who are at high risk of developing atherosclerotic CVD and type 2 diabetes because of the associations of metabolic syndrome and its components with CVD risk.\textsuperscript{13-16}

The effectiveness of pharmacist-physician collaboration is consistent with previous published investigations of the role of pharmacists in the treatment of dyslipidemia, diabetes, and hypertension.\textsuperscript{17-19,21,22} In a randomized controlled trial by Carter et al. (2009) that evaluated pharmacist-physician collaboration in the treatment of hypertension in community-based medical offices, a greater mean reduction in SBP over a 6-month follow-up was reported for intervention group versus control group patients; BP was controlled in 63.9% of intervention group patients compared with 29.9% of patients in the control group.\textsuperscript{19} A randomized trial by McLean et al. (2008) of combined community pharmacist and nurse care in patients with diabetes found that SBP reduction was a mean 5.6 mm Hg greater in intervention than control group patients after 6 months of follow-up.\textsuperscript{21} In a pooled analysis of 2 randomized controlled trials conducted in outpatients with CVD (heart failure or hypertension), Murray et al. (2009) found that the risk of adverse drug events and medication errors was reduced by approximately 34% in patients who received monitoring and instruction from pharmacists compared with those receiving routine dispensing alone.\textsuperscript{20} In a study by Ramser et al. (2008), triglycerides were reduced by a mean 43.2 mg per dL, from 150.7 mg per dL to 107.5 mg per dL, in patients with diabetes who were resistant to usual care and received a collaborative pharmacist-physician intervention. This study was not controlled and primarily targeted diabetes clinical indicators, and no significant reductions in DBP or SBP were observed.\textsuperscript{17} The present study is the first to evaluate a physician-pharmacist collaborative practice addressing lifestyle changes and drug therapy in patients with metabolic syndrome using a randomized controlled trial design.

**Limitations**

First, the study’s 6-month follow-up period may not have been long enough to measure improvements in weight reduction and waist circumference, which may require longer and extensively focused health education programs. A study with longer follow-up is also needed to assess effects on cardiovascular events and

### TABLE 4  Pharmacist Interventions with Physicians and Patients

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate drug therapy</td>
<td>90</td>
<td>Simvastatin was initiated for a patient who failed to achieve recommended values for lipid parameters after 4 months of therapeutic lifestyle changes (total cholesterol 245 mg per dL, LDL-C 160 mg per dL). Metformin was initiated for an obese patient presenting with fasting blood glucose more than 126 mg per dL.</td>
</tr>
<tr>
<td>Monitor or administer prophylactic therapy for potential adverse drug reactions</td>
<td>27</td>
<td>Omeprazole 20 mg daily before breakfast was recommended for gastro-protection for patient prescribed NSAID.</td>
</tr>
<tr>
<td>Laboratory monitoring</td>
<td>24</td>
<td>Potassium-level monitoring was recommended for a patient presenting with elevated levels of potassium. Liver function testing was recommended for a patient who was prescribed simvastatin and gemfibrozil for the treatment of mixed dyslipidemia.</td>
</tr>
<tr>
<td>Cost-effective interchange</td>
<td>19</td>
<td>An ACE inhibitor was recommended instead of the initial physician choice of an ARB for a patient with diabetes; the patient had no history of cough or other therapeutic contraindications.</td>
</tr>
<tr>
<td>Increase doses of existing drug therapy</td>
<td>13</td>
<td>Increase daily dose of amiodipine from 5 mg to 10 mg for a patient whose blood pressure readings exceeded recommended goals. Increase simvastatin dose to attain recommended lipid parameters.</td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>6</td>
<td>Patient developed dry cough a few weeks after lisinopril was started. Chest examination excluded other causes, and discontinuation of lisinopril was recommended.</td>
</tr>
<tr>
<td>Identification of drug-drug interaction</td>
<td>3</td>
<td>Atenolol was discontinued when patient was started on trandolapril/verapamil single-pill combination therapy to avoid additive risk of cardiac suppression.</td>
</tr>
</tbody>
</table>

**Description**

- Initiate drug therapy
- Monitor or administer prophylactic therapy for potential adverse drug reactions
- Laboratory monitoring
- Cost-effective interchange
- Increase doses of existing drug therapy
- Drug discontinuation
- Identification of drug-drug interaction

**Number**

- 90
- 27
- 24
- 19
- 13
- 6
- 3

**Examples**

- Simvastatin was initiated for a patient who failed to achieve recommended values for lipid parameters after 4 months of therapeutic lifestyle changes (total cholesterol 245 mg per dL, LDL-C 160 mg per dL).
- Metformin was initiated for an obese patient presenting with fasting blood glucose more than 126 mg per dL.
- Omeprazole 20 mg daily before breakfast was recommended for gastro-protection for patient prescribed NSAID.
- Potassium-level monitoring was recommended for a patient presenting with elevated levels of potassium.
- Liver function testing was recommended for a patient who was prescribed simvastatin and gemfibrozil for the treatment of mixed dyslipidemia.
- An ACE inhibitor was recommended instead of the initial physician choice of an ARB for a patient with diabetes; the patient had no history of cough or other therapeutic contraindications.
- Increase daily dose of amiodipine from 5 mg to 10 mg for a patient whose blood pressure readings exceeded recommended goals.
- Increase simvastatin dose to attain recommended lipid parameters.
- Patient developed dry cough a few weeks after lisinopril was started. Chest examination excluded other causes, and discontinuation of lisinopril was recommended.
- Atenolol was discontinued when patient was started on trandolapril/verapamil single-pill combination therapy to avoid additive risk of cardiac suppression.

**ACE = angiotensin-converting enzyme; ARB = angiotensin-II receptor blocker; dL = deciliter; LDL-C = low-density lipoprotein cholesterol; mg = milligrams; NSAID = non-steroidal anti-inflammatory drug.**
development of type 2 diabetes mellitus. It is also possible that the effects observed in this study diminished over time.

Second, the physician team was the same for both study arms. Physicians worked with the clinical pharmacist for 9 months (full study period) and were aware of recommendations and educational materials given to patients in the intervention arm, which may have produced a cross-over effect and biased the results in the usual care group. Moreover, usual care patients received phone calls from the pharmacist encouraging their attendance for monthly appointments. They were questioned about drug therapy adherence and/or lifestyle habits and were aware of the various components of metabolic syndrome. The combined effects of physicians and pharmacists on the control group may have contributed to improved outcomes in the usual care group and reduced the observed differences in outcomes between the 2 study groups.

Third, physicians were also aware of their roles in the study. Thus, it is possible that they were more cooperative in accepting pharmacist interventions than they would be in routine day-to-day practice settings.

Fourth, the study was conducted in a single teaching hospital in Jordan, and its intervention methods and results may not generalize to other health systems and cultural settings. However, the study’s findings are consistent with those of prior research documenting favorable effects of physician-pharmacist collaboration on patients with chronic disease.17-22

Conclusions

Compared with usual care provided by physicians only, physician-pharmacist collaboration improved 6-month outcomes in a sample of patients with metabolic syndrome attending family medicine clinics in a teaching hospital in the Middle East. The effects of careful periodic pharmacological and dietary screening, education, and monitoring of metabolic syndrome should be assessed in routine health care provided in a variety of health care system settings.

DISCLOSURES

This study was supported by a grant from the Deanship of Research, The University of Jordan, Amman, Jordan. The U.S. National Institutes of Health (ClinicalTrials.gov) study registry number is NCT01099306.

Concept and design were performed by all authors. Data were collected with Hammad with the assistance of Albsoul-Younes. Data interpretation and writing of the manuscript were performed by Albsoul-Younes and Hammad. The manuscript was revised by Albsoul-Younes and Hammad with the assistance of Tahaineh and Yasein.

ACKNOWLEDGEMENTS

The authors would like to extend a deep appreciation to all the physicians practicing at the family medicine clinic at Jordan University Hospital for providing patient care services during this study.

REFERENCES

A Randomized Controlled Trial to Assess Pharmacist-Physician Collaborative Practice in the Management of Metabolic Syndrome in a University Medical Clinic in Jordan


Prevalence of Achievement of A1c, Blood Pressure, and Cholesterol (ABC) Goal in Veterans with Diabetes

Scott Martin Vouri, PharmD; Robert F. Shaw, PharmD, MPH; Nancie V. Waterbury, PharmD; Jason A. Egge, PharmD, MS, BCPS; and Bruce Alexander, PharmD, BCPP

ABSTRACT

BACKGROUND: The “ABCs of Diabetes” are defined as hemoglobin A1c < 7.0%, blood pressure < 130/80 millimeters mercury (mm Hg), and low-density lipoprotein cholesterol (LDL-C) < 100 milligrams per deciliter (mg per dl). Assessments of 3-part goal attainment of A1c, blood pressure, and cholesterol have been reported using data from the National Health and Nutrition Examination Survey (NHANES) for several time periods (e.g., 1988-1994, 1999-2000, 1999-2002, and 2003-2004), Look Action for Health in Diabetes (Look AHEAD, 2001-2004), and community-based endocrinology practice (CBEP, 2000-2004). In 2002, an unpublished analysis of data from 2001-2002 at the Iowa City Veterans Affairs (ICVA) Medical Center found less than 50% of patients met each of the 3 individual goals. In the 5 years following the 2001-2002 assessment, the care for veterans with diabetes at the ICVA was enhanced to include (a) an increased number of diabetes classes and clinics, (b) implementation of the diabetes Care Coordination/Home Telehealth (CCHT) program, and (c) clinical reminders for diabetes performance measures that were added to the electronic medical record (EMR).

OBJECTIVES: To (a) describe the prevalence of veterans meeting the ABC goals of diabetes in 1 VA medical center; (b) differentiate the proportion of diabetes patients who met the individual targets for A1c, blood pressure, and LDL-C and compare the results for 2008 through September 2009 with the earlier data from this facility (2001-2002); and (c) examine results reported previously in the literature for NHANES, Look AHEAD, and CBEP data sources.

METHODS: Single-center, retrospective analysis of veterans at the ICVA for dates of service from January 1, 2008, through September 30, 2009, who (a) filled at least 1 prescription for an antidiabetic medication and (b) had each of the 3 biomarker values recorded in the EMR for A1c, blood pressure, and LDL-C after the antidiabetic prescription fill date.

