volume eighteen • number seven
September 2012

Peer-Reviewed Journal of the
Academy of Managed Care Pharmacy

JMCP

JOURNAL OF MANAGED CARE PHARMACY

Page

JMCP
Volume 18, No. 7

CONTENTS

AMCP Academy of Managed Care Pharmacy®

AMCP HEADQUARTERS

100 North Pitt St., Suite 400
Alexandria, VA 22314
Tel: 703.683.8416 • Fax: 703.683.8417

ADVERTISING

Advertising for the ***Journal of Managed Care Pharmacy*** is accepted in accordance with the advertising policy of the Academy of Managed Care Pharmacy.

For advertising information, contact:
Bob Heiman
RH Media LLC
1814 East Route 70, Suite 350
Cherry Hill, NJ 08003
Tel.: 856.673.4000
Fax: 856.673.4001
E-mail: bob.rhmedia@comcast.net

EDITORIAL

Questions related to editorial content should be directed to *JMCP* Peer Review Administrator Jennifer Booker: jmcpreview@amcp.org.

Manuscripts should be submitted electronically at jmcp.msubmit.net. For questions about submission, contact Peer Review Administrator Jennifer A. Booker: jmcpreview@amcp.org; 703.317.0725.

SUBSCRIPTIONS

Annual subscription rates: USA, individuals, institutions–$90; other countries–$120. Single copies cost $15. Missing issues are replaced free of charge up to 6 months after date of issue. Send requests to AMCP headquarters.

REPRINTS

For **article reprints and Eprints,** contact Tamara Smith at Sheridan Reprints, 800.352.2210, ext. 8230; tsmith@tsp.sheridan.com. Information for ordering reprints or Eprints and instructions for permission for use of *JMCP* content are available at www.amcp.org.

COVER IMPRESSIONS

About the *JMCP* September Cover

Beginning this month, *JMCP* will highlight one of the numerous National Health Observances[1] on the cover of the publication. This month, we chose sickle cell disease.

Sickle cell disease is one of the most common genetic diseases in the United States. For a child to inherit the disease, both parents must carry the sickle cell gene. This pattern of inheritance is called autosomal recessive inheritance. If both parents have the gene, the child has a 25% chance of contracting the disease.

The terms *sickle cell anemia* and *sickle cell disease* are used interchangeably, since the hallmark of the disease is chronic anemia. In the disease, a mutation occurs in the gene that codes for hemoglobin, causing red blood cells to become sickle or crescent-shaped, rigid, and sticky.

Today, there are approximately 100,000 Americans with sickle cell disease, and every year nearly 1,000 babies are born with the disease. Globally, the sickle cell gene is most common in families from Africa, India, South and Central America, and the Caribbean, Mediterranean, and Middle East regions. In the United States, the African-American and Hispanic populations are affected.

The prognosis over the past 40 years has increased tremendously. With new treatments, early interventions, and mandatory newborn screening, the disease has become manageable, and most of those affected live well into their adult lives. There are many promising treatments for sickle cell anemia. A bone marrow or stem cell transplant will cure the disease; however, it is very risky. Because of the expense of the procedure and the need for a full-match donor, only 400 patients were cured through stem cell transplants over the past 20 years. Management of symptoms such as anemia; episodes of pain (sickle cell crises); swelling of the hands, feet, and abdomen; infections and fever; and vision problems are a priority. This is accomplished through blood transfusions, immunizations to prevent infections, oral antibiotics, hydroxyurea, and general health maintenance such as proper nutrition, hydration, plenty of sleep, and avoidance of stress. Complications can be serious or even life threatening and include serious infections, stroke, and acute chest syndrome.

Recent research developments to treat or cure the disease include gene therapy. Researchers are exploring whether inserting a normal gene into the bone marrow of patients with sickle cell disease will result in normal hemoglobin production. Another possibility is to "turn off" the defective gene and "turn on" the gene that produces normal hemoglobin in the marrow. Patients with sickle cell disease have low levels of nitric oxide in their blood and seem to respond well to nitric oxide therapy, which prevents sickle cells from clumping and keeps the blood flowing throughout the vessels. Researchers are also looking at ways to increase the production of fetal hemoglobin, which prevents sickle cells from forming. For resources and more information on sickle cell disease, visit the CDC website at: http://www.cdc.gov/ncbddd/sicklecell/documents/SickleCellDIRECTORY_508.pdf.

SOURCE

1. 2012 National Health Observances, National Health Information Center, Office of Disease Prevention and Health Promotion, U.S. Department of Health and Human Services, Washington, DC. Available at: http://healthfinder.gov/nho/.

JMCP Author Guidelines

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.

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/JMCPhome.aspx.
- A subsection in the Discussion labeled "Limitations" is required 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/JMCPhome.aspx).
- 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/JMCPhome.aspx).

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:

1. Journal article — (list up to 6 authors; if 7 or more, list only the first 3 and add et al.): Kastelein JJ, Akdim F, Stroes ES, et al.; the ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med.* 2008;358(14):1431-43. Available at: http://content.nejm.org/cgi/reprint/358/14/1431.pdf. Accessed January 4, 2011.

2. No author given — Anonymous. More patients leaving Rxs at pharmacy counter. *Manag Care.* 2010;19(4):49. Available at: http://www.managedcaremag.com/archives/1004/1004.formfiles.html. Accessed January 4, 2011.

3. Journal or magazine paginated by issue — McKinney M. Alarm fatigue sets off bells. *Mod Healthc.* 2010;40(15):14.

4. Book or monograph — Tootelian DH, Gaedeke RM. *Essentials of Pharmacy Management.* St. Louis, MO: C.V. Mosby; 1993.

5. Book or monograph with editor, compiler, or chairperson as author — Chernow B, ed. *Critical Care Pharmacotherapy.* Baltimore, MD: Williams & Wilkins; 1995.

6. Chapter in a book — Kreter B, Michael KA, DiPiro JT. Antimicrobial prophylaxis in surgery. In: DiPiro JT, Talbert RL, Hayes PE, Yee GC, Matzke GR, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach.* Norwalk, CT: Appleton & Lange; 1992:1811-12.

7. Government agency publication — National Heart, Lung, and Blood Institute. Expert panel report 3: guidelines for the diagnosis and management of asthma. Full report 2007. August 28, 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed January 4, 2011.

8. Website - other online publication — Minnesota Department of Health. Essential Benefit Set Work Group. Background paper. September 4, 2009. Available at: http://www.health.state.mn.us/healthreform/essential/EBS_Background.pdf. Accessed January 4, 2011.

9. Newspaper article — Abelson R, Pollack A. Medicare widens drugs it accepts for cancer. *NY Times.* January 26, 2009. Available at: http://www.nytimes.com/2009/01/27/health/27cancer.html?_r=2&ref=health. Accessed January 4, 2011.

10. Online news article — Marchione M. Study finds many patients shun free heart drugs. AP. November 14, 2011. Available at: http://articles.boston.com/2011-11-14/lifestyle/30398405_1_heart-drugs-medicines-patients. Accessed April 26, 2012.

11. Drug label – prescribing information — Xolair (omalizumab) for subcutaneous use. Genentech. July 2010. Available at: http://www.gene.com/gene/products/information/pdf/xolair-prescribing.pdf. Accessed January 4, 2011.

12. Dissertation or thesis — Youssef NM. School adjustment of children with congenital heart disease [dissertation]. Pittsburgh, PA: University of Pittsburgh; 1988.

13. Paper or poster presented at a meeting — Gleason PP, Starner CI, Hyland-Marciniak B. Erythropoiesis-stimulating agent trends and utilization management opportunity. Poster presented at: 2010 AMCP Annual Meeting; April 9, 2010; San Diego, CA. Available at. http://www.amcp.org/data/jmcp/141-168.pdf.

14. Letter or editorial — Barbuto JP. Categorizing patients from medical claims data – the influence of GIGO [letter]. *J Manag Care Pharm.* 2004;10(6):559-60. Available at: http://www.amcp.org/data/jmcp/Letters_559-566.pdf.

15. Journal supplement — Academy of Managed Care Pharmacy. AMCP guide to pharmaceutical payment methods, 2009 update (version 2.0). *J Manag Care Pharm.* 2009;15(6 Suppl A):S1-S61. Available at: http://www.amcp.org/data/jmcp/1002.pdf.

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.

Manuscript Submission

A complete list of documents needed for submission to *JMCP* appears on the Manuscript Submission Checklist at www.amcp.org/JMCPhome.aspx and the Supplement Submission Checklist at www.amcp.org/JMCPhome.aspx. 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 review the *JMCP Author Guidelines* and please check to see that your package includes all items in the *JMCP* Manuscript Submission Checklist. Both are available at www.amcp.org/JMCPhome.aspx.

REFERENCE

1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. Updated April 2010. Available at: http://www.icmje.org/urm_full.pdf. Accessed August 25, 2011.

JMCP

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

EDITORIAL ADVISORY BOARD

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; 703.683.8416; 800.TAP.AMCP; 703.683.8417 (fax). The paper used by the *Journal of Managed Care Pharmacy* meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper) effective with Volume 7, Issue 5, 2001; prior to that issue, all paper was acid-free. Annual membership dues for AMCP include $90 allocated for the *Journal of Managed Care Pharmacy.* 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; articles undergo blinded peer review. Letters may be peer reviewed to ensure accuracy. The fundamental departments for manuscript submission are:

- Research
- Subject Reviews
- Formulary Management
- Contemporary Subjects
- 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.

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.

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 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 Office

Academy of Managed Care Pharmacy
100 North Pitt St., Suite 400
Alexandria, VA 22314
Tel.: 703.683.8416
Fax: 703.683.8417
E-mail: jmcpreview@amcp.org

Advertising Sales Office

RH Media LLC
1814 East Route 70, Suite 350
Cherry Hill, NJ 08003
Tel.: 856.673.4000
Fax: 856.673.4001
E-mail: bob.rhmedia@comcast.net

RESEARCH

Treatment of Vitamin D Deficiency Within a Large Integrated Health Care Delivery System

Moxie J. Stratton-Loeffler, DO; Joan C. Lo, MD; Rita L. Hui, PharmD, MS; Ashley Coates, MPH; Jerome R. Minkoff, MD; and Amer Budayr, MD

ABSTRACT

BACKGROUND: In the past decade, increasing attention has focused on identification and treatment of vitamin D deficiency although repletion outcomes of pharmacologic vitamin D therapy have not been examined at a population level.