RESULTS: Of the 5,426 (97.6% male) patients meeting inclusion criteria in 2008-2009, 17.3% (n = 936) achieved the 3-part ABC goal. In this managed care setting, achievement of the 3-part ABC goal surpassed the proportions reported in previous studies in NHANES data (5.2% in 1988-1994, 7.3% in 1999-2000, 7.0% in 1999-2002, 13.2% in 2003-2004), and 10.1% in Look AHEAD 2001-2004, but fell short of the 22.0% reported in the 2000-2004 CBEP performance (22.0%).

CONCLUSIONS: The proportion of patients achieving each of the 3 goals for A1c, blood pressure, and LDL-C improved significantly in 2008-2009 compared with the 2001-2002 assessment in this medical center, following implementation of yearly clinical reminders for diabetes care, enhanced patient education, and other program changes that included home-based telephone monitoring with diabetes case management for some patients. Achievement of the 3-part ABC goal in 2008-2009 (17.3%) surpassed 5 assessments reported in the literature but was lower than the CBEP (2000-2004) performance (22.0%).

J Manag Care Pharm. 2011;17(4):304-12

Copyright © 2011, Academy of Managed Care Pharmacy. All rights reserved.
The National Diabetes Education Program (NDEP)\(^1\,^2\) and the Diabetes Quality Improvement Project (DQIP)\(^3\) were established in 1997 to improve diabetes care. From these programs and published literature, the American Diabetes Association (ADA) established biomarker goals for successful management of diabetes: hemoglobin Alc < 7.0%, blood pressure < 130/80 millimeters mercury (mm Hg), and low-density lipoprotein cholesterol (LDL-C) < 100 milligrams per deciliter (mg per dL). These goals are collectively known as the “ABCs of Diabetes.” Despite the inception of programs such as NDEP and DQIP, providers and patients are often unaware of these treatment goals. The NDEP report in 2007 showed that in 2005 only about 20% of physicians and slightly less than 40% of nurse practitioners were aware of the term “ABCs of Diabetes.” However, physicians in 2005 self-reported monitoring diabetes patients “frequently” (every 0-3 months) for Alc (almost 80%), blood pressure (more than 80%), and cholesterol (about 25%).

Although many studies have examined individual components of the ABCs of diabetes, only a few have reported the proportion of patients achieving all 3 goals, and a direct comparison between the studies is difficult due to differences in patient samples and study methodology (Tables 1 and 2). The National Health and Nutrition Examination Survey (NHANES) data were analyzed for several different time periods for achievement of the 3-part ABC goal and have been reported for several time periods, for example, 5.2% for 1988-1994,\(^4\) 7.3% for 1999-2000,\(^5\) 7.0% for 1999-2002,\(^6\) and 13.2% for 2003-2004.\(^7\)

From 2001 to 2004, the Look Action for Health in Diabetes (Look AHEAD) study reported 10.1% of people with diabetes who were overweight or obese met the ABC goal.\(^8\) From 2000 to 2004, the community-based endocrinology practice (CBEP) study evaluated consecutive patients with diabetes followed aggressively by endocrinology providers and found 22.0% achieved the ABC goal.\(^9\)

In 2002, the cardiovascular management of a random sample of 380 patients with type 2 diabetes from the Iowa City Veterans Affairs (ICVA) Medical Center was reported in a poster abstract.\(^10\) This cross-sectional analysis from 2001-2002 found 43.2% of patients (n = 164) had an Alc < 7.0%, and 29.2% (n = 111) had a blood pressure < 130/80 mm Hg. Of the 287 patients with type 2 diabetes who had lipid laboratory values, 49.5% (n = 142) had calculated LDL-C < 100 mg per dL. This poster abstract did not report the percentage of patients achieving the 3-part ABC goal.

Clinical reminders were added to the electronic medical record (EMR) at the ICVA after the 2001-2002 study, and these were standardized for all facilities in the Veterans Integrated Service Network (VISN) 23 (Midwest) in 2004. These reminders help clinicians comply with specific performance measures and guidelines in an effort to help improve patient care; they can be displayed in 4 areas of the EMR, including the main cover sheet and notes section. Clicking on the reminder provides more details about the individual alert. From 2004-2007, the Veterans Affairs/Department of Defense (VA/DOD) diabetes performance measures were supported by clinical reminders that included targeting Alc < 9%, outpatient blood pressure < 140/90 mm Hg, and LDL-C < 120 mg per dL (note: these reminder thresholds are higher than the ABC goals of Alc < 7%, blood pressure < 130/80 mm Hg, and LDL-C < 100 mg per dL used in both the 2001-2002 and 2008-2009 ICVA studies). Evidence-based VA/DOD guidelines promote risk stratification, guiding providers to assess the risk and benefits of therapeutic targets for individual patients; these guidelines do not represent the ideal target values for all patients.\(^11\)

To accommodate an increase in the number of veterans requesting diabetes-related care (based on referrals from health care providers), the number of diabetes clinics and classes expanded. At the end of 2003, the number of monthly diabetes endocrine clinics (clinics established to focus on the management of diabetes and staffed by endocrinologists, an advanced-practice nurse who is a certified diabetes educator, and a clinical pharmacy specialist who reviews medication use with patients prior to the appointment with the endocrinologist) increased from 3 to 4 and further expanded to 5 in 2007. In 2007, the frequency of diabetes education classes increased to at least 1 per calendar quarter, and class schedules were expanded to all ICVA-affiliated community-based outpatient clinics. The diabetes education class is a 4-hour class emphasizing the importance of carbohydrate counting, exercise, oral and injectable medications, and microvascular and macrovascular complications of diabetes. The clinical pharmacy specialist uses 1 hour of the 4-hour class to review the mechanisms of actions of diabetes medications along with proper dosing and use, explain the definition and proper treatment for hypoglycemia, and describe the importance of exercise and proper foot care.

Other quality of care initiatives included implementation of a network-wide, systematic effort in the VISN 23 (Midwest) region in 2006 to target high-risk patients with chronic illnesses including diabetes. In 2007, the diabetes Care Coordination/Home Telehealth (CCHT) program was implemented at the ICVA Medical Center. Patients self-enroll in CCHT based on referral from a provider, and the target population is composed of patients with Alc > 9%.

We believed these clinical care changes would contribute to quality improvement in the number and proportion of veterans achieving the individual and 3-part ABC goal at our medical center.

### Methods

#### Patients and Study Measures

Our objective was to determine the proportion of veterans with diabetes who received at least 1 prescription for an antidiabetic...

<table>
<thead>
<tr>
<th>Study</th>
<th>A1c</th>
<th>Blood Pressure</th>
<th>Cholesterol</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES&lt;sup&gt;6&lt;/sup&gt; Included 2 samples: 1988-1994&lt;sup&gt;a&lt;/sup&gt; 1999-2000&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Measured once</td>
<td>Mean of 2nd &amp; 3rd reading (1988-1994)</td>
<td>Measured once (TC &lt; 200 mg per dL considered to be at goal); measured only in morning session after self-reported 8.5- to 24-hour fast; TC was used because of too few participants with valid LDL-C measurements</td>
<td>Patients (male and nonpregnant females) aged 0 years or older (except for women who were diabetic during a pregnancy) Non-Hispanic Whites in study sample: 1988-1994: 74.6% 1999-2000: 59.8% Mean years since diabetes diagnosis: 1988-1994: 10.2 (1999-2000): 12.5</td>
</tr>
<tr>
<td>NHANES (1999-2006)&lt;sup&gt;7&lt;/sup&gt; Included 2 samples: 1999-2002&lt;sup&gt;a&lt;/sup&gt; 2003-2006</td>
<td>Measured once</td>
<td>Mean of 3rd or 4th readings excluding the 1st reading</td>
<td>Measured once; LDL-C calculated using Friedewald equation; measured only in morning session after self-reported 8.5- to 24-hour fast</td>
<td>Patients (male and nonpregnant females) aged 20 years or older (except for women who were diabetic during a pregnancy) Non-Hispanic Whites in study sample: (1999-2002) 11.7 (2003-2006) 11.2</td>
</tr>
<tr>
<td>NHANES (1999-2004)&lt;sup&gt;8&lt;/sup&gt; Included 3 samples: 1999-2000 2001-2002 2003-2004&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Measured once</td>
<td>Mean of 3rd or 4th readings excluding the 1st reading</td>
<td>Measured once (TC &lt; 200 mg per dL considered to be at goal); measured only in morning session after self-reported 8.5- to 24-hour fast; TC &lt; 200 mg per dL used based on NCEP ATP III guideline</td>
<td>Patients (male and nonpregnant females) aged 20 years or older (except for women who were diabetic during a pregnancy) Non-Hispanic Whites in study sample: (1999-2000) 59.3% (2001-2002) 64.6% (2003-2004) 69.9% Mean years since diabetes diagnosis: (1999-2000) 12.5 (2001-2002) 11.0 (2003-2004) 12.6</td>
</tr>
<tr>
<td>Look AHEAD&lt;sup&gt;9&lt;/sup&gt; 2001-2004&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Measurement closest to randomization (fasting); patients with A1c &gt; 11% were excluded</td>
<td>Mean of 2 seated readings 30 seconds apart after 5-minute rest period; excluded if blood pressure ≥ 160/100 mm Hg</td>
<td>Measurement closest to randomization (fasting); LDL-C calculated using Friedewald equation; excluded if fasting triglycerides ≥ 600 mg per dL</td>
<td>Patients aged 45-74 years All 5,145 participants were either overweight or obese (defined as a BMI ≥ 25 kg/m² or ≥ 27 kg/m² if on insulin) Whites: 63.2% of study sample Mean years since diabetes diagnosis: 6.8 Many exclusion criteria including: weight loss exceeding 10 pounds within previous 3 months, history of weight loss surgery, chronic treatment with systemic corticosteroids, current use of medications for weight, pregnant or nursing, any CVD comorbidity, serum creatinine &gt; 1.4 mg per dL (females) or 1.5 mg per dL (males), or receiving dialysis</td>
</tr>
<tr>
<td>CBEP&lt;sup&gt;10&lt;/sup&gt; 2001-2004&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mean of at least 2 measurements throughout study</td>
<td>Mean of at least 2 blood pressure measurements throughout study</td>
<td>Mean of at least 2 TC measurements; TC &lt; 200 mg per dL considered to be at goal in ABC assessment Mean LDL-C was calculated by Friedewald equation and reported as a secondary analysis</td>
<td>Patients aged 18 years or older Analyzed consecutive patients seen in consultation for diabetes management Non-Hispanic Whites: 92.7% of study sample Mean years since diabetes diagnosis: 11.2 Providers were endocrinologists Blood glucose checked 2-4 times per day in insulin-requiring patients and at least 2 times per day in patients on oral therapy; all patients were encouraged to contact CBEP at least once per week for adjustments to their treatment regimen; office follow-up every 1-2 months in patients not meeting ABC goal and 3-4 months in patients meeting ABC goal</td>
</tr>
<tr>
<td>ICVA&lt;sup&gt;11&lt;/sup&gt; 2001-2002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No details available</td>
<td>Only 75.5% of the sample had a fasting lipid panel drawn during study period. Calculated LDL-C was used</td>
<td>No details available</td>
<td>Inclusion criteria: diagnosis of type 2 diabetes for at least 1 year Race of sample not collected Mean years since diagnosis not collected</td>
</tr>
<tr>
<td>ICVA&lt;sup&gt;12&lt;/sup&gt; 2008-2009&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Last measured A1c prior to end of study period (mean if 2 or more were collected on the same day)</td>
<td>Last measured blood pressure prior to end of study period (mean if 2 or more were measured on the same day)</td>
<td>Last measured direct LDL-C prior to end of study period (mean if 2 or more were collected on the same day) Fasting status was unknown</td>
<td>Veterans aged 18 years or older filling at least 1 antidiabetic agent during study period Race of sample not collected Mean years since diabetes diagnosis not collected</td>
</tr>
</tbody>
</table>

<sup>a</sup>These samples are reported in Figure 2 and in grey shade in Table 2. A1c = hemoglobin A1c; ABC = hemoglobin A1c < 7%; blood pressure < 130/80 mm Hg, and LDL < 100 mg per dL; BMI = body mass index; CBEP = community-based endocrinology practice; CVD = cardiovascular disease; ICVA = Iowa City Veterans Affairs; kg per m² = kilogram per square meter; LDL-C = low density lipoprotein cholesterol; Look AHEAD = Look Action for Health in Diabetes; mg per dL = milligrams per deciliter; mm Hg = millimeters mercury; NCEP ATP III = National Cholesterol Education Program Third Adult Treatment Panel; NHANES = National Health and Nutrition Examination Survey; TC = total cholesterol.
Prevalence of Achievement of A1c, Blood Pressure, and Cholesterol (ABC) Goal in Veterans with Diabetes

### Table 2: Patient Characteristics for NHANES, Look AHEAD, CBEP, and ICVA

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Subjects</th>
<th>Mean Age in Years</th>
<th>% Male</th>
<th>% Type 2 Diabetes</th>
<th>% BMI ≥ 30</th>
<th>% on Antidiabetic Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES (1988-1994)</td>
<td>1,265b</td>
<td>60.2</td>
<td>43.2</td>
<td>100.0c</td>
<td>41.6</td>
<td>75.2</td>
</tr>
<tr>
<td>NHANES (1999-2000)</td>
<td>441b</td>
<td>59.3</td>
<td>50.0</td>
<td>100.0c</td>
<td>54.6</td>
<td>81.3</td>
</tr>
<tr>
<td>NHANES (1999-2006)</td>
<td>1,780</td>
<td>NRd</td>
<td>NRd</td>
<td>100.0c</td>
<td>NRd</td>
<td>NRd</td>
</tr>
<tr>
<td>NHANES (1999-2002)</td>
<td>827</td>
<td>58.8</td>
<td>49.9</td>
<td>100.0c</td>
<td>52.3</td>
<td>81.6</td>
</tr>
<tr>
<td>NHANES (2003-2006)</td>
<td>953</td>
<td>59.2</td>
<td>45.4</td>
<td>100.0c</td>
<td>56.7</td>
<td>82.2</td>
</tr>
<tr>
<td>NHANES (1999-2004)</td>
<td>1,318</td>
<td>NRd</td>
<td>NRd</td>
<td>100.0c</td>
<td>NRd</td>
<td>NRd</td>
</tr>
<tr>
<td>NHANES (1999-2000)</td>
<td>415</td>
<td>59.1</td>
<td>49.8</td>
<td>100.0c</td>
<td>NRc</td>
<td>80.4</td>
</tr>
<tr>
<td>NHANES (2001-2002)</td>
<td>412</td>
<td>57.3</td>
<td>50.3</td>
<td>100.0c</td>
<td>NRc</td>
<td>81.8</td>
</tr>
<tr>
<td>NHANES (2003-2004)</td>
<td>491</td>
<td>59.7</td>
<td>46.7</td>
<td>100.0c</td>
<td>NRc</td>
<td>81.8</td>
</tr>
<tr>
<td>Look AHEAD (2001-2004)</td>
<td>5,145</td>
<td>58.7</td>
<td>40.5</td>
<td>100.0</td>
<td>85.1</td>
<td>86.3</td>
</tr>
<tr>
<td>CBEP (2000-2004)</td>
<td>395</td>
<td>60.4</td>
<td>59.2</td>
<td>84.1</td>
<td>NRc</td>
<td>99.8</td>
</tr>
<tr>
<td>ICVA (2001-2002)</td>
<td>380</td>
<td>68.4</td>
<td>NR</td>
<td>100.0</td>
<td>NR</td>
<td>91.0</td>
</tr>
<tr>
<td>ICVA (2008-2009)</td>
<td>5,426</td>
<td>67.3</td>
<td>97.6</td>
<td>98.9%</td>
<td>54.5b</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Overall number of subjects used to determine 3-part ABC goal was not reported.

In NHANES diabetes was not categorized as type 1 versus type 2; subjects with diabetes diagnosed at 30 years of age or younger and treated with insulin alone were excluded because they were considered likely to have type 1 diabetes.

#### Statistical Analysis

Descriptive statistics were used for the primary measure (proportion of veterans who met the 3-part ADA-defined ABC goal) and the secondary measure (proportion who met individual targets for A1c, blood pressure, and LDL-C) as well as summarizing baseline sample characteristics. Pearson chi-square was used to compare the individual goals from 2001-2002 with the 2008-2009 findings. Analysis was 2-tailed and performed using SPSS version 15.0 (SPSS Inc., Chicago, IL).

#### Results

Of 52,452 total ICVA medical center patients, 7,337 (14.0%) received at least 1 antidiabetic prescription fill for service dates from January 1, 2008, through September 30, 2009 (Figure 1). A diagnosis of diabetes was confirmed, and laboratory documentation after the prescription fill date was available for the 3 biomarker values for 5,426 patients (74.0%, Figure 1). The mean and [median] number of days after the prescription fill date for each biomarker was as follows: A1c (373.6 [387]), blood pressure, and LDL-C.

**Table 2**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Subjects</th>
<th>Mean Age in Years</th>
<th>% Male</th>
<th>% Type 2 Diabetes</th>
<th>% BMI ≥ 30</th>
<th>% on Antidiabetic Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES (1988-1994)</td>
<td>1,265b</td>
<td>60.2</td>
<td>43.2</td>
<td>100.0c</td>
<td>41.6</td>
<td>75.2</td>
</tr>
<tr>
<td>NHANES (1999-2000)</td>
<td>441b</td>
<td>59.3</td>
<td>50.0</td>
<td>100.0c</td>
<td>54.6</td>
<td>81.3</td>
</tr>
<tr>
<td>NHANES (1999-2006)</td>
<td>1,780</td>
<td>NRd</td>
<td>NRd</td>
<td>100.0c</td>
<td>NRd</td>
<td>NRd</td>
</tr>
<tr>
<td>NHANES (1999-2002)</td>
<td>827</td>
<td>58.8</td>
<td>49.9</td>
<td>100.0c</td>
<td>52.3</td>
<td>81.6</td>
</tr>
<tr>
<td>NHANES (2003-2006)</td>
<td>953</td>
<td>59.2</td>
<td>45.4</td>
<td>100.0c</td>
<td>56.7</td>
<td>82.2</td>
</tr>
<tr>
<td>NHANES (1999-2004)</td>
<td>1,318</td>
<td>NRd</td>
<td>NRd</td>
<td>100.0c</td>
<td>NRd</td>
<td>NRd</td>
</tr>
<tr>
<td>NHANES (1999-2000)</td>
<td>415</td>
<td>59.1</td>
<td>49.8</td>
<td>100.0c</td>
<td>NRc</td>
<td>80.4</td>
</tr>
<tr>
<td>NHANES (2001-2002)</td>
<td>412</td>
<td>57.3</td>
<td>50.3</td>
<td>100.0c</td>
<td>NRc</td>
<td>81.8</td>
</tr>
<tr>
<td>NHANES (2003-2004)</td>
<td>491</td>
<td>59.7</td>
<td>46.7</td>
<td>100.0c</td>
<td>NRc</td>
<td>81.8</td>
</tr>
<tr>
<td>Look AHEAD (2001-2004)</td>
<td>5,145</td>
<td>58.7</td>
<td>40.5</td>
<td>100.0</td>
<td>85.1</td>
<td>86.3</td>
</tr>
<tr>
<td>CBEP (2000-2004)</td>
<td>395</td>
<td>60.4</td>
<td>59.2</td>
<td>84.1</td>
<td>NRc</td>
<td>99.8</td>
</tr>
<tr>
<td>ICVA (2001-2002)</td>
<td>380</td>
<td>68.4</td>
<td>NR</td>
<td>100.0</td>
<td>NR</td>
<td>91.0</td>
</tr>
<tr>
<td>ICVA (2008-2009)</td>
<td>5,426</td>
<td>67.3</td>
<td>97.6</td>
<td>98.9%</td>
<td>54.5b</td>
<td>100.0</td>
</tr>
</tbody>
</table>
pressure (398.0 [411]), and LDL-C (352.5 [369]). The majority of patients (98.9%) had type 2 diabetes, and this percentage is higher than national statistics, which may be explained in part by restrictions on military enlistment for individuals with diabetes (Table 2). The mean age was 67.3 years, with many patients being obese (54.5%) and predominantly male (97.6%). During the 21-month study period in 2008-2009, 62.5% (n = 3,389) of the patients received at least 1 prescription fill for metformin; sulfonylureas were received by 56.6% (n = 3,073), insulins by 38.9% (n = 2,112), thiazolidinediones by 8.8% (n = 478), alpha-glucosidase inhibitors by 1.0% (n = 55), and incretins/exenatide by 0.5% (n = 28). During the study period, a small percentage of our patients were managed by the endocrinology clinic (4.7%), participated in diabetes class (7.1%), or were enrolled in the CCHT program (6.2%).