OBJECTIVE: To investigate population trends and outcomes of pharmacologic treatment of vitamin D deficiency.

METHODS: We conducted a retrospective cohort study using data from an integrated health system with approximately 3.2 million members. Automated laboratory and pharmacy databases were used to identify patients aged 18 years or older with hypovitaminosis D (defined as a 25-hydroxy-vitamin D [25(OH)D] serum level < 20 nanograms [ng] per mL) who newly initiated pharmacologic ergocalciferol (50,000 international units [IU] per week) during 2007-2010 and did not have a prescription for ergocalciferol in the prior 12 months. Patients were required to be continuously enrolled for 12 months before and 6 months after ergocalciferol initiation. Age, gender, race/ethnicity, body mass index, and 25(OH)D levels were obtained from health plan electronic medical records and administrative, laboratory, and pharmacy databases. Outcome and predictors of repletion among the subset who received 12 weekly doses of 50,000 IU ergocalciferol (total dose 600,000 IU) were examined using multivariable logistic regression.

RESULTS: There were 72,093 vitamin D-deficient patients who newly initiated pharmacologic ergocalciferol. During the study period, the use of ergocalciferol increased nearly 8-fold from 161 per 100,000 adult members in 2007 to 1,241 per 100,000 adult members in 2010. One-fifth (n = 14,727) had severe vitamin D deficiency (25[OH]D level < 10 ng per mL). Among 23,322 patients receiving 50,000 IU ergocalciferol for 12 weeks in whom subsequent 25(OH)D levels were measured between 90 and 365 days after the index ergocalciferol prescription date, 74.0% achieved 25(OH)D of at least 20 ng per mL, and 35.8% achieved 25(OH)D of at least 30 ng per mL. Increasing age (adjusted odds ratio [OR] 1.02, 95% CI 1.02-1.02) and higher baseline 25(OH)D level (OR 1.11, 95% CI 1.10-1.12) were associated with greater odds of successful repletion. Asian race (OR 0.80, 95% CI 0.73-0.88), Hispanic ethnicity (OR 0.71, 95% CI 0.65-0.77), and increasing overweight/obesity (OR 0.78, 95% CI 0.72-0.85 for body mass index [BMI], 25.0-29.9 kg/m^2; OR 0.66, 95% CI 0.60-0.71 for BMI 30.0-39.9 kg/m^2; OR 0.53, 95% CI 0.48-0.60 for BMI ≥ 40 kg/m^2) were associated with lower odds of repletion compared with BMI 18.5-24.9 kg/m^2.

CONCLUSIONS: There is increasing recognition and treatment of vitamin D deficiency within the health care setting. Patients of younger age, Asian and Hispanic race/ethnicity, and those who are obese or with more severe vitamin D deficiency may be at greater risk for incomplete repletion using standard regimens and may require additional treatment to achieve optimal levels.

J Manag Care Pharm. 2012;18(7):497-505

What is already known about this subject

- There is a high prevalence of vitamin D deficiency within the U.S. adult population, with estimates as high as 42%, based on data from nationwide surveys. In the past decade, attention has focused on screening and identification of patients who will benefit from pharmacologic vitamin D therapy.
- Vitamin D status varies by race/ethnicity and adiposity status. Repletion outcomes vary depending on vitamin D treatment dose, body mass index, and other patient factors. Few studies have examined repletion outcomes in various population subgroups receiving pharmacologic therapy for hypovitaminosis D.

What this study adds

- Within a large integrated health care delivery system, the use of pharmacologic ergocalciferol for treatment of vitamin D deficiency increased nearly 8-fold from 161 per 100,000 enrollees in 2007 to 1,241 per 100,000 enrollees in 2010, demonstrating the growing clinical burden of recognized vitamin D deficiency.
- The severity of vitamin D deficiency and response to treatment varies by age, race/ethnicity, and body mass index.
- Using a standard pharmacologic regimen of ergocalciferol (50,000 international units [IU] weekly) administered over 12 weeks, the majority of patients achieved repletion, defined as a 25-hydroxy-vitamin D (25[OH]D) level of at least 20 nanograms (ng) per mL. Increasing age (adjusted odds ratio [OR] 1.02, 95% CI 1.02-1.02) and higher baseline vitamin D level (OR 1.11, 95% CI 1.10-1.12) were associated with greater odds of repletion, while Asian race (OR 0.80, 95% CI 0.73-0.88), Hispanic ethnicity (OR 0.71, 95% CI 0.65-0.77), and higher body mass index (BMI; OR 0.78, 95% CI 0.72-0.85 for BMI 25.0-29.9 kg/m^2; OR 0.66, 95% CI 0.60-0.71 BMI 30.0-39.9 kg/m^2; OR 0.53, 95% CI 0.48-0.60 for BMI ≥ 40 kg/m^2) were associated with lower odds of repletion. Further studies are needed to determine the optimal pharmacologic protocols for vitamin D deficiency in specific patient subsets.

Vitamin D deficiency is a common underdiagnosed condition that has received increasing attention in the United States, particularly in the past decade.[1-3] Historically, vitamin D deficiency has been more prevalent in homebound elderly individuals, hospitalized patients, and persons with darker skin color who have a nutritional deficiency or gastrointestinal malabsorptive conditions,[1,2,4-6] but in recent years, several studies also demonstrate that vitamin D status and the efficacy of vitamin D replacement differ depending on body mass index (BMI) and adiposity.[6-8] The relationship between vitamin D and body fat remains complex and likely varies by race.[9] While the optimal level of vitamin D (measured as the level of 25-hydroxy-vitamin D [25(OH) D]) continues to be examined,[10] it is known that vitamin D deficiency is highly prevalent in the U.S. adult population. According to the National Health and Nutrition Examination Survey (NHANES), from 2000-2004, 6% of adults aged 20 years or older had a 25(OH)D level at or below 11 nanograms per milliliter (ng per mL), or 27.5 nanomoles per liter (nmol per L).[6] Using a 25(OH)D threshold of 20 ng per mL (50 nmol per L), the proportion with vitamin D deficiency increased to 42%, with the highest rates among blacks (82%) and Hispanics (69%) in the NHANES 2005-2006.[11] Vitamin D levels vary by race, with mean 25(OH)D levels highest among whites, lower among Hispanics, and lowest among blacks of all ages.[6] Common manifestations of vitamin D deficiency include osteomalacia, bone pain, muscle weakness, and gait disorder.[1,12,13]

According to the Institute of Medicine (Ross et al. 2011), evidence is strong for achieving optimal levels of 25(OH)D (≥ 20 ng per mL) to support bone health, while the role of vitamin D in prevention of autoimmune disease, cancer, diabetes, and cardiovascular disease is less clear.[14] Supplementation with calcium and vitamin D reduces the risk of clinical fractures with efficacy at a dose range of 700-800 international units (IU) daily.[15] Besides the role of vitamin D in bone health and bone mineral density,[16,17] treatment with vitamin D has been shown to reduce the risk of falls, particularly in patients with pre-existing deficiency.[18,19] However, in one study among elderly community-dwelling women, treatment was associated with an increased risk of falls and fractures; interestingly, this study used a single dose of vitamin D (500,000 IU) once annually, suggesting there may be an optimal range (and/or dosing frequency) of vitamin D supplementation for patients without vitamin D deficiency.[20]

As research accumulates on the many possible roles of this prohormone, the need remains to better understand the burden of vitamin D deficiency in various clinical populations and factors relevant to pharmacologic treatment. Furthermore, outcome data with regard to successful vitamin D repletion are limited, particularly the availability of population data examining pharmacologic management of vitamin D deficiency and factors associated with optimal repletion. The increase in physician, patient, and public awareness of vitamin D deficiency has resulted in greater vitamin D screening efforts and an expanding proportion of physician time spent testing, treating, and educating patients, particularly in the primary care setting. In this study, we analyzed data from a large integrated health care delivery system to assess population trends in ergocalciferol treatment and demographic and clinical factors associated with severity of vitamin D deficiency at baseline. We also evaluated factors associated with repletion adequacy in patients who received 600,000 IU of ergocalciferol administered in 12 weekly doses of 50,000 IU.

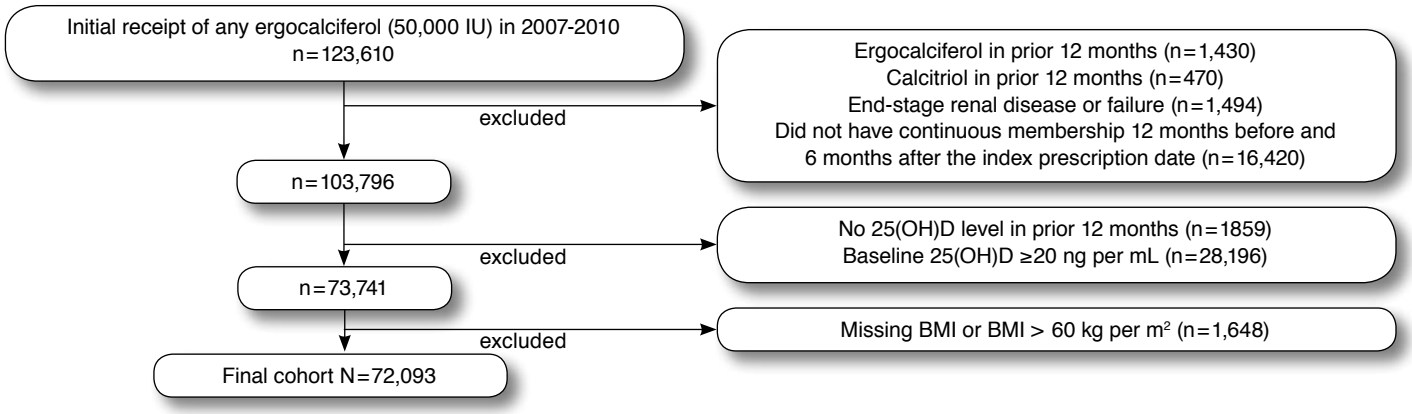
Methods

Source Population and Identification of the Study Cohort

Kaiser Permanente of Northern California (KPNC) is an integrated health care delivery system caring for more than 3.2 million members annually across northern California. Within the San Francisco and greater Bay Area, approximately one-third of insured adults receive their care through KPNC. The population is racially and ethnically diverse and generally representative of the surrounding regional population except for lower representation of those with extremely low household income.[21] Among health plan members, more than 95% have drug benefits and receive prescriptions from KPNC pharmacies tracked through automated databases. Educational materials pertaining to vitamin D deficiency are available to all KPNC health providers and have increased awareness and screening for vitamin D deficiency in the context of clinical care. However, systematic measurement of vitamin D levels is currently not conducted for the entire adult health plan population.