**ABC Goal Attainment**

In our study, 17.3% of patients (n = 936) achieved the 3-part ABC goal for diabetes management (Table 3). The remaining participants achieved 2 goals (39.1%, n = 2,122), 1 goal (32.4%, n = 1,795), and 11.2% (n = 609) did not meet any of the 3 goals. The individual goals were achieved by 2,932 patients (54.0%) for A1c < 7.0%, 2,266 (41.8%) for blood pressure < 130/80 mm Hg, and 3,613 (66.6%) for LDL-C < 100 mg per dL. The proportion of patients achieving the A1c goal improved by an absolute 10.8%; blood pressure goal improved by 12.6%; and LDL-C goal increased by 17.1% compared with the 2002 results (P < 0.001 for all 3 comparisons, Table 3). Figure 2 shows the proportion of patients meeting individual goals among NHANES, Look AHEAD, CBEP, and the ICVA patient sample. The 3-part ABC goal attainment by 17.3% of the study sample exceeds proportions reported in NHANES 1988-1994 (5.2%), 1999-2000 (7.3%), 1999-2002 (7.0%), 2003-2004 (13.2%), and Look AHEAD, 2000-2004 (10.1%).

**Discussion**

There are significant differences in the patient samples and methodology for the studies of ABC goal attainment that have been described in the literature (Tables 1 and 2), preventing definitive comparisons with the data from the ICVA. However, recognition of the differences in the patient samples and study methods permits informed comparison of the results of the present study with the results that have been reported previously (Figure 2).

The NHANES studies, comprising 4 of the 6 evaluations of ABC goal attainment reported in the literature, are very similar with regards to patient characteristics. Derived from the same survey, the inclusion criteria in these studies included male and nonpregnant females aged 20 years or older with diabetes.
Whereas patients in the NHANES studies were included based on self-reported diabetes, the participants in Look AHEAD and CBEP had diabetes diagnosed by health care providers, similar to the inclusion criteria in the present (2008-2009) ICVA study. Because the present ICVA study involved patients with diabetes who received at least 1 fill of an antidiabetic medication, this patient sample most closely resembles the sample in the CBEP study in which 99.8% received antidiabetic medication and contrasts with the NHANES and Look AHEAD data where 13.8% to 24.8% of the subjects were diet controlled. The exclusion of diet-controlled diabetes in our study may contribute to a lower proportion of all diabetes patients with ABC goal attainment because an analysis in the Look AHEAD trial showed that patients not on antidiabetic medications were more likely to meet the ABC goals and A1c goal compared with patients who used oral antidiabetic medications or insulin.9

Body mass index (BMI) is an important assessment for patients with diabetes. In a multivariate analysis of the Look
AHEAD trial, patients with a BMI < 30 kilogram per square meter (kg per m²) were more likely to meet all 3 goals compared with patients with a BMI > 40 kg per m². The Look AHEAD study had the highest percentage of obese patients (84.1%), defined as BMI > 30 kg per m².2,9 The NHANES, CBEP, and ICVA (2008-2009) studies had much lower proportions of patients with BMI > 30 kg per m²—between 41.6% and 56.7% (Table 2).6-8,10

NHANES (1999-2004)8 and NHANES (1999-2006)7 also differed from the previous NHANES,6 Look AHEAD,9 CBEP,10 ICVA (2001-2002),11 and ICVA (2008-2009) in the study objectives. All studies reported attainment of the 3-part ABC goal (except ICVA 2001-2002), along with the 3 individual goals. However, the aim of NHANES (1999-2004) and NHANES (1999-2006) was to examine trends in both diagnosis of diabetes and treatment of diabetes via sample populations. Although these studies showed similar achievement of ABC goals—11.4% and 10.0%,7 respectively—the longitudinal trend in improvement in ABC goal attainment was not significant. Achievement of the 3-part ABC goal in the NHANES samples for 1999-2000, 2001-2002, and 2003-2004 were 7.5%, 13.1%, and 13.2%, respectively (P > 0.05).8 For NHANES, during the 8-year period from 1999 through 2006, achievement of the 3-part ABC goal in the samples for 1999-2002 and 2003-2006 were 7.0% and 12.2%, respectively (P = 0.06).8

The results from the CBEP study demonstrate the effect of aggressive diabetes management, with 4.7% more patients achieving the 3-part ABC goal compared with our 2008-2009 data (22.0% vs. 17.3%). The CBEP intervention included endocrinology follow-up every 1 to 2 months if the A1c was not at goal or every 3 to 4 months if at goal. Patients were also encouraged to contact the clinic on a weekly basis to reassess labs and to make medication adjustments. Along with pharmacologic diabetes treatment, CBEP also focused on nonpharmacologic options to improve diabetes. Patients were directed to pamphlets and handouts detailing the risks associated with microvascular and macrovascular complications, offered grocery shopping guides to aid in selecting healthy food choices (low fat, low glycemic, and high fiber), and encouraged to engage in physical activity when feasible. Aggressive pharmacological management and promotion of nonpharmacologic options for treatment of diabetes contributed to the CBEP study having the highest percentage of patients meeting the ABC goals.10

Control of hypertension and cholesterol are also important to reduce the risk of microvascular and macrovascular disease. Blood pressure was at goal in less than one-half of our patients (41.8%). Our results for blood pressure goal attainment were higher than NHANES 1988-1994, 1999-2000, and 1999-2002 but lower than NHANES 2003-2004, CBEP, and Look AHEAD studies. In our study, we included the patient’s last blood pressure during the study period, and we could not control for the method of blood pressure measurement. The likelihood of different staff taking blood pressures with different methods (automatic/manual) is considerable. In the other studies, an average of at least 2 readings was used to determine the blood pressure for each patient.

In our 2008-2009 study, 66.6% of patients achieved their cholesterol (LDL-C) goal, similar to 68.8% reported in the CBEP study (Figure 2). However, CBEP used total cholesterol (TC) < 200 mg per dL to determine goal attainment; LDL-C was collected as part of a secondary analysis.10 The individual goal of TC < 200 mg per dL was also used as the cholesterol benchmark to determine the 3-part ABC goal in NHANES 1988-1994, 1999-2000, and 2003-2004. LDL-C assessment was used in NHANES 1999-2002, Look AHEAD, ICVA 2001-2002, and 2008-2009, and the Friedewald equation was used to calculate LDL-C except in the 2008-2009 ICVA data in which direct laboratory values were available in the EMR. Accordingly, use of direct LDL-C meant that values were not excluded for elevated A1c or significantly elevated triglycerides. In 2004, Lindsey et al. revealed a slight difference between calculated LDL-C and direct LDL-C where calculated LDL-C underestimated actual LDL-C by up to 20 mg per dL.14 The differences in methodology for the measurement of cholesterol among the studies should be acknowledged when comparing these data.

Overall, the proportion of patients with diabetes achieving the 3-part ABC goal and individual goals remains less than optimal. However, NHANES data from 1999-2004 and 1999-2006 showed improvement over time, suggesting advancement in diabetes care.7,8 We have identified several factors that may have contributed to improvement in achieving the 3 individual ABC goals at the ICVA in 2008-2009 compared with 2001-2002. Programs such as NDEP2 and DQIP3 encourage providers to emphasize to their patients the importance of reducing A1c, blood pressure, and LDL-C for the prevention of microvascular and macrovascular complications, as the CBEP intervention did as part of the nonpharmacological interventions.10 In addition, the VA has worked to improve adherence to diabetes goals including improvements in the EMR with the implementation of computerized clinical reminders for performance measures and expansion of diabetes clinics, classes, and programs. However, patient participation in voluntary education and other care interventions is low.

The Veteran’s Health Administration’s (VHA) performance measures have similarities with the Health Plan Employer Data and Information Set (HEDIS) measures. For the majority of health plans in the United States, HEDIS assesses annually the quality of care performance via 75 measures across 8 domains, including “comprehensive diabetes care.”15 For January 1, 2009, through December 31, 2009, mean attainment of 3 diabetes goals among commercial U.S. health plans on the HEDIS measures was 61.6% for A1c (<8%), 65.1% for blood pressure < 140/90 mm Hg (33.9% for blood pressure < 130/80 mm Hg),
and 47.0% for LDL-C.\textsuperscript{16} According to the HEDIS FY 2011 Q1 Technical Manual, the patient selection criteria for the HEDIS “comprehensive diabetes care” measures include members with diabetes aged 18 to 75 years and at least 2 encounters with ICD-9-CM codes 250.xx, 357.2, 362.0x, 366.41, or 648.0x. Exclusions include patients with gestational diabetes, hyperglycemia not otherwise specified, or steroid-induced hyperglycemia/diabetes. The HEDIS A1c and blood pressure goals differ somewhat from the current ADA goals (i.e., A1c < 7.0% and blood pressure < 130/80 mm Hg) and from the 2010 VA/DOD performance measures (i.e., A1c target is individualized based on the provider’s evaluation of the risk-benefit ratio and discussion with the patient [goal A1c < 9% for any patient with diabetes and blood pressure ≤ 140/90 mm Hg]).\textsuperscript{17} HEDIS data are reported to employers, and the VHA measures are reported to facility administrators.\textsuperscript{18} These measures and reports provide the basis for assessment of quality improvement initiatives.

In the present study, we did not specifically assess the effects of diabetes care interventions in our medical facility, including the use of clinical reminders. In directly relevant research, Hunt et al. (2009) found that implementation of a physician-directed, multifaceted health information system, including clinical reminders in primary care, was associated with a 24 percentage-point improvement in the proportion of patients attaining the LDL-C goal of < 100 mg per dL (from 32% to 56%), a 22% absolute improvement in goal blood pressure < 130/80 mm Hg (from 30% to 52%), and a 3% absolute improvement in the proportion of patients achieving A1c goal < 7.0% (from 47% to 50%).\textsuperscript{19} Agrawal and Mayo-Smith (2004) found that provider adherence to 15 clinical reminders was highly variable across 49 clinics in 8 VA medical centers (ranging from 67% to 97%), and adherence among physicians ranged from 29% to 100%.\textsuperscript{20}

We also did not assess the effects of the other interventions that were initiated at the ICVA between 2001-2002 and 2008-2009, including expansion in the number of diabetes clinics and education classes. During the ICVA 2008-2009 study period, 47% of patients were managed by the endocrinology clinic, a consulting clinic that does not manage patients long term—patients are returned to their primary care provider when stabilized on their antidiabetic regimens. Also during the 2008-2009 study period, 7.1% of the patients participated in a diabetes education class, a 1-time offering for each patient (i.e., patients who attended classes in years prior to 2008-2009 were not counted). During 2008-2009, clinicians could also refer patients with an A1c > 9.0% to the diabetes CCHT program in which patients are asked to upload their readings (e.g., A1c) on a weekly or bi-weekly basis, and these readings are included in the EMR. The primary care provider or the advanced practice nurse certified in diabetes education reviews the uploaded information and makes recommendations to the patient for any changes in diabetes care. The CCHT program was still in its infancy during the 2008-2009 study period, and only 6.2% of the patients were enrolled in CCHT.

Limitations

Foremost among the limitations of the present study is the absence of assessment of the 3-part ABC goal attainment for the ICVA sample in 2001-2002 and different sample selection criteria for the 2001-2002 study versus the follow-up analysis in 2008-2009. Third, only 287 of 380 patients (75.5%) had LDL-C values recorded in the 2001-2002 assessment, and the LDL-C values were calculated via the Freidewald equation versus the direct laboratory values recorded in the EMRs for the 2008-2009 assessment. Fourth, we did not assess the effects of several changes in diabetes care management that occurred over the period between 2001-2002 and the current evaluation period 2008-2009. Fifth, comparisons with the national studies are merely suggestive and not definitive because of the significant differences in the methods of data collection, inclusion/exclusion criteria, biomarker measures, and the characteristics of the patients in the samples. Sixth, our study sample was limited to patients filling at least 1 antidiabetic agent during the study period, thereby excluding patients with diet-controlled diabetes and making our study sample different than the national studies with the exception of CBEP in which 99.8% of the participants received antidiabetic medication. Seventh, biomarkers were collected for prevalence analysis and do not represent clinical endpoints. Finally, the generalizability of the present study is limited by the gender, race, and geographical characteristics of the sample.

Conclusions

The proportion of patients attaining the 3 individual goals of A1c, blood pressure, and LDL-C in 2008-2009 improved in each category compared with the 2001-2002 assessment. The improvement in these biomarker performance measures followed several changes in diabetes care processes, including an increased number of diabetes classes and clinics, implementation of a telephone-based home care coordination program, and adoption of clinical reminders in EMRs for suboptimal A1c, blood pressure, and LDL-C goal attainment in this VA medical center. Clinical reminders in EMRs potentially affected all patients in the present study whereas patient participation rates in the other diabetes interventions were low.
Prevalence of Achievement of A1c, Blood Pressure, and Cholesterol (ABC) Goal in Veterans with Diabetes

Authors

SCOTT MARTIN VOURI, PharmD, is a Post-Graduate Year 2 (PGY-2) Geriatrics Pharmacotherapy Resident, Texas Tech University Health Sciences Center School of Pharmacy, Dallas, Texas. ROBERT F. SHAW, PharmD, MPH, is a Clinical Pharmacy Specialist in Critical Care, Iowa City Veterans Affairs Medical Center, and Assistant Professor in the Clinical and Administrative Pharmacy Division, College of Pharmacy, University of Iowa, Iowa City, Iowa. NANCEE V. WATERBURY, PharmD, is a Clinical Pharmacy Specialist in Ambulatory Care; JASON A. EGGE, PharmD, MS, BCPS, is a Clinical Pharmacy Specialist in Ambulatory Care; and BRUCE ALEXANDER, PharmD, BCPP, is a Clinical Pharmacy Specialist VISN 23 in Mental Health, Iowa City Veterans Affairs Medical Center, Iowa City, Iowa.

AUTHOR CORRESPONDENCE: Scott Martin Vouri, PharmD, Texas Tech University Health Sciences Center School of Pharmacy, 4500 S. Lancaster Rd., Bldg. 7, Rm119A, Dallas, TX 75216. Tel.: 214.742.8387. ext. 70592; Fax:214.372.5020; E-mail: scott.vouri.pharmd@gmail.com.

DISCLOSURES

There was no external funding for this research, and the authors report no financial or other potential conflicts of interest related to the subject of this article. Study concept and design were performed by Vouri and Waterbury. Data were collected primarily by Egge and Alexander and interpreted primarily by Shaw. The manuscript was written primarily by Vouri and Waterbury and revised by Waterbury, with the assistance of the other authors.

REFERENCES


Analysis of Drug and Administrative Costs Allowed by U.S. Private and Public Third-Party Payers for 3 Intravenous Biologic Agents for Rheumatoid Arthritis

Bruce J. Wong, MBChB, FRACP; Mary A. Cifaldi, PhD, MSHA, RPh; Sanjoy Roy, MS; Dean C. Skonieczny, MBA, BSE; and Spyros Stavrakas, PhD

ABSTRACT

BACKGROUND: Rheumatoid arthritis (RA) is a common chronic condition with substantial morbidity that can now be treated with disease-modifying biologic agents that target tumor necrosis factor (TNF) or related mechanisms. The anti-TNF biologic agents are available in either intravenous (IV) or subcutaneous dose forms. The biologic agents with an indication for rheumatoid arthritis and administered only by IV infusion in medical offices include abatacept, infliximab, and rituximab. Although the literature on RA treatments, their outcomes, and aspects of their costs is substantial, the costs of administration by the IV route have not been directly studied.

OBJECTIVE: To assess the detailed costs of administering IV biologic agents for the treatment of RA in relation to the total cost of the medication itself in the United States.

METHODS: The sample included all patients with at least 1 medical claim with an ICD-9-CM diagnosis code for RA (codes 714.XX) in any claim field and at least 1 claim for infliximab, abatacept, or rituximab (HCPCS codes J1745, J0129, and J9310, respectively) at any time from January 1, 2006, through December 31, 2008, in a database associated with billing and claims administration for 72 U.S. medical clinics. Costs were determined using the payer allowed payment, which is the total contractual amount that the provider should receive, including the patient cost share. Costs were measured as the average cost per IV administration visit and in relation to the dose of medication billed. The authors verified that an RA diagnosis was present on 100% of infusion claims for the study drugs.

RESULTS: Over the study period for claims with dates of service from January 1, 2006, through December 31, 2008, 72 medical clinics had claims for a total of 4,248 unique patients with RA and a total of 33,354 clinic visits during the period from January 1, 2006, through December 31, 2008. These studies used either private payer or Medicare data, but not both.

• Mean annual costs for adalimumab, etanercept, and infliximab in the United States ranged from $12,692 to $16,013 in a retrospective analysis of claims data from January 2003 through June 2005. These studies used either private payer or Medicare data, but not both.

• Mean intravenous (IV) infusion time was found to differ significantly by biologic agent in a study of patients with RA by Yazici et al. (2009): abatacept (42 minutes), infliximab (131 minutes), and rituximab (274 minutes).

• Kruse et al. (2008) found that the costs for the administration of IV agents in metastatic breast cancer were 10.2% of the cost of a visit in which an infusion took place.

CONCLUSION: For patients who received an IV biologic agent to treat RA, IV administration costs accounted for 7.9% of the total cost of the visit.

What is already known about this subject

• Therapeutic choice between different routes of administration is a common clinical decision. Infused therapies, such as infliximab, abatacept, and rituximab, are commonly used over long periods of time to treat rheumatoid arthritis (RA).

• Total costs for the leading RA treatments have been studied in the aggregate using analyses of administrative claims data. For example, mean annual costs for adalimumab, etanercept, and infliximab in the United States ranged from $12,692 to $16,013 in a retrospective analysis of claims data from January 2003 through June 2005. These studies used either private payer or Medicare data, but not both.

What this study adds

• The authors of the present study analyzed administrative data for private and government third-party payers obtained from a large contracting and claims management system representing 72 U.S. medical clinics in which 4,248 patients received at least 1 IV infusion of a biologic RA treatment (abatacept, infliximab, or rituximab) in a total of 33,354 clinic visits during the period from January 1, 2006, through December 31, 2008.

• The average cost of administering IV infusions for 3 biologic drugs for RA was 7.9% of the total cost of the clinic visit, or 8.6% of the cost of the drug.

• The mean cost of administration was significantly (P<0.001) higher for rituximab ($390) than for infliximab ($224) or abatacept ($171).
Rheumatoid arthritis (RA) is a debilitating chronic illness with a substantial impact on an individual’s cost of care and quality of life and a moderate impact on duration of life. In the United States, RA is estimated to affect 1.3 million adults. In 1998, the first tumor necrosis factor (TNF) antagonist, infliximab, was approved for the treatment of RA. TNF antagonists inhibit biochemical pathways thought to be directly involved in the pathogenesis of RA as opposed to prior disease-modifying agents, which had uncertain mechanisms of action.

Prior to the introduction of TNF antagonists, both anti-inflammatory and disease-modifying agents to treat RA were given orally or by intramuscular injection in the case of gold. Biologic molecules, such as the new generation of TNF antagonists, are large protein molecules that are inactivated by gastric action and therefore need to be administered parenterally. Intravenous (IV) and subcutaneous routes of administration are variably available for existing agents. Specialized facilities and trained staff were developed to accommodate administration of the IV agents; for agents administered subcutaneously, patient training mechanisms were established. Although these technologies and procedures were already available for many therapies, they had not been deployed within a rheumatology practice. In addition to the traditional reasons for choosing a particular therapy, the type of physical infrastructure available to a prescribing physician may influence the choice of medication prescribed.

Traditional reasons for medication choice have been efficacy, effectiveness, and safety, with more recent additions of formulary availability and reimbursement status. Medication decisions based on formularies and reimbursement status are greatly influenced by the cost-effectiveness of a medication. Patient preference also can be a strong influence on medication choice in RA, with route of administration being an important factor in anti-TNF therapy and the IV route being the least preferred among patients currently receiving therapy.