Using health plan pharmacy records, we identified all adult members aged 18 years or older who newly initiated ergocalciferol (vitamin D2, 50,000 IU) during 2007-2010 and had documented vitamin D deficiency at a threshold of 25(OH)D less than 20 ng per mL within 12 months prior to initiating ergocalciferol. Patients without at least 12 months of continuous health plan enrollment before and at least 6 months after ergocalciferol initiation were excluded. Ergocalciferol is one of the most commonly used forms of prescription vitamin D (in the absence of advanced chronic kidney disease and hypoparathyroidism)[22] and the primary prescription strength vitamin D formulation used within KPNC. We excluded patients with end-stage renal disease defined by receipt of dialysis (using health plan dialysis registry data) or diagnosis of kidney failure (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 584.5-584.9, 585.5, 585.6, and 586) and those receiving calcitriol in the 12 months before the index date (date of the initial ergocalciferol prescription). In addition, because our purpose was to examine the relation of BMI and vitamin D status across a general adult population, we excluded the 2.2% of individuals with missing BMI or values greater than 60 kilograms per squared meter (kg per m^2). The study was approved by the Kaiser Foundation Research Institute Institutional Review Board.

FIGURE 1 Cohort Assembly of 72,093 Adults with Vitamin D Deficiency Who Newly Initiated Pharmacologic Ergocalciferol



BMI = body mass index; IU = international units; kg = kilograms; m^2 = squared meters; mL = milliliter; ng = nanograms; 25(OH)D = 25-hydroxy-vitamin D.

Patient Characteristics and Laboratory Data

Demographic variables, including age at first (index) ergocalciferol prescription, sex, and race/ethnicity were obtained from automated health plan administrative databases. BMI was calculated from height and weight obtained from the electronic medical record, ascertaining the BMI value closest to the index prescription date (more than 80% had BMI measured within 1 year of index prescription). BMI was further classified as underweight (BMI < 18.5 kg per m^2), normal (BMI 18.5-24.9 kg per m^2), overweight (BMI 25.0-29.9 kg per m^2), obese (BMI 30.0-39.9 kg per m^2), and severely obese (BMI ≥ 40.0 kg per m^2). Levels of 25(OH)D before and after treatment initiation were ascertained using laboratory data from assays conducted using the DiaSorin assay (99% of assays) and assays conducted at Quest Diagnostics (1% of assays). Severe vitamin D deficiency was defined as baseline 25(OH)D level less than 10 ng per mL and moderate vitamin D deficiency as 25(OH)D level between 10-19 ng per mL.

Among the subset of patients who received an initial ergocalciferol prescription for 12 weekly tablets of 50,000 IU (total dose 600,000 IU) and who had 25(OH)D levels measured 90 to 365 days after the index prescription date, we ascertained the proportion of patients achieving 25(OH)D level ≥ 20 ng per mL. The latest 25(OH)D level measured during the 90- to 365-day window and prior to a second ergocalciferol prescription (or refill) was selected to assess treatment outcome. The seasons during which the post-treatment 25(OH)D levels were measured were defined as winter (December through February), spring (March through May), summer (June through August), or fall (September through November).

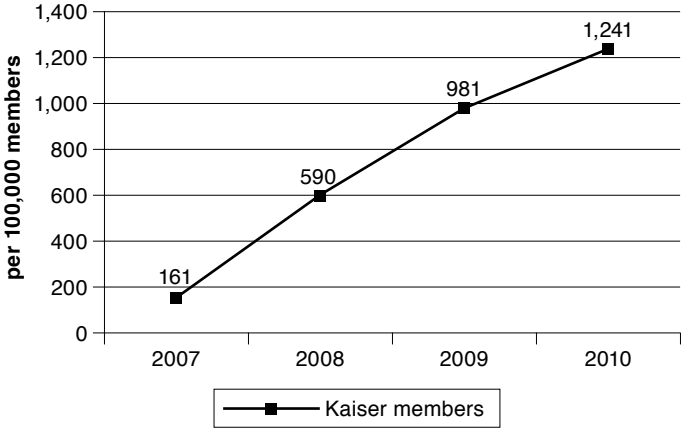
Statistical Analyses

We calculated the number of vitamin D-deficient patients who newly initiated pharmacologic ergocalciferol per 100,000 adult KPNC members, using the KPNC adult membership as the denominator for each year. Point estimates are documented with 95% confidence intervals. Comparisons between subgroups were conducted using the Pearson chi-square test or Student's *t* test. Among the subset of patients who received 12 tablets of ergocalciferol and had post-treatment vitamin D levels measured 90 to 365 days after the index prescription, multivariable logistic regression was used to examine independent predictors of repletion to a nondeficient level, defined as 25(OH)D of 20 ng per mL or more. We also tested for a potential interaction between race/ethnicity and BMI category. All analyses were conducted using SAS version 9.1 (SAS Inc., Cary, NC). A 2-sided *P* value of < 0.05 was considered statistically significant.

Results

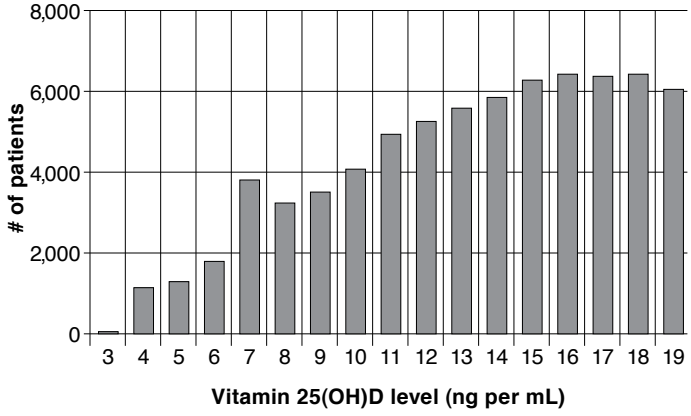
As shown in Figure 1, we identified a final cohort of 72,093 adult individuals with 25(OH)D levels less than 20 ng per mL, who received pharmacologic ergocalciferol during the study period and met inclusion and exclusion criteria. The mean (standard deviation [SD]) age was 58.2 (15.9) years, and 76.6% were female. The rate of newly identified patients comprised 161 per 100,000 of the adult KPNC population in 2007 to 1,241 per 100,000 in 2010, increasing nearly 8-fold during the 4-year observation period (Figure 2). The largest increase occurred in the 31- to 64-year age group, which constituted more than one-half of the total number of newly identified patients each year.

FIGURE 2 Population Trends in New Initiation of Ergocalciferol 50,000 IU for Treatment of Vitamin D Deficiency in Adults Aged 18 Years or Older



IU = international units.

FIGURE 3 Baseline 25-Hydroxy-Vitamin D Level[a]



[a]*There were 72,093 patients with vitamin D deficiency who newly initiated pharmacologic ergocalciferol (50,000 IU) during 2007-2010.*
IU = international units; mL = milliliter; ng = nanogram.

As specified by study criteria, all patients had a baseline vitamin D level less than 20 ng per mL, and one-fifth (20.4%) had severe vitamin D deficiency, defined as a level less than 10 ng per mL (Figure 3). Table 1 shows the demographic and clinical characteristics of the cohort by baseline vitamin D status. A somewhat higher proportion of black patients and those with BMI greater than 40 kg per m^2 were seen among those with severe vitamin D deficiency, defined as 25(OH)D level less than 10 ng per mL, compared with moderate vitamin D deficiency, defined as 25(OH)D level 10-19 ng per mL. Differences in the proportions of newly identified patients with severe versus moderate vitamin D deficiency were also similar across study years, despite the nearly 8-fold increase in the rate of new ergocalciferol initiation identified over time.

Overall, 53,773 (74.6%) patients received 12 tablets of 50,000 IU (total dose of 600,000 IU) for the first ergocalciferol prescription; most of these prescriptions (> 94%) had instructions for once-weekly dosing, the standard dosing interval in KPNC for pharmacologic ergocalciferol. Among the 53,773 individuals with an initial prescription for 12 tablets, 23,322 had a subsequent vitamin D level measured 90 to 365 days after the index prescription date. The median number of days from the index prescription date to the latest 25(OH)D level within 365 days was 195 days (interquartile range 124-282 days). Of these 23,322 patients (included in the repletion analysis subcohort), 74.0% achieved a final post-treatment 25(OH)D level of at least 20 ng per mL, and 35.8% achieved a final post-treatment 25(OH)D level of at least 30 ng per mL. Five individuals (0.02%) had a final 25(OH)D level at or exceeding 100 ng per mL with values between 100-115 ng per mL, considered at the upper border of the safety limit.[23]

Within this same subset of 23,322 individuals who received 12 weekly tablets of ergocalciferol and had follow-up levels of vitamin D measured 90-365 days after the index prescription, we examined the proportion achieving a post-treatment level of at least 20 ng per mL stratified by baseline 25(OH)D status (Table 2). For patients with baseline 25(OH)D level of 0-9 ng per mL, 63.6% (2,896 of 4,557 patients) achieved a final post-treatment level of at least 20 ng per mL, significantly lower than the proportion for those with a baseline 25(OH)D level of 10-19 ng per mL (76.6%, 14,369 of 18,765 patients; $P < 0.001$). For both severe and moderate vitamin D deficient groups, older age, nonobesity, and white race were associated with achieving post-treatment 25(OH)D level ≥ 20 ng per mL.

In multivariable logistic regression that adjusted for age, gender, race, BMI category, year of treatment initiation, pre-treatment vitamin D level, season, and time to post-treatment 25(OH)D measurement, increasing age and higher baseline 25(OH)D levels were associated with higher odds of repletion to 25(OH)D levels of at least 20 ng per mL, while Asian race and Hispanic ethnicity were associated with lower odds of repletion compared with white race (Table 3). Furthermore, having a BMI in the overweight, obese, or severely obese range was associated with sequentially lower odds of repletion to 25(OH)D levels of at least 20 ng per mL. No significant interaction was seen between race/ethnicity and BMI category ($P = 0.71$). The results were also similar for a repletion outcome of 25(OH)D levels of at least 30 ng per mL (data not shown).

TABLE 1 Comparison of Patients with Severe and Moderate Vitamin D Deficiency at Baseline

	Total Number of Patients N = 72,093		Severe Deficiency[a] n = 14,727		Moderate Deficiency[a] n = 57,366		*P* Value[b]
Age mean [SD]	58.2	[15.9]	59.0	[16.3]	58.0	[15.9]	<0.001
	%	(n)	%	(n)	%	(n)	
Age category (years)							
18 to 30	4.4	(3,193)	4.1	(598)	4.5	(2,595)	<0.001
31 to 49	25.6	(18,453)	25.2	(3,712)	25.7	(14,741)	
50 to 64	35.0	(25,224)	33.8	(4,973)	35.3	(20,251)	
65 to 74	17.6	(12,703)	17.3	(2,553)	17.7	(10,150)	
75 or older	17.4	(12,520)	19.6	(2,891)	16.8	(9,629)	
Female	76.6	(55,217)	78.7	(11,587)	76.1	(43,630)	<0.001
Race/ethnicity							
White	43.8	(31,584)	38.2	(5,627)	45.3	(25,957)	<0.001
Black	10.0	(7,236)	17.5	(2,572)	8.1	(4,664)	
Hispanic	16.8	(12,072)	17.0	(2,501)	16.7	(9,571)	
Asian	15.5	(11,208)	13.3	(1,957)	16.1	(9,251)	
Other/unknown	13.9	(9,993)	14.1	(2,070)	13.8	(7,923)	
Body mass index[c]							
Less than 18.5 kg per m^2	1.7	(1,219)	2.4	(347)	1.5	(872)	<0.001
18.5-24.9 kg per m^2	27.0	(19,451)	24.1	(3,550)	27.7	(15,901)	
25.0-29.9 kg per m^2	31.6	(22,813)	29.2	(4,306)	32.3	(18,507)	
30.0-39.9 kg per m^2	31.0	(22,335)	32.1	(4,733)	30.7	(17,602)	
40.0 kg per m^2 or more	8.7	(6,275)	12.2	(1,791)	7.8	(4,484)	
Year of cohort entry							
2007	5.4	(3,901)	5.1	(752)	5.5	(3,149)	<0.001
2008	19.9	(14,352)	18.3	(2,697)	20.3	(11,655)	
2009	33.3	(23,982)	34.2	(5,029)	33.0	(18,953)	
2010	41.4	(29,858)	42.4	(6,249)	41.2	(23,609)	

Column percentages are presented.

[a]*Severe deficiency was defined as a 25(OH)D level of 0-9 ng per mL. Moderate deficiency was defined as a 25(OH)D level of 10-19 ng per mL. Baseline was the 1 year prior to the initial prescription for ergocalciferol.*

[b]*Comparing those with moderate versus severe deficiency using a Pearson chi-square test.*

[c]*Body mass index classifications include underweight (< 18.5 kg per m^2), normal weight (18.5-24.9 kg per m^2), overweight (25.0-29.9 kg per m^2), obese (30.0-39.9 kg per m^2), and severely obese (≥ 40.0 kg per m^2).*

kg = kilograms; m^2 = squared meters; mL = milliliter; ng = nanograms; SD = standard deviation; 25(OH)D = 25-hydroxy-vitamin D.

Discussion

Within a large integrated health care delivery system of more than 3 million members, we observed a dramatically rising trend in the identification and treatment of vitamin D deficiency, with a nearly 8-fold increase in the number of patients initiating pharmacologic ergocalciferol between 2007 and 2010. These findings may be due to a general increase in provider-initiated screening for vitamin D deficiency, particularly among the middle-aged population where vitamin D testing has not been routinely conducted, in contrast to older populations who may have vitamin D levels measured during evaluation for osteoporosis or post-fracture management. The time period of our study also corresponded with a period of increased attention towards hypovitaminosis D in the medical literature and lay press[1,24]; the resulting impact on provider and public awareness of vitamin D deficiency might have contributed to increased vitamin D screening and consequent treatment. As most patients had vitamin D levels measured using the same assay, there were no changes in the laboratory assay for 25(OH)D that could have accounted for the dramatic rise in use of pharmacologic ergocalciferol. Whether additional secular trends are driving factors for this dramatic increase in pharmacologic D therapy is an area for further investigation. Among treated patients, the proportions with severe and less severe vitamin D deficiency identified across the 4-year interval were similar, indicating that the increasing numbers were not due to greater treatment of more mild disease. We also found that a larger proportion of patients with severe compared with moderate vitamin D deficiency were of black race and had a BMI of 40 kg per m^2 or greater.

Numerous studies in adults indicate that individuals of African-American ancestry and Hispanic ethnicity have a higher risk of vitamin D deficiency.[6] The variation by race/ethnicity is likely due to multiple factors, including skin

TABLE 2 Repletion Outcome for Sample Subgroup Stratified by Baseline Severity of Vitamin D Deficiency

	Severe Vitamin D Deficiency[a] n = 4,557				Moderate Vitamin D Deficiency[a] n = 18,765			
	Post-Treatment < 20 ng per mL n = 1,661		Post-Treatment ≥ 20 ng per mL n = 2,896		Post-Treatment < 20 ng per mL n = 4,396		Post-Treatment ≥ 20 ng per mL n = 14,369	
	%	(n)	%	(n)	%	(n)	%	(n)
Female	36.2	(1,318)	63.8	(2,323)	23.9	(3,469)	76.2	(11,075)[b]
Age category (years)[b]								
18 to 49	46.4	(620)	53.6	(715)	31.0	(1,727)	69.0	(3,845)
50 to 74	33.8	(788)	66.2	(1,545)	20.9	(2,129)	79.2	(8,084)
75 or older	28.5	(253)	71.5	(636)	18.1	(540)	81.9	(2,440)
Race/ethnicity[b]								
White	30.6	(538)	69.4	(1,221)	20.6	(1,750)	79.5	(6,764)
Black	35.5	(301)	64.5	(546)	22.2	(362)	77.8	(1,267)
Hispanic	46.4	(356)	53.7	(412)	28.8	(890)	71.2	(2,203)
Asian	42.3	(265)	57.7	(362)	24.0	(739)	76.0	(2,342)
Other/unknown	36.2	(201)	63.9	(355)	26.8	(655)	73.2	(1,793)
Body mass index[b,c]								
Less than 18.5 kg per m^2	32.3	(32)	67.7	(67)	16.0	(38)	84.0	(199)
18.5-24.9 kg per per m^2	29.9	(315)	70.1	(737)	19.6	(987)	80.4	(4,046)
25.0-29.9 kg per m^2	34.8	(464)	65.2	(870)	22.5	(1,372)	77.5	(4,736)
30.0-39.9 kg per m^2	38.2	(577)	61.8	(932)	26.1	(1,518)	74.0	(4,310)
40.0 kg per m^2 or more	48.5	(273)	51.5	(290)	30.9	(481)	69.2	(1,078)

Row percentages are presented.

[a]Results for 23,322 individuals who received 12 doses of ergocalciferol (administered weekly, total dose 600,000 IU). Severe deficiency was defined as a 25(OH)D level of 0-9 ng per mL. Moderate deficiency was defined as a 25(OH)D level of 10-19 ng per mL. Baseline was within 1 year prior to the initial prescription for ergocalciferol. The median time from the index ergocalciferol prescription date to the post-treatment level was 195 days (interquartile range 124 to 282 days).

[b]P ≤ 0.01 comparing those achieving post-treatment 25(OH)D of 20 ng per mL or more versus less than 20 ng per mL.

[c]Body mass index classifications include underweight (< 18.5 kg per m^2), normal weight (18.5-24.9 kg per m^2), overweight (25.0-29.9 kg per m^2), obese (30.0-39.9 kg per m^2), and severely obese (≥ 40.0 kg per m^2).