Previous research with administrative claims has estimated the mean costs of medications for various TNF infusion regimens. Mean (standard deviation [SD]) annual unadjusted costs, measured as plan reimbursed amount, for TNF antagonists in the United States (January 1, 2003, to June 30, 2005) were estimated to be $12,872 ($9,828); $12,692 ($11,899); and $16,013 ($12,770), respectively, for adalimumab, etanercept, and infliximab in a retrospective analysis of a large managed care claims database. However, these studies typically only report the direct costs of the drugs. Costs of drug administration are calculated by multiplying clinical estimates of infusion frequency by costs from fee schedules rather than from collected data on the actual allowed costs, which could potentially underestimate an important cost component when cost-effectiveness is a factor in drug choice.

The objective of the present study was to assess the cost components of IV biologic therapy for RA with infliximab, abatacept, or rituximab from a payer perspective based on the actual amounts allowed by payers. Each of these agents has unique attributes and labeled administration instructions (Table 1) that affect both the duration and cost of administration. In addition to different costs of administration for label indications other than RA, these 3 drugs will likely be prescribed by different physician specialties and likely have different payer mix for indications other than RA.

### Methods

#### Data Source

Data for this study were obtained from the database of Medical Present Value, Inc. (MPV, Austin, TX), a contract management company. This database was described previously in a *Journal of Managed Care Pharmacy* article on the subject of the costs associated with administration of IV drug therapies for metastatic breast cancer (Kruse et al. 2008). MPV maintains a contract and claims management system in approximately 200 clinics in the United States. For the present study, data were obtained from 72 clinics that treated patients with RA (identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 714.XX) and provided infusions for at least 1 of the target biologic agents at the clinic. The clinics were multispecialty clinics with at least 25 physicians per clinic, including both academic and private practices. The database contains diagnoses (ICD-9-CM codes), procedures, and drug therapies for care received by the patients in the clinics, as well as patient demographics (e.g., age, sex, and geographic region); insurance type (e.g., managed care, indemnity, Medicare, and Medicaid); insurance product type (e.g., health maintenance organization and preferred provider organization, including third-party payers for private insurance); and medical specialty of the physician. For every patient clinic visit, MPV maintains the service dates, total charged, and total actual payments, with individual services, procedures, and drugs broken out by line item (Current Procedural Terminology, Fourth Edition [CPT-4] and Healthcare Common Procedure Coding System [HCPCS] codes). Treatment costs were determined using the payer allowed payment, which is the total contractual amount that the provider should receive, including the patient cost share. Actual allowed payment is composed of insurer plus patient payments. This calculation does not account for potential patient portions that remain uncollected or bad debts, which are considered by MPV to be very small.

#### Study Cohort

The study extracted all claims for patients with at least 1 diagnosis code for RA (ICD-9-CM codes 714.XX) and at least 1 claim for infliximab, abatacept, or rituximab (HCPCS codes J1745, J0129, and J9310, respectively) at any time from...
January 1, 2006, to December 31, 2008. At the time of the study, all claims to the end of December 2008 had been fully adjudicated. RA diagnosis codes could be reported in any position on the claim (each claim contained up to 3 diagnostic codes). No additional exclusions were applied. Unique patients who had these claims were identified, and all claims for these patients were additionally extracted. Numbers of patients are reported together with the overall procedure and diagnostic codes to provide a description of the patient cohort.

**Outcome Measures and Analysis**

Costs were calculated as the mean cost per visit in which the IV

---

**TABLE 1** Indications, Dosing, and Administration and Wholesale Acquisition Costs for Infliximab, Abatacept, and Rituximab

<table>
<thead>
<tr>
<th>Indication</th>
<th>Infliximab</th>
<th>Abatacept</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage and administration instructions</strong></td>
<td>For RA in combination with methotrexate for reducing signs and symptoms,</td>
<td>For moderately to severely active RA in adults. May be used as monotherapy</td>
<td>For RA in combination with methotrexate in adult patients with moderately</td>
</tr>
<tr>
<td></td>
<td>inhibiting the progression of structural damage, and improving physical</td>
<td>or concomitantly with DMARDs other than TNF antagonists.</td>
<td>to severely active RA who have inadequate response to 1 or more TNF</td>
</tr>
<tr>
<td></td>
<td>function in patients with moderately to severely active disease.</td>
<td></td>
<td>antagonist therapies.</td>
</tr>
<tr>
<td><strong>Dosage forms and strengths</strong></td>
<td>The recommended dose is 3 mg/kg given as an IV induction regimen at 0, 2,</td>
<td>Abatacept should be administered as a 30-minute IV infusion utilizing the</td>
<td>Administer rituximab as two 1,000 mg IV infusions separated by 2 weeks.</td>
</tr>
<tr>
<td></td>
<td>and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks</td>
<td>weight range-based dosing specified (body weight of patient, dose, vials):</td>
<td>• Glucocorticoids administered as methylprednisolone 100 mg IV or its</td>
</tr>
<tr>
<td></td>
<td>thereafter for the treatment of moderately to severely active RA.</td>
<td>• &lt; 60 kg, 500 mg, 2</td>
<td>equivalent 30 minutes prior to each infusion are recommended to reduce</td>
</tr>
<tr>
<td></td>
<td>Infliximab should be given in combination with methotrexate. For patients</td>
<td>• 60 to 100 kg, 750 mg, 3</td>
<td>the incidence and severity of infusion reactions.</td>
</tr>
<tr>
<td></td>
<td>who have an incomplete response, consideration may be given to adjusting</td>
<td>• &gt; 100 kg, 1000 mg, 4</td>
<td>• Subsequent courses should be administered every 24 weeks or based on</td>
</tr>
<tr>
<td></td>
<td>the dose up to 10 mg/kg or treating as often as every 4 weeks, bearing</td>
<td>Following initial dose, give at 2 and 4 weeks, then every 4 weeks.</td>
<td>clinical evaluation, but not sooner than every 16 weeks.</td>
</tr>
<tr>
<td></td>
<td>in mind that risk of serious infections is increased at higher doses.</td>
<td>Prepare using only the silicone-free disposable syringe.</td>
<td>• Rituximab is given in combination with methotrexate.</td>
</tr>
<tr>
<td><strong>WAC prices per vial</strong></td>
<td>100 mg lyophilized infliximab in a 20 mL vial to be reconstituted in 10 mL</td>
<td>250 mg single-use vial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of sterile water for injection.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acquisition Costs</strong></td>
<td>$657.87 per 20 mL vial (100 mg)</td>
<td>$525.47 per 250 mg vial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$58.30 per 10 mg, $583 per 100 mg vial, and $2,915 per 500 mg vial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from U.S. Food and Drug Administration package inserts. 61, 74, 18

†WAC from www.analysource.com (DMD America, Syracuse, NY) as of November 2010

DMARD = disease-modifying antirheumatic drug; IV = intravenous; kg = kilogram; mg = milligram; mL = milliliter; RA = rheumatoid arthritis; TNF = tumor necrosis factor; WAC = wholesale acquisition cost.

---

**TABLE 2** HCPCS and CPT-4 Codes Used to Define IV Infusion Administration Costs

<table>
<thead>
<tr>
<th>HCPCS or CPT-4 Code and Description</th>
<th>Total Allowed Charges ($)</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>96413 Chemotherapy administration, IV infusion technique; up to 1 hour</td>
<td>6,517,013</td>
<td>65.6</td>
</tr>
<tr>
<td>96415 Chemotherapy administration, IV infusion technique; each additional hour; 1 to 8 hours</td>
<td>1,780,781</td>
<td>17.9</td>
</tr>
<tr>
<td>90765 IV infusion, for therapy, prophylaxis, or diagnosis; initial; up to 1 hour</td>
<td>384,446</td>
<td>3.9</td>
</tr>
<tr>
<td>90780 IV infusion, for therapy/diagnosis; administered by physician</td>
<td>339,245</td>
<td>3.4</td>
</tr>
<tr>
<td>G0359 Chemotherapy administration, IV infusion technique; up to 1 hour</td>
<td>287,269</td>
<td>2.9</td>
</tr>
<tr>
<td>90781 Add sequential infusion, up to 1 hour</td>
<td>156,835</td>
<td>1.6</td>
</tr>
<tr>
<td>90766 IV infusion, for therapy, prophylaxis, or diagnosis; each additional hour; up to 8 hours</td>
<td>125,307</td>
<td>1.3</td>
</tr>
<tr>
<td>96410 Chemotherapy administration, IV infusion technique; up to 1 hour</td>
<td>103,523</td>
<td>1.0</td>
</tr>
<tr>
<td>G0360 Irrigation of implanted venous access device for drug delivery systems</td>
<td>100,825</td>
<td>1.0</td>
</tr>
<tr>
<td>90775 Therapeutic, prophylactic, or diagnostic injection</td>
<td>62,526</td>
<td>0.6</td>
</tr>
<tr>
<td>96412 Chemotherapy administration, IV infusion technique; 1 to 8 hours; each additional hour</td>
<td>48,954</td>
<td>0.5</td>
</tr>
<tr>
<td>36000 Introduction of needle or intracatheter; vein</td>
<td>26,447</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>9,933,171</td>
<td>100.0</td>
</tr>
</tbody>
</table>

administration of a biologic agent occurred (IV administration visit). IV administration visits were selected based on administration of an IV therapy with 1 of the 3 target biologic agents during a clinic visit and identified by the claim identification and date. All services and materials used in the IV therapy administration visit cost analysis were identified by CPT-4 codes and HCPCS codes (Table 2). The primary interest was the IV administration cost as a proportion of the cost of the biologic medication; however, the cost of administration was also calculated as a proportion of the total visit cost.

Statistical tests included analysis of variance (ANOVA) and Student’s t-tests, comparing outcome measures by biologic drug administered during the visit and by physician specialty. Statistical analyses were performed using the STATA release 10 statistical package (StataCorp LP, College Station, TX) and an a priori alpha level of 0.05.

Results

Study Cohort Characteristics

A total of 4,248 patients with 33,354 visits for IV therapy for at least 1 of the study drugs was identified: infliximab, 26,586 visits; abatacept, 4,807 visits; and rituximab, 1,961 visits (Figure 1). Demographic characteristics are presented in Table 3. Approximately one-half (49.2%) of the patients were aged 55 to 74 years. Geographically, there were more patients from the southern and western parts of the United States than from other regions, and fewer patients were from the northeastern part of the United States. Most (51.3%) patients had Medicare followed by private insurance (41.4%), which included employer-based, managed care, or indemnity health insurance.