IU = international units; kg = kilograms; m^2 = squared meters; mL = milliliter; ng = nanograms; 25(OH)D = 25-hydroxy-vitamin D.

pigmentation, amount of sun exposure based on lifestyle and sunscreen use, nutritional factors, obesity, and dietary and over-the-counter supplement intake of vitamin D. Indeed, Hall et al. (2010) found that vitamin D requirements may be up to 2-fold higher in patients with African ancestry (dark skin pigmentation) and low sun exposure compared with patients who have European ancestry (light skin pigmentation) and high sun exposure.[25] This same study also reported differing levels of sun exposure by ancestry, with those from European heritage having the highest sun exposure, followed in decreasing order by African, North Asian, and Hispanic ethnicity.[25] Race has been found to be an important predictor of vitamin D deficiency independent of BMI and sun exposure.[9,26]

We found that the highest prevalence of severe vitamin D deficiency was among patients with severe obesity. While we excluded less than 0.5% of patients with extremely high BMI (> 60 kg per m^2), there may be unique pharmacokinetic and lifestyle differences that affect those with a BMI of 40 kg per m^2 or more. One mechanism for the relationship between obesity and vitamin D is the sequestration of vitamin D in adipose tissue.[9,27] It is well known that the bioavailability of vitamin D, a fat-soluble vitamin, is much lower in obese individuals compared with nonobese individuals.[23,27] In a study of 60 severely obese women, 62% had levels below the normal range, with much greater mean BMI (51 vs. 42 kg per m^2) among those with low vitamin D levels.[28] A large cross-sectional study of 2,026 severely obese Norwegian adults found that about one-half were vitamin D deficient, with male gender associated with a significantly greater odds of vitamin D deficiency.[29] Data from NHANES also demonstrate a strong association between higher 25(OH)D and lower percent body fat, particularly among patients who are centrally obese.[8] Nutritional deficiencies, compounded by higher intake of calorie-dense foods lacking nutrient value and limited access to unprocessed nutritious foods, may be important contributing factors in select obese and minority populations from disadvantaged neighborhoods.[30]

The efficacy of vitamin D replacement is also dependent on BMI, with higher doses required for overweight and obese individuals with hypovitaminosis D.[7] Post-operative bariatric patients represent a growing subgroup that may require extremely large repletion doses due to fat malabsorption.[31]

TABLE 3 *Multivariable Logistic Regression Analysis of Repletion to 25(OH)D ≥ 20 ng per mL for Patients Treated with 600,000 IU Ergocalciferol in 12 Divided Doses (50,000 IU Weekly)*[a]

	Achieving Final 25(OH)D ≥ 20 ng per mL	
	Adjusted Odds Ratio	95% Confidence Interval
Age (years)	1.02	1.02-1.02
Female gender	0.97	0.90-1.05
Baseline 25(OH)D level	1.11	1.10-1.12
Race/ethnicity		
White (reference)	- - -	Reference
Black	1.12	1.00-1.24
Hispanic	0.71	0.65-0.77
Asian	0.80	0.73-0.88
Other	0.83	0.76-0.92
Body mass index category[b]		
Less than 18.5 kg per m^2	1.05	0.79-1.40
18.5-24.9 kg per m^2	- - -	Reference
25.0-29.9 kg per m^2	0.78	0.72-0.85
30.0-39.9 kg per m^2	0.66	0.60-0.71
40.0 kg per m^2 or more	0.53	0.48-0.60
Season[c] of post-treatment 25(OH)D level		
Spring	1.07	0.98-1.16
Summer	1.92	1.76-2.10
Fall	1.51	1.38-1.65
Winter	- - -	Reference
Days between index ergocalciferol initiation and post-treatment 25(OH)D lab value	0.99	0.99-1.00

[a] *C-statistic = 0.698 for outcome 25(OH)D of 20 ng per mL.*

[b] *Body mass index classifications include underweight (< 18.5 kg per m^2), normal weight (18.5-24.9 kg per m^2), overweight (25.0-29.9 kg per m^2), obese 30.0-39.9 kg per m^2), and severely obese (≥ 40.0 kg per m^2).*

[c] *Seasons are defined as winter (December-February), spring (March-May), summer (June-August), and fall (September-November).*

IU = international units; kg = kilograms; m^2 = squared meters; mL = milliliter; ng = nanograms; 25(OH)D = 25-hydroxy-vitamin D.

Pre-operatively, these patients already have a high prevalence of hypovitaminosis D, ranging from at least one-third of whites to more than 70% of black and Hispanic patients reported in the bariatric surgery literature.[31-33] Recently published guidelines from the Endocrine Society (Holick et al. 2011)[23] recommend vitamin D treatment to achieve a 25(OH)D level exceeding 30 ng per mL (contrasting with recommendations from the Institute of Medicine,[14] which target a threshold of 20 ng per mL), with higher treatment doses often necessary for patients who are obese or have malabsorption syndromes. One of the goals of the present study was to determine which patients are more likely to demonstrate persistent vitamin D deficiency following pharmacologic repletion therapy. For this reason, we examined the last 25(OH)D level available within the specified 1-year observation window, since early measurements obtained during pharmacologic treatment are more likely to be in the normal range. Our findings suggest that correction of vitamin D deficiency may be more challenging in younger individuals (possibly due to comorbidities that prompted vitamin D screening), in those of Asian and Hispanic race/ethnicity, and in individuals who are obese. Further studies are needed to examine specific clinical subsets within these subgroups with poor repletion outcomes.

Few studies have examined the efficacy of specific pharmacologic regimens of vitamin D. Current guidelines suggest that ergocalciferol 50,000 IU administered weekly for 8 weeks is often effective in correcting vitamin D deficiency in adults,[23,34] with the recognition that obese adults, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism will need higher doses.[23] In a small series of 306 patients receiving 36 discrete prescribing regimens, regimens containing a total ergocalciferol dose of more than 600,000 IU achieved vitamin D sufficiency at 25(OH)D levels of at least 30 ng per mL for the majority of cases (64%).[22] The proportion in the present study is somewhat lower, likely due to our focus on the final achieved level of 25(OH)D. A more recent study, conducted with 1,446 patients receiving 29 different ergocalciferol regimens, found that patients prescribed 50,000 to 100,000 IU per week were more likely to achieve 25(OH)D levels of 30 ng per mL or greater when compared with those prescribed less than 50,000 IU.[35] This study also found that obesity was associated with a lower odds of attaining sufficient vitamin D levels.[35] There is currently little published research information pertaining to the interaction of race/ethnic differences, adiposity, and other patient factors on rates of vitamin D repletion following pharmacologic therapy with ergocalciferol. Future studies should examine the specific relationship of these factors, the role of treatment optimization, and the utility of alternative forms of vitamin D in treatment-resistant patients. For instance, vitamin D3 has been shown to be effective in maintaining sufficient levels of circulating 25(OH)D levels, and as little as one-third the equivalent dose may be needed.[1,36,37]

Limitations

Our study has several limitations. First, we did not examine the efficacy of other ergocalciferol regimens (repletion success was only examined with 12 weekly ergocalciferol tablets), provider prescribing practices, patient adherence, and intake of additional over-the-counter cholecalciferol (D3), and we were able to ascertain post-treatment status based only on measured vitamin D levels obtained in the context of patient care. As such, we cannot exclude the potential influence of demographic and clinical factors on the timing of vitamin D measurement following the first prescription. Second, the treatment outcome at less than 90 days or greater than 365

days following the index prescription (or after a second prescription) was not examined in this study. Nonetheless, this is one of the first population-based studies investigating the clinical characteristics and treatment outcomes of patients receiving pharmacologic ergocalciferol. Third, these data were obtained in a northern California population receiving health care and may not be generalizable to the larger U.S. population, where sunlight exposure, the intensity of ultraviolet radiation, and access to health care or coverage may vary.

Conclusions

Among patients with hypovitaminosis D receiving pharmacologic ergocalciferol repletion therapy, 20% had severe vitamin D deficiency. Among the subset who received a total dose of 600,000 IU ergocalciferol in 12 weekly divided doses in whom follow-up vitamin D levels were measured up to 1 year following treatment initiation, age, race/ethnicity, BMI, and severity of vitamin D deficiency were associated with differential rates of repletion to a 25(OH)D level at or above 20 ng per mL. Future studies should examine predictors of repletion failure, parathyroid hormone function and response to repletion, and the role of optimal repletion strategies and/or alternatives for treatment-resistant patients.

Authors

MOXIE J. STRATTON-LOEFFLER, DO, is Resident Physician, Department of Medicine, and AMER BUDAYR, MD, is Senior Physician and Sub-Chief, Division of Endocrinology, Department of Medicine, Kaiser Permanente Oakland Medical Center, Oakland, California. JOAN C. LO, MD, is Research Scientist and Senior Physician, and ASHLEY COATES, MPH, is Senior Consulting Data Analyst, Kaiser Permanente Division of Research, Oakland, California. RITA L. HUI, PharmD, MS, is Pharmacoeconomics and Outcomes Research Pharmacist, Kaiser Permanente Outcomes Research Group, Oakland, California. JEROME R. MINKOFF, MD, is Senior Physician, Division of Endocrinology, Department of Medicine, Kaiser Permanente Santa Rosa Medical Center, Santa Rosa, California.

AUTHOR CORRESPONDENCE: Joan C. Lo, MD, Kaiser Permanente Division of Research, 2000 Broadway, Oakland, CA 94612. Tel.: 510.627.2986; Fax: 510.627.2573; E-mail: Joan.C.Lo@kp.org.

DISCLOSURES

This study was funded by the Kaiser Permanente Community Benefits Program and received no other external funding. The authors report no conflicts of interest.

Study concept and design were contributed to equally by Lo, Stratton-Loeffler, Hui, Coates, and Budayr. Hui had primary responsibility for data collection and analyses, with assistance from Coates, Lo, and Budayr. Data interpretation was primarily the work of Lo, Hui, Coates, Budayr, Minkoff, and Stratton-Loeffler. The manuscript was written primarily by Lo, Stratton-Loeffler, and Budayr, with assistance from Hui, Coates, and Minkoff and was revised by all authors.

REFERENCES

1. Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007;357(3):266-81. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMra070553. Accessed August 23, 2012.

2. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. *Bone*. 2002;30(5):771-77.

3. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. *Am J Clin Nutr.* 2008;88(6):1519-27. Available at: http://www.ajcn.org/content/88/6/1519.full.pdf+html. Acccessed August 23, 2012.

4. Gloth FM 3rd, Gundberg CM, Hollis BW, Haddad JG Jr, Tobin JD. Vitamin D deficiency in homebound elderly persons. *JAMA*. 1995;274(21):1683-86.

5. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med*. 1998;338(12):777-83. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJM199803193381201. Accessed August 23, 2012.

6. Yetley EA. Assessing the vitamin D status of the U.S. population. *Am J Clin Nutr.* 2008;88(2):S558-S564. Available at: http://www.ajcn.org/content/88/2/558S.full.pdf+html. Accessed August 23, 2012.

7. Lee P, Greenfield JR, Seibel MJ, Eisman JA, Center JR. Adequacy of vitamin D replacement in severe deficiency is dependent on body mass index. *Am J Med.* 2009;122(11):1056-60.

8. Beydoun MA, Boueiz A, Shroff MR, Beydoun HA, Wang Y, Zonderman AB. Associations among 25-hydroxyvitamin D, diet quality, and metabolic disturbance differ by adiposity in adults in the United States. *J Clin Endocrinol Metab.* 2010;95(8):3814-27. Available at: http://jcem.endojournals.org/content/95/8/3814.full.pdf. Accessed August 23, 2012.

9. Looker AC. Do body fat and exercise modulate vitamin D status? *Nutr Rev.* 2007;65(8 Pt 2):S124-S126. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1753-4887.2007.tb00339.x/pdf. Accessed August 23, 2012.

10. Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D status: United States, 2001-2006. *NCHS Data Brief.* 2011(59):1-8. Available at: http://www.cdc.gov/nchs/data/databriefs/db59.pdf. Accessed August 23, 2012.

11. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in U.S. adults. *Nutr Res.* 2011;31(1):48-54.

12. Beauchet O, Annweiler C, Verghese J, Fantino B, Herrmann FR, Allali G. Biology of gait control: vitamin D involvement. *Neurology.* 2011;76(19):1617-22.

13. Bhan A, Rao AD, Rao DS. Osteomalacia as a result of vitamin D deficiency. *Endocrinol Metab Clin North Am J.* 2010;39(2):321-31.

14. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab.* 2011;96(1):53-58. Available at: http://jcem.endojournals.org/content/96/1/53.full.pdf+html. Accessed August 23, 2012.

15. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA*. 2005;293(18):2257-64. Available at: http://jama.ama-assn.org/content/293/18/2257.full.pdf+html. Accessed August 23, 2012.

16. Rabenda V, Bruyère O, Reginster JY. Relationship between bone mineral density changes and risk of fractures among patients receiving calcium with or without vitamin D supplementation: a meta-regression. *Osteoporos Int*. 2011;22(3):893-901.

17. Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. *J Bone Miner Res*. 2009;24(5):935-42. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3312737/pdf/jbmr-24-5-935.pdf. Accessed August 23, 2012.

18. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ*. 2009;339:b3692. Available at: http://www.bmj.com/highwire/filestream/392958/field_highwire_article_pdf/0.pdf. Accessed August 23, 2012.

19. Murad MH, Elamin KB, Abu Elnour NO, et al. Clinical review: the effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2011;96(10):2997-3006.

20. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010;303(18):1815-22. Available at: http://jama.ama-assn.org/content/303/18/1815.full.pdf+html. Accessed August 23, 2012.

21. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health*. 1992;82(5):703-10. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1694121/pdf/amjph00542-0057.pdf. Accessed August 23, 2012.

22. Pepper KJ, Judd SE, Nanes MS, Tangpricha V. Evaluation of vitamin D repletion regimens to correct vitamin D status in adults. *Endocr Pract*. 2009;15(2):95-103. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683376/pdf/nihms-110700.pdf. Accessed August 23, 2012.

23. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-30. Available at: http://jcem.endojournals.org/content/96/7/1911.full.pdf+html. Accessed August 23, 2012.

24. Jorde R, Grimnes G. Vitamin D and lipids: do we really need more studies? *Circulation*. 2012;126(3):252-54.

25. Hall LM, Kimlin MG, Aronov PA, et al. Vitamin D intake needed to maintain target serum 25-hydroxyvitamin D concentrations in participants with low sun exposure and dark skin pigmentation is substantially higher than current recommendations. *J Nutr*. 2010;140(3):542-50. Available at: http://jn.nutrition.org/content/early/2010/01/06/jn.109.115253.full.pdf+html. Accessed August 23, 2012.

26. Looker AC. Body fat and vitamin D status in black versus white women. *J Clin Endocrinol Metab*. 2005;90(2):635-40. Available at: http://jcem.endojournals.org/content/90/2/635.full.pdf+html. Accessed August 23, 2012.

27. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*. 2000;72(3):690-93. Erratum in: *Am J Clin Nutr*. 2003;77(5):1342. Available at: http://www.ajcn.org/content/72/3/690.full.pdf. Accessed August 23, 2012.

28. Buffington C, Walker B, Cowan GS Jr, Scruggs D. Vitamin D deficiency in the morbidly obese. *Obes Surg*. 1993;3(4):421-24.

29. Johnson LK, Hofsø D, Aasheim ET, et al. Impact of gender on vitamin D deficiency in morbidly obese patients: a cross-sectional study. *Eur J Clin Nutr*. 2012;66(1):83-90. Available at: http://www.nature.com/ejcn/journal/v66/n1/pdf/ejcn2011140a.pdf. Accessed August 23, 2012.

30. Gordon C, Purciel-Hill M, Ghai NR, Kaufman L, Graham R, Van Wye G. Measuring food deserts in New York City's low-income neighborhoods. *Health Place*. 2011;17(2):696-700.

31. Xanthakos SA. Nutritional deficiencies in obesity and after bariatric surgery. *Pediatr Clin North Am*. 2009;56(5):1105-21. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2784422/pdf/nihms132186.pdf. Accessed August 23, 2012.

32. Carlin AM, Rao DS, Meslemani AM, et al. Prevalence of vitamin D depletion among morbidly obese patients seeking gastric bypass surgery. *Surg Obes Relat Dis*. 2006;2(2):98-103.

33. Gemmel K, Santry HP, Prachand VN, Alverdy JC. Vitamin D deficiency in preoperative bariatric surgery patients. *Surg Obes Relat Dis*. 2009;5(1):54-59.

34. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet*. 1998;351(9105):805-06.

35. Vande Griend JP, McQueen RB, Linnebur SA, Vondracek SF. Prescription ergocalciferol dosing for vitamin D repletion: a retrospective evaluation. *Pharmacotherapy*. 2012;32(2):135-41.

36. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab*. 2004;89(11):5387-91. Available at: http://jcem.endojournals.org/content/89/11/5387.full.pdf+html. Accessed August 23, 2012.

37. Heaney RP, Recker RR, Grote J, Horst RL, Armas LA. Vitamin D(3) is more potent than vitamin D(2) in humans. *J Clin Endocrinol Metab*. 2011;96(3):E447-52. Available at: http://jcem.endojournals.org/content/96/3/E447.full.pdf+html. Accessed August 23, 2012.

RESEARCH

Long-Term Medicaid Excess Payments from Alleged Price Manipulation of Generic Lorazepam

Boyang Bian, BPharm, MS; Elizabeth Gorevski, PharmD, MS;
Christina M.L. Kelton, PhD; Jeff J. Guo, PhD; and Jill E. Martin Boone, PharmD

ABSTRACT

BACKGROUND: Cost savings from the use of generic drugs versus brand-name drugs are well known. Both private and public prescription drug plans encourage the use of generic drugs through a variety of mechanisms. The magnitude of cost savings for a given generic drug is dependent on the degree to which the generic market is competitive. Should the competitive structure become compromised, higher prices and reduced cost savings may result. An alleged conspiracy between Mylan Laboratories and its active-ingredient suppliers in 1997 was associated with an increase in seller concentration in the generic lorazepam market. The Federal Trade Commission (FTC) alleged that Mylan raised costs to consumers by $120 million because of price increases for generic lorazepam from March through December 1998 and for generic clorazepate from January through December 1998. In November 2002, a settlement with Mylan was approved by the FTC, and a federal district court required Mylan to pay $147 million, including $28.2 million to state agencies including Medicaid.

OBJECTIVES: To (a) describe the seller concentration in the national Medicaid generic lorazepam market over a 19-year period from January 1991 through December 2009, (b) estimate the excess payments for generic lorazepam by Medicaid between 1998 and 2009, and (c) investigate potentially increased utilization and prices of 2 substitute pharmaceuticals: branded lorazepam (Ativan) and generic alprazolam (another widely used intermediate-acting benzodiazepine).

METHODS: Using Medicaid State Drug Utilization Data from the Centers for Medicare & Medicaid Services, we calculated the 4-firm concentration ratio (CR_4) and the Herfindahl-Hirschman Index (HHI) for the Medicaid generic lorazepam market, along with pre-rebate reimbursement for pharmacy claims, number of claims (utilization), and average pre-rebate reimbursement per claim (average "price") for generic lorazepam, from 1991 through 2009. Medicaid's excess payments were estimated under 2 different assumptions regarding what the average generic lorazepam price would have been in the absence of the alleged conspiracy. To find counterfactual prices, the average per-claim reimbursement for lorazepam for the 4 quarters prior to the alleged conspiracy, $6.80, was inflated using (a) the quarterly change in the average per-claim reimbursement for generic alprazolam and (b) the Consumer Price Index (CPI) for all urban consumers, all goods. Potential impact of the alleged conspiracy on the branded lorazepam and generic alprazolam markets was investigated.

RESULTS: The average pre-rebate reimbursements per claim for generic lorazepam were $10.25, $23.12, and $8.48 in 1991, 1998, and 2009, respectively. For the same 3 years, CR_4 = 52.80, 76.02, and 86.74, while HHI = 905.71, 2,166.25, and 2,233.36. Medicaid's excess payments from 1998-2009 were estimated at approximately $625-$657 million. The data also suggest the possibility of small impacts on the utilization of branded lorazepam and the price of generic alprazolam.

CONCLUSIONS: Prior to the alleged conspiracy in 1997, average pre-rebate reimbursement per claim for generic lorazepam was declining, while seller concentration was rising. After a jump in average payment per claim in the years immediately following the alleged conspiracy, prices have gradually returned to their pre-1998 levels. However, the generic lorazepam market was more concentrated in 2009 than prior to the alleged conspiracy.