Overall Payments for Patients with RA

The mean (SD) total payment for all drugs and cost categories was $2,874 ($1,515) per visit (Table 4). In the per-visit analysis, the mean cost for IV biologic medication accounted for 91.0% ($2,616) of the total, IV administration accounted for 7.9% ($226), and other services provided at the visit for 1.1% ($33). Other services consist of items identified on the claims as supplies and equipment, the most common being IV needles, sterile water, dressing pads, and infusion supplies; miscellaneous drugs, such as anti-emetics, steroids, sedatives, and supplements (calcium, magnesium, vitamin B);
TABLE 4  Cost Breakdown by Drug for Medical Visits with IV Drug Administration

<table>
<thead>
<tr>
<th>Specialty of Physician Administering the Infusion</th>
<th>Number of patients</th>
<th>Abatacept (Mean ($) SD ($))</th>
<th>Infliximab (Mean ($) SD ($)</th>
<th>Rituximab (Mean ($) SD ($)</th>
<th>Total (Mean ($) SD ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal medicine</td>
<td>4,206</td>
<td>2,713 [1,411]</td>
<td>2,503 [1,378]</td>
<td>196 [104]</td>
<td>2,899 [80]</td>
</tr>
<tr>
<td>Hematology/oncology</td>
<td>1,633</td>
<td>2,849 [1,874]</td>
<td>2,616 [1,831]</td>
<td>205 [101]</td>
<td>2,899 [213]</td>
</tr>
<tr>
<td>Family practice</td>
<td>1,008</td>
<td>2,473 [1,284]</td>
<td>2,266 [1,230]</td>
<td>200 [91]</td>
<td>2,733 [41]</td>
</tr>
<tr>
<td>Medical oncology</td>
<td>259</td>
<td>2,346 [1,423]</td>
<td>2,048 [1,443]</td>
<td>185 [122]</td>
<td>2,048 [360]</td>
</tr>
<tr>
<td>All othersb</td>
<td>644</td>
<td>2,448 [1,432]</td>
<td>2,203 [1,383]</td>
<td>210 [207]</td>
<td>2,651 [212]</td>
</tr>
</tbody>
</table>

\[P < 0.001, t-test.\] All other specialties include gastroenterology, neurosurgery, nurse practitioner, allergy immunology, and pediatric rheumatology, as well as others.

ANOVA = analysis of variance; IV = intravenous; SD = standard deviation.

TABLE 5  Cost Breakdown by Physician Specialty

<table>
<thead>
<tr>
<th>Specialty</th>
<th>N (%)</th>
<th>Visits (n)</th>
<th>Total (Mean ($) SD ($))</th>
<th>Study Drug (Mean ($) SD ($))</th>
<th>IV Administration (Mean ($) SD ($))</th>
<th>Other Services (Mean ($) SD ($))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatology</td>
<td>1,901</td>
<td>574</td>
<td>171 [82]</td>
<td>3,345 [185]</td>
<td>637 [185]</td>
<td>4,556 [185]</td>
</tr>
<tr>
<td>N (%) visits with private insurance</td>
<td>2,447</td>
<td>10,165 (38.2)</td>
<td>875 [44.6]</td>
<td>12,941 (38.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%) visits with Medicare coverage</td>
<td>2,447</td>
<td>10,165 (52.1)</td>
<td>856 [43.7]</td>
<td>17,162 (51.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%) visits with Medicaid coverage</td>
<td>14</td>
<td>(0.3)</td>
<td>319 (1.2)</td>
<td>347 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%) visits with other coverage</td>
<td>445</td>
<td>(9.3)</td>
<td>2,243 (8.4)</td>
<td>2,904 (8.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [SD] infused drug cost ($)</td>
<td>1,626</td>
<td>[581]</td>
<td>2,571 [1,245]</td>
<td>5,653 [1,611]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [SD] IV administration cost ($)b</td>
<td>171</td>
<td>[82]</td>
<td>224 [100]</td>
<td>226 [118]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [SD] cost of other services ($)a</td>
<td>30</td>
<td>[135]</td>
<td>33 [195]</td>
<td>33 [186]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [SD] total cost ($)b</td>
<td>1,827</td>
<td>[622]</td>
<td>2,828 [1,282]</td>
<td>6,076 [1,689]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[P < 0.001, from ANOVA across 3 category means.\]

ANOVA = analysis of variance; IV = intravenous; SD = standard deviation.

additional hydration); and a miscellaneous administration-related services category primarily including fluid collection and laboratory tests. Many of the items classified as other services from their description could be logically related to the cost of IV administration; however, they were not classified as an IV administration cost within the claim.

**Payments by IV Biologic Agent**

The most commonly administered agent was infliximab, and the least commonly administered agent was rituximab. It should be noted that the labeled dosing interval for rituximab is longer than that for the other agents, which is evident in the lower relative number of visits for infusion shown in Table 4. Average total allowed payments significantly differed by drug (P<0.001 from ANOVA), with the greatest total payment per visit ($6,076) observed for rituximab compared with both abatacept and infliximab (P<0.001, t-test). Rituximab was also associated with the greatest average cost of IV administration ($390) compared with both abatacept ($171) and infliximab ($224, P<0.001, t-test). Expressed as a percentage of drug cost, IV administration costs were 10.5%, 8.7%, and 6.9% for abatacept, infliximab, and rituximab, respectively.

**Specialty of Physician Administering the Infusion**

As expected, rheumatology was the predominant specialty that administered IV biologic medications to treat RA, followed by internal medicine (Table 5). Within each drug category, rheumatology was associated with the greatest cost of IV administration (P<0.001 from ANOVA), and medical oncology incurred greater costs for other services.

**Payment by Payer Type, Patient Age, and Geography**

Significant differences in costs for study drug, IV administration, and other visit-related services and drugs were observed across payer types (Table 6). The overall mean payment per visit was $3,373 for private insurance, $2,483 for Medicare,
and $2,773 for Medicaid, although the amount for Medicaid is based on a small number of patients. The allowed costs for IV administration were highest for private insurers ($278) and lower for Medicare ($181) and Medicaid ($105, $P<0.001 from ANOVA). Comparisons of mean drug costs, IV administration costs, and other related costs by patient age and by geographic groups showed no significant differences (data not shown).

### Discussion

Previous models of the cost-effectiveness of RA drugs estimated the costs of IV administration for inclusion in their calculations. These estimates often were extracted from fee schedules, rather than from actual costs of infusions or from unreferenced or data-on-file sources. In comparison with the mean estimate of $226 determined here, other models have used lesser estimates of $129 or $181. Differences in these costs could reflect the present study’s determination of costs using the allowed payment from payers to providers, whereas other cost calculations relied on estimated rather than collected values and studied different time periods.

Although it could be argued that the costs of IV administration are small compared with drug costs, the relevant comparison should be any marginal differences in comparative cost-effectiveness among medications. When choosing among medications that have different routes of administration and similar efficacy, the cost of administration could become an important consideration. The relatively high cost associated with the infusion of a medication has previously been quantified in the treatment of other conditions for which both an IV agent and an oral agent were available. The costs of administering IV agents for RA are of a similar magnitude, which is likely because of the reimbursement amount associated with the J-code used in both circumstances. Consistent with previous research, we also found that payments for administrative costs from private insurers were greater than those from public insurers, Medicare, and Medicaid, which likely represents mandatory payment levels from these agencies rather than the negotiated rates from private payers.

The cost of administration was found to be significantly higher for rituximab than for infliximab and abatacept. The differences in the costs of administration among the medications to treat RA is most likely due to the longer administration time and other factors, such as biases in patient selection for each medication, specific labeled infusion instructions for each medication, co-administered medications, volume of medication to be infused, or potential medication adverse effects. Rituximab in particular requires pre-medication with a glucocorticoid, which could affect the IV administration time. Mean IV infusion time was found to differ significantly by biologic agent in a study of patients with RA by Yazici et al. (2009): abatacept (42 minutes), infliximab (131 minutes), and rituximab (274 minutes). These factors could not be examined within the current reimbursement dataset and could be the subject of further research.

We found, as expected, that rheumatologists administered biologic agents to treat RA more commonly than did other specialists. Why rheumatologists had the highest allowed payments for the cost of administration is unclear; however, we speculate that they may be treating patients with more severe or advanced disease. Among the additional specialists treating RA with infused biologic agents, hematologists/oncologists and medical oncologists were unexpectedly common. Potential explanations could be their familiarity in administering infusions overall, the existence of facilities for administering infusions in oncology settings, or specific familiarity with rituximab as an oncology treatment. Importantly, the inclusion criteria for the study required an RA diagnosis to occur on at least 1 claim, and an RA diagnosis code was subsequently found to be recorded on each claim with each infusion of a biologic agent within the resulting sample.

Biologic agents were a breakthrough for the treatment of RA following the approval of infliximab in 1998 and with subsequent approval of multiple agents with similar or related mechanisms of action. The need for simplified administration regimens was among the reasons that subcutaneously administered agents, such as etanercept and adalimumab, were introduced. The quantification of the cost of the IV administration of biologic agents provides payers, pharmacists, and physicians with another piece of evidence with which to guide their choice of therapy, in addition to the medications’ safety, efficacy, and convenience.
Analysis of Drug and Administrative Costs Allowed by U.S. Private and Public Third-Party Payers for 3 Intravenous Biologic Agents for Rheumatoid Arthritis

LIMITATIONS
First, the data for this study were retrieved from a convenience sample generated at a particular commercial claims adjudication service, MPV. Although it is a large sample, it remains weighted toward the U.S. South and Southwest. Although it is uncertain whether there was a specific bias associated with the relative lack of East Coast clinics, the lack of significant variation between existing geographic groupings suggests good geographic generalizability to all patients who received biologic agents for RA. Second, costs of IV administration were determined only from clinic claims and were limited to services identified on the claim as an infusion administration cost. This method could have resulted in a conservative estimate of infusion costs because nonclinic and other costs are likely to be incurred. For example, indirect costs, such as travel to the clinic, lost time at work, or lost productivity were not accounted for, and potential nonclinic medical costs could also be incurred, such as late infusion reactions and complications. Third, the study was limited to patients receiving IV infusions for RA; results may not generalize to other patient populations, including those currently receiving subcutaneous treatment with biologics.

CONCLUSIONS
Analysis of a large U.S. claims database showed that the average cost of administering IV biologic agents to treat RA was $226 per infusion visit, or approximately 9% of the cost of the drug itself. The percentage of costs per infusion were highest for abatacept and lowest for rituximab. Along with the usual considerations of efficacy, safety, and drug cost, infusion costs should be considered when choosing an agent and route of administration for the treatment of RA.