J Manag Care Pharm. 2012;18(7):506-15

What is already known about this subject

- There are often significant cost savings available through the use of generic rather than brand-name drugs. Individual branded lorazepam and alprazolam prescription claims cost Medicaid more than 20 times as much as their generic counterparts in 2009 (pre-rebate). Similar cost savings have been found for many other drugs in different drug classes. On average, in 2010, the price of a generic prescription under Medicaid was approximately one-ninth the price of a brand. Cost savings depend on a competitive market structure in which generic drug companies charge low, competitive prices. Concentrated markets, on the other hand, may be susceptible to collusive (implicit or explicit) behavior.
- An alleged conspiracy between Mylan Laboratories and its active-ingredient suppliers in 1997 was associated with a rise in concentration in the generic lorazepam market, along with 1998 price escalations by Mylan and other lorazepam producers. The Federal Trade Commission (FTC) alleged that Mylan raised its price of generic lorazepam tablets by amounts ranging approximately from 1,900%-2,600%, depending on the bottle size and strength. According to the FTC, Mylan's competitors matched these price increases. In 2002, a $147 million settlement was reached between Mylan and the FTC.
- Switching from lorazepam to a less expensive benzodiazepine is difficult. First, patients are not very knowledgeable about alternatives. Second, prescribing physicians are often unaware of the prices of available drugs and may be reluctant, especially in the case of a central nervous system drug, to consider a substitution not based on efficacy or safety.

What this study adds

- This study describes a counterexample to generic drug cost savings. In the generic lorazepam market, prices dropped slowly after 1998 and did not return to pre-1998 levels for more than a decade. Moreover, as of 2009, the market structure for generic lorazepam had not returned to the level of concentration observed prior to the alleged Mylan conspiracy; both the 4-firm concentration ratio and the Herfindahl-Hirschman Index exceeded standard accepted cutoffs (40 and 1,000, respectively) for a presumptive competitive market structure in 2009. Because collusion generally is more prevalent in more concentrated markets, the potential for future collusion remains.
- Depending on 2 models with counterfactual scenario assumptions regarding the average generic lorazepam pre-rebate payment per claim in the absence of the alleged conspiracy, the 12-year excess payments for Medicaid were estimated to be between $624.9 million and $657.4 million in 2009 dollars.
- There was a negligible association between the rise in price in the generic lorazepam market and the per-prescription spending on and utilization of branded lorazepam and generic alprazolam, arguably the 2 closest substitutes for generic lorazepam. A small percentage increase in the use of branded lorazepam and a small transitory increase in the price of generic alprazolam in Medicaid occurred in the years immediately following the alleged conspiracy. Overall, however, there appeared to be limited spillover into these 2 closely related markets.

The U.S. system of patent monopoly in the pharmaceutical industry attempts to balance the interests of patients and third-party payers (who want low-cost medicines) with higher prices and profits for pharmaceutical manufacturers. This system grants to pharmaceutical companies patents that bestow monopoly status for a specific period of time commonly known as the "effective patent life," which varies across drugs with an average of about 12 years.[1] The profits earned during this period of patent protection encourage the development of new drugs by the firms. However, once a drug's patents expire, other generally lower-price generic manufacturers are free to enter the market, and purchasers generally realize significant reductions in prices.[2] On average in the Medicaid program in 2010, the price of a generic prescription was approximately one-ninth the price of a brand-name prescription.[3] Individual branded lorazepam and alprazolam prescription claims cost Medicaid more than 20 times as much as their generic counterparts in 2009 (pre-rebate).[4]

Savings in the use of generic drugs are well known by health policy makers.[5] Both private and public prescription drug plans encourage the use of generic drugs through a variety of mechanisms. For example, state Medicaid programs include generic drugs on the state's preferred drug list (PDL); mandate generic dispensing of drugs in the absence of a dispense-as-written (DAW) code; and educate physicians on the use of generic drugs.[6] Moreover, according to several previous studies, Medicaid has been reasonably successful in switching patients to generic drugs from their branded counterparts fairly quickly following the patent expiration of the branded drug.[7-9] In fact, Medicaid's generic substitution rate has been estimated in the mid-90th percentile, and generics currently represent approximately 66% of all Medicaid prescriptions (though only 22% of Medicaid spending).[3]

However, maximum cost savings for a specific generic drug may not be achieved if the generic market is noncompetitive. This article focuses on generic drug market structure, specifically seller concentration in the Medicaid generic lorazepam market, and its relationship to total spending and spending per prescription claim by Medicaid on this generic drug. On September 30, 1977, branded lorazepam (Ativan), an intermediate-acting benzodiazepine, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of anxiety.[10,11] Barr Laboratories had the first generic lorazepam tablets approved on December 10, 1985. Mylan Laboratories' generic lorazepam approval came on October 13, 1987.[12]

In a complaint filed 11 years later on February 8, 1999, the Federal Trade Commission (FTC) alleged that Mylan raised its price of generic lorazepam tablets by amounts ranging approximately from 1,900%-2,600%, depending on the bottle size and strength. Mylan's competitors were alleged to have matched these price increases.[13] Four companies—Mylan Laboratories, Cambrex Corporation, Profarmaco S.R.L., and Gyma Laboratories of America—were accused of violating Sections 1 and 2 of the Sherman Antitrust Act by entering into an exclusive licensing agreement that ultimately restrained trade. Specifically, the companies were accused of conspiring to monopolize the markets for the generic drugs lorazepam and clorazepate (a long-acting benzodiazepine).[13] An alleged agreement made between Mylan and Profarmaco in November 1997 stated that Profarmaco would supply the active pharmaceutical ingredients for lorazepam and clorazepate exclusively to Mylan Laboratories in exchange for a share of the profits obtained by Mylan from the sales of those products. (Cambrex Corporation was the parent company of Profarmaco, and Gyma Laboratories of America distributed Profarmaco products.) The FTC alleged that, through these arrangements and 1998 price escalations, Mylan "[raised] the cost that pharmacies, hospitals, insurers, managed care organizations, wholesalers, government agencies, consumers, and others pay for lorazepam and clorazepate tablets;" the FTC requested "equitable relief" in the amount of $120 million plus interest.[13] In November 2002, a settlement with Mylan Laboratories was approved by the FTC, and a federal district court required Mylan to pay $147 million, including $100 million to "indirect purchasers" ($71.8 million for consumer claims and $28.2 million to state agencies

including Medicaid), and $39 million for attorneys' fees in class action suits filed by private consumers suing under state law.[14]

The present study was conducted to follow up on the generic lorazepam market. We chose not to study the market for generic clorazepate because of its relatively small size (a $2.0 million Medicaid market in 1997).[4] The main purpose of the study was to put the $147 million settlement in the context of overall, long-term consumer loss from the high generic lorazepam prices following the alleged conspiracy. The generic lorazepam market never returned to its pre-1997 market structure. Seller concentration has remained high over the last decade. Some of the companies that competed before the alleged conspiracy did not compete afterward. The noncompetitive market structure leaves open the possibility of additional collusion in the future.

Methods

Data Source

For the descriptive analysis of the Medicaid generic lorazepam market from 1991-2009, we used the publicly available National Summary Files from the Medicaid State Drug Utilization Data (SDUD) maintained by the Centers for Medicare & Medicaid Services (CMS).[15] The database includes pharmacy claims records for outpatient drugs dispensed to Medicaid beneficiaries in 49 states and the District of Columbia. Since the pharmacy claims data are collected as part of the Medicaid Rebate Program, only fee-for-service (FFS) claims are included. States differ in how their drug benefit programs are managed, and the SDUD do not include pharmacy claims from Arizona, which is 100% managed care.[16] Other managed care states, however, have pharmacy-benefit carve outs, resulting in FFS claims, in order to take advantage of the federal rebate program. When we summed all Medicaid FFS claims in 2008 in the national database, we found that Medicaid had a total of $24.3 billion in (pre-rebate) expenditures on all outpatient prescription drugs.

Each data record in the Medicaid SDUD includes the National Drug Code (NDC), drug name (trade or generic), year and quarter of Medicaid expenditure, number of pharmacy claims, number of units (e.g., individual capsules or tablets), and total pharmacy reimbursement amount (ingredient cost plus dispensing fee plus other fees but no breakout of individual components); the SDUD claims records do not include manufacturer rebates.[17] The first 5 digits of the NDC number (the labeler code) identify the drug manufacturer, while the remaining digits identify specific drug product by strength, dose formulation, and packaging. We searched the database for all lorazepam products as well as branded lorazepam and generic alprazolam products as the closest substitutes for generic lorazepam. Because the database identifies the companies from which the pharmacies purchased the lorazepam dispensed to Medicaid beneficiaries, quarterly claim counts and pharmacy payment amounts (not accounting for rebates) attributed to each of the generic lorazepam manufacturers were calculated by summing data across individual NDCs for each of the different labeler codes.

Measures of Market Concentration and Price

A concentration ratio (CR_4) was calculated as the percentage of generic lorazepam prescriptions accounted for by the top 4 firms (labeler codes). CR_4 can range between 0 (with an infinite number of small firms) and 100 (where the top 4 firms account for the entire market). In addition, seller concentration was calculated using the Herfindahl-Hirschman Index (HHI), the sum of squared market shares (based on total claims counts) for all firms from which the pharmacies purchased generic lorazepam. The HHI ranges from 0 (an infinite number of small firms) to 10,000 for a pure monopoly (with 100% of the market). By squaring the market shares, the HHI accounts for market-share inequality (i.e., it gives greater weight to larger market shares).[18] Because of the HHI's advantages over CR_4 for measuring seller concentration, the Department of Justice (DOJ) has adopted the HHI over the CR_4 in its horizontal merger guidelines.[19,20] Over the time period of this study, when the 1997 Merger Guidelines were in effect, an HHI of less than 1,000 was considered by the DOJ to represent an "unconcentrated" market; 1,000-1,800 indicated that the market was "moderately concentrated;" and more than 1,800 indicated a "highly concentrated" market.[19]

Quarterly per-claim pharmacy reimbursement, as a proxy for drug price, was computed for each manufacturer and overall for lorazepam. The calculation was based on total reimbursed amount (ingredient cost plus dispensing fee plus other fees) pre-rebate.

Calculations

After converting all values to 2009 dollars using the Consumer Price Index (CPI) for urban consumers, all goods, we summed over the 47 calendar quarters (from 1998 Q2, when Medicaid first experienced the results of the alleged conspiracy-based price increase, through 2009 Q4, the last quarter of data collected) to determine the 12-year total excess payments.