AUTHORS
BRUCE J. WONG, MBChB, FRACP, is Principal and Owner, Bruce Wong & Associates Inc., Philadelphia, Pennsylvania. MARY A. CIFALDI, PhD, MSHA, RPh, is Director, and SANJOY ROY, MS, at the time this study was performed was Senior Manager, Abbott Laboratories, Abbott Park, Illinois. DEAN C. SKONIECZNY, MBA, BSE, is Vice President, Product Management, Medical Present Value Inc., Austin, Texas. SPYROS STAVRAKAS, PhD, is Partner, Market Strategy Group Healthcare, Inc., Willow Grove, Pennsylvania.

AUTHOR CORRESPONDENCE: Bruce J. Wong, MBChB, FRACP, Bruce Wong & Associates Inc., 1254 Gulph Creek Drive, Wayne, PA 19087. Tel: 610.772.1310; E-mail: Brucejowong@gmail.com.

DISCLOSURES
Wong is the principal and sole owner of the company that was contracted to undertake this project for Abbott Laboratories, manufacturer of adalimumab (Humira), an alternative biologic agent with an indication for rheumatoid arthritis that is administered subcutaneously. Wong has worked for Abbott Laboratories as a consultant and member of an advisory board. Cifaldi is an employee of Abbott Laboratories, and Roy was employed by Abbott at the time these analyses were conducted and is now an employee of Johnson & Johnson.

Concept and design were performed primarily by Wong with the assistance of Cifaldi and Stavrakas. Data collection was performed primarily by Skonieczny with the assistance of Stavrakas. Data were interpreted by Cifaldi, Roy, Stavrakas, and Wong. The manuscript was written primarily by Wong with the assistance of Stavrakas and revised primarily by Wong.

ACKNOWLEDGEMENTS
Editorial support in the preparation of this manuscript was provided by Cathryn M. Carter, MS, of Arbor Communications, Inc., and was funded by Abbott Laboratories. Michelle Marvel, BA, provided the copyediting and journal formatting for the manuscript.

REFERENCES


The Case for Standardizing the Appearance of Bioequivalent Medications

Alfred B. Engelberg, JD

It is common knowledge that patients rely on the color, size, and shape of medication for reassurance that they are taking the right pill. Yet, not only do most bioequivalent generic drugs not look like the brand-name medicine, they don't even look like each other. As a result, patients can receive a drug that looks different when they refill a prescription leading to confusion, failure to take medications as prescribed, and the waste of valuable time of physicians and pharmacists in counseling patients to reduce their anxiety. The problem is particularly troublesome for elderly patients who often take several medications concurrently and are more susceptible to confusion. The U.S. Food and Drug Administration (FDA) has recently decided that the current system of providing medical information to consumers about drugs is inadequate and is developing more patient-friendly information to accompany prescriptions. Standardization of appearance for bioequivalent medicines should be at the top of the FDA's list of concerns as it seeks to improve patient medication information.

More than 30 years ago, prior to the enactment of the Federal Hatch-Waxman Act promoting the use of generic drugs and state laws mandating the substitution of lower-cost bioequivalent generic drugs for brand name drugs, a number of court decisions held that the appearance features of a medication were entitled to protection against copying on the theory that these features constituted protectable “trade dress,” (i.e., they functioned like trademarks to identify the product's manufacturer). Given these precedents, it may have been reasonable for the FDA to assume that it lacked the authority to regulate the appearance of a medication in a manner that might undermine the proprietary rights of brand name manufacturers. That assumption is no longer true—if it ever was. Judicial precedent has significantly restricted the circumstances under which a valid claim to trademark rights in the appearance of any product can exist, and industry practices in the sale and dispensing of medications in an era of mandated substitution have evolved in a manner that makes it highly unlikely that valid trademark rights can ever be established for the appearance of a medicine. The appearance of a product may well be commercially important where a consumer actually sees the product before it is purchased, but a patient rarely, if ever, sees a medicine before it is dispensed. Moreover, state laws mandating the substitution of lower-cost, FDA-approved generic drugs have eliminated any basis for asserting that substitution of a look-alike medicine by the pharmacist is an act of unfair competition, “passing off” or counterfeiting—a pivotal issue in the early precedents that protected the appearance of drugs as a proprietary right. The United States Supreme Court has stated that an appearance feature of a product, such as its color, cannot be protected under trademark principles unless it can be proven that the primary significance of that appearance in the minds of consumers is to identify the source of a product and not the product itself. In addition, no valid trademark rights can ever be acquired in the appearance of a product if that appearance serves a functional purpose. In the words of the Supreme Court: “The functionality doctrine ... forbids the use of a product’s feature as a trademark where doing so will put a competitor at a significant disadvantage because the feature is ‘essential to the use or purpose of the article’ or ‘affects [its] cost or quality.’” For example, this Court has written that competitors might be free to copy the color of a medical pill where that color serves to identify the kind of medication (e.g., a type of blood medicine) in addition to its source.

Relying on the Supreme Court's functionality doctrine, the Third Circuit Court of Appeals has held that “by being physically similar to Adderall, Barr's generic amphetamine salts tablets materially benefitted the patient population” because “similarity in tablet appearance enhances patient safety by promoting psychological acceptance.” The Court also credited expert testimony from an executive of Rite-Aid that generic drugs which looked like the branded drug had a competitive advantage because such products enhance patient safety and compliance. The dispositive facts establishing functionality in the Adderall case are applicable to all drugs. Publications promoting medication safety from such trusted sources as the FDA, Consumers Union, the Institute of Safe Medication Practices, and Pfizer all encourage patients to rely on the appearance of their medication for reassurance that they are taking the right medicine at the right time and to refrain from taking any medication that looks different without getting professional reassurance. The American Medical Association has concluded that differences in the appearance of bioequivalent brand and generic medicines as well as between bioequivalent generic products produced by different manufacturers were the cause of significant confusion and anxiety for patients and has formally recommended that (a) pharmacists avoid refilling prescriptions with a different looking generic drug manufactured by a different source, when possible; (b) patients be individually counseled about appearance changes when they do occur; and (c) refill prescriptions carry an additional label indicating that: “This medication contains the same
active ingredient you have been getting. Color, size, or shape may appear different.” These recommendations have been implemented by many pharmacists.

Brand-name drug manufacturers also routinely rely on the appearance of a medication to gain a competitive advantage in the sale of generic drugs to pharmacies. During the last decade, hundreds of brand-name medicines have been launched as “authorized generics.” An “authorized generic” is a drug manufactured under the originally approved New Drug Application (NDA) and is identical to the branded product except that the brand name and the original manufacturer’s name are removed from both the product and its packaging and are replaced by the drug’s generic name and the name of a different distributor. Prasco, an independent distributor of authorized generics, relies on the fact that its authorized generics look exactly like the branded product to gain a competitive advantage by marketing with a message that “with authorized generics you can avoid lengthy explanations about product characteristics” during the generic conversion process.13 And Patriot Pharmaceuticals, a subsidiary of Johnson & Johnson (J & J) created to distribute generic versions of J & J products, proclaims that “store level patient counseling may be streamlined due to the fact that authorized generic pharmaceutical products have the same taste, color, mouth feel, size and shape as the innovator product.”14 The claim that look-alike generics enjoy a commercial advantage because their appearance has functional value for patients forecloses any claim to trade dress rights5 under the principles of law enunciated by the Supreme Court. Moreover, removal of the brand name and the manufacturer’s name from the authorized generic blinds consumers to the fact that the authorized generic is made by the same manufacturer as the brand drug. That deliberate separation of the manufacturer’s identity from the appearance of a product is also totally inconsistent with the efforts normally made by manufacturers to connect a product’s appearance to a single manufacturing source.

Generic manufacturers individually and arbitrarily select an appearance for each product simply to avoid expensive litigation with brand-name manufacturers wrongfully claiming trademark rights in the appearance of a medicine. The generic manufacturers make no effort to associate the appearance of their products with a particular source and have never asserted any trade dress claims of their own. Absent leadership from the FDA, generic manufacturers are unlikely to set industry standards regarding uniformity of appearance because of antitrust concerns that arise whenever competitors take joint action. Formal recognition by the FDA of the important functional role that product appearance plays in reducing patient anxiety and enhancing medication safety would bring an end to most trade dress claims because it is ultimately up to the FDA, and not the courts, to determine which attributes of a medicine play an important role in making drugs safe and efficacious.

**DISCLOSURES**

The author is an intellectual property attorney who formerly represented generic drug manufacturers and was a principal participant in the negotiations that led to the enactment of the Hatch-Waxman Act. The author has not actively practiced law on behalf of clients since 1995. He has no financial interest in or current relationship with any generic drug company. The Engelberg Foundation supported creation of the Engelberg Center for Health Care Reform at the Brookings Institution.

**REFERENCES**


6. See cases cited in Shire U.S. v. Barr Laboratories, Inc., No. 02-3647, 329 F.3d 348 (3rd Circuit, 2003) at p 355 Available at: http://scholar.google.com/scholar_case?case=374949416391160258&hl=en&as_sd=2&as_vis=1&oi=scholar. Accessed April 2, 2011. At the time these cases were decided, substitution of a look-alike product was generally believed to be an act of unfair competition (i.e., an attempt to “pass off” the copy as if it was the original product—a behavior similar to counterfeiting).


**DISCLOSURES**

The author is an intellectual property attorney who formerly represented generic drug manufacturers and was a principal participant in the negotiations that led to the enactment of the Hatch-Waxman Act. The author has not actively practiced law on behalf of clients since 1995. He has no financial interest in or current relationship with any generic drug company. The Engelberg Foundation supported creation of the Engelberg Center for Health Care Reform at the Brookings Institution.

**REFERENCES**


6. See cases cited in Shire U.S. v. Barr Laboratories, Inc., No. 02-3647, 329 F.3d 348 (3rd Circuit, 2003) at p 355 Available at: http://scholar.google.com/scholar_case?case=374949416391160258&hl=en&as_sd=2&as_vis=1&oi=scholar. Accessed April 2, 2011. At the time these cases were decided, substitution of a look-alike product was generally believed to be an act of unfair competition (i.e., an attempt to “pass off” the copy as if it was the original product—a behavior similar to counterfeiting).


The Case for Standardizing the Appearance of Bioequivalent Medications