We used 2 different approaches to estimate the counterfactual average payment per lorazepam prescription post-1997 in the absence of the alleged conspiracy. To find counterfactual prices, the average per-claim reimbursement for lorazepam for the 4 quarters prior to the alleged conspiracy, $6.80, was inflated using (a) the quarterly change in the average per-claim reimbursement for generic alprazolam (generic alprazolam per-claim reimbursement amounts computed from reimbursement and claims data in the Medicaid SDUD file) and (b) the CPI for urban consumers, all goods. The rationale for the first approach is that it assumes lorazepam prices over time would have been affected by similar "demand and supply forces" as those affecting alprazolam prices. The rationale for the second is that it assumes that real (inflation-adjusted) lorazepam prices over

TABLE 1 Description of the National Medicaid Generic Lorazepam Market from 1991-2009

Year	Total Number of Generic Lorazepam Prescriptions in U.S. (in 1,000s)[a]	Total Number of Medicaid Generic Lorazepam Prescriptions Reimbursed	Total Medicaid Payments for Generic Lorazepam ($)[b]	Average Payment Per Prescription for Generic Lorazepam ($)[b]	CR_4[c]	HHI[d]	Number of Labeler Codes	Number of Labeler Codes with ≥ 1% of Medicaid Market
1991	na	1,415,890	14,516,510	10.25	52.80	905.71	41	16
1992	na	1,896,115	19,395,701	10.23	54.92	961.24	43	14
1993	na	2,177,388	17,811,391	8.18	57.46	1,025.23	38	16
1994	na	2,231,157	17,652,665	7.91	59.22	1,096.45	36	15
1995	na	2,268,928	17,709,799	7.81	59.83	1,130.84	35	15
1996	na	2,488,634	17,289,274	6.95	58.79	1,175.50	39	13
1997	na	2,644,807	18,515,317	7.00	66.36	1,465.24	40	14
1998	na	2,804,349	64,827,824	23.12	76.02	2,166.25	39	13
1999	na	3,019,274	91,315,955	30.24	83.40	2,447.78	30	8
2000	16,842	3,215,127	96,639,375	30.06	83.93	2,126.31	31	7
2001	17,702	3,778,047	100,934,654	26.72	85.75	2,046.97	32	7
2002	17,453	4,035,466	96,818,447	23.99	78.56	1,797.50	31	8
2003	17,545	4,257,529	93,099,961	21.87	81.42	1,861.24	27	7
2004	18,436	4,401,819	85,093,949	19.33	81.41	1,946.98	26	6
2005	19,002	4,326,616	79,027,327	18.27	85.73	2,050.98	25	6
2006	19,789	5,504,358	66,523,326	12.09	94.40	2,393.22	28	5
2007	21,022	4,276,290	55,600,057	13.00	93.27	2,359.12	27	5
2008	22,043	4,400,862	46,692,296	10.61	91.07	2,416.30	29	5
2009	22,436	4,327,388	36,703,876	8.48	86.74	2,233.36	22	7

[a]*The total number of generic lorazepam prescriptions in the United States was found for various years at http://drugtopics.modernmedicine.com/Pharmacy+Facts+&+Figures.*[21] *The reports for various years were entitled Top 200 Generic Drugs by Total Prescriptions.*

[b]*Average payment estimate includes ingredient cost plus fees and does not account for manufacturer rebates.*

[c]*CR_4 (4-firm concentration ratio) is computed as the share of Medicaid-reimbursed prescriptions accounted for by the top 4 manufacturer labels.*

[d]*HHI (Herfindahl-Hirschman Index) is computed as the sum of squared market shares of Medicaid-reimbursed prescriptions of all the manufacturer labels (e.g., 41 labels in 1991 and 22 labels in 2009).*

na = not available.

time would have remained constant. Such a counterfactual price would not be affected by alleged conspiracy-based spillover into the generic alprazolam market.

All the data analyses were conducted using the SAS software package for Windows (Version 9.2, SAS Institute Inc., Cary, NC) and Excel 2007 (Microsoft, Redmond, WA).

Results

The Evolving Medicaid Generic Lorazepam Market

In 1991, the $14.5 million Medicaid generic lorazepam market (excluding branded lorazepam, which had a very small share of the Medicaid lorazepam market by that time—0.60% of claims and 10.82% of spending) had more than 35 suppliers with 41 different labeler codes (a few firms had several different labeler codes), with 16 labeler codes (15 firms) each having at least a 1% market share (Table 1).[21] With an HHI of 905.71, the market would be considered presumptively competitive according to both the 1997 Merger Guidelines (in effect during our study period)[19] and the more recent 2010 Merger Guidelines.[20] The average price of $10.25 per generic lorazepam prescription in 1991 was 73% less than the average price of $38.55 per branded lorazepam prescription (data presented later).

In 1997, the Medicaid generic lorazepam market had grown to 2.6 million prescriptions and $18.5 million in total pre-rebate Medicaid spending (Table 1). The average price per prescription had fallen to $7.00. The number of firms participating in the Medicaid market had not fallen much; there were 14 labeler codes with at least 1% of the market. However, relative to 1991, market concentration had increased, with HHI = 1,465.24, considered moderately concentrated under the 1997 Merger Guidelines[19] (competitive under the 2010 Merger Guidelines[20]). In 1998, Medicaid experienced a 250% increase in spending on lorazepam from $18.5 million to $64.8 million. Whereas the number of prescriptions rose by 6.03% from 1997 to 1998, the average prescription price increased to $23.12 in 1998 from $7.00 in 1997, representing a 230% increase, as state Medicaid programs began to adjust their maximum allowable cost (MAC) for generic lorazepam.[22] That year, the HHI rose above 2,000, considered concentrated by the 1997 Merger Guidelines[19] (and moderately concentrated under the 2010 Merger Guidelines[20]). In 1999 and 2000, Medicaid was spending more than $30 per prescription for generic loraz-

TABLE 2 Prescription Share for the Top 7 Labeler Codes for National Medicaid Generic Lorazepam: 1997-2002

	Year					
Labeler Rank	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**
			1			
NDC labeler code	00378	00378	00378	00378	00781	00781
Manufacturer	Mylan Labs	Mylan Labs	Mylan Labs	Mylan Labs	Sandoz	Sandoz
Rx share (%)	24.96	39.74	41.26	32.56	27.50	26.50
			2			
NDC labeler code	00228	00228	00781	00781	00378	00378
Manufacturer	Actavis Elizabeth	Actavis Elizabeth	Sandoz	Sandoz	Mylan Labs	Mylan Labs
Rx share (%)	23.35	19.40	21.49	25.09	27.13	24.76
			3			
NDC labeler code	51875	52544	00228	52544	52544	52544
Manufacturer	Royce Labs	Watson	Actavis Elizabeth	Watson	Watson	Watson
Rx share (%)	9.26	8.61	12.60	14.01	17.94	13.91
			4			
NDC labeler code	00182	00781	59911	00228	00228	00228
Manufacturer	Goldline Labs	Sandoz	Wyeth	Actavis Elizabeth	Actavis Elizabeth	Actavis Elizabeth
Rx share (%)	8.79	8.26	8.04	12.27	13.17	13.38
			5			
NDC labeler code	00536	00182	52544	59911	59911	00591
Manufacturer	Rugby Labs	Goldline Labs	Watson	Wyeth	Wyeth	Watson
Rx share (%)	6.01	4.34	6.75	8.97	6.55	8.25
			6			
NDC labeler code	00781	51875	51079	51079	53489	63304
Manufacturer	Sandoz	Royce Labs	UDL	UDL	Mutual	Ranbaxy
Rx share (%)	5.71	3.98	2.71	2.39	3.23	5.19
			7			
NDC labeler code	52544	00536	51875	53489	51079	53489
Manufacturer	Watson	Rugby Labs	Royce Labs	Mutual	UDL	Mutual
Rx share (%)	5.70	3.87	1.55	1.29	2.11	3.21
Total for top 4 suppliers (%)	66.36	76.02	83.40	83.93	85.75	78.56
Total for top 7 suppliers (%)	83.78	88.21	94.41	96.58	97.64	95.21

NDC = National Drug Code; Rx = prescription.

epam, and CR_4 rose above 80 (well above a competitive cutoff of 40 or "loose oligopoly" cutoff of 60[18]). The HHI reached 2,447.78 in 1999, its highest value over the 2 decades. By the year 2000, there were only 7 labeler codes that held at least 1% of the Medicaid generic lorazepam market. From 1999 to 2003, Medicaid spent more than $90 million annually on generic lorazepam. In 2001, Medicaid spent more than $100 million.

Over the last decade, following the FTC settlement, the Medicaid average reimbursement per generic lorazepam claim has come down slowly, to $8.48 in 2009, near the pre-1998 levels. In 2009, Medicaid spent $36.7 million for 4.3 million prescriptions. However, the market structure has not returned to the pre-1998 structure because in 2009 the top 4 firms accounted for 86.74% of the prescriptions and HHI = 2,233.36. Note that there was no drop in the number of generic lorazepam prescriptions for which Medicaid reimbursed in 2006 as might have been expected with the movement of individuals dually eligible for Medicaid and Medicare Part D to Medicare Part D in January 2006. Because Medicare Part D does not provide coverage for benzodiazepines, Medicaid was left with the primary public burden for these drugs even after 2006.[23] It is unlikely, however, that by 2006 there was much utilization of benzodiazepines by elderly Medicaid beneficiaries. Benzodiazepines have a significant effect on cognitive impairment, balance, and somnolence, resulting in their placement on the Beers List, which is a list of medications that are generally considered to be inappropriate for use by elderly patients.[24,25]

Table 2 shows the top firms in the lorazepam market during the years surrounding the alleged conspiracy. Mylan had the highest Medicaid market share from 1997 to 2000, commanding more than 40% of the market in 1999. In 2001, Mylan dropped to second place, following Sandoz, but it still held a 24.76% market share in 2002. Whereas Actavis Elizabeth dropped in rank over the 6 years, Watson rose in the rankings, with 2 labeler codes among the top 7 in 2002. Royce Labs, Rugby Labs (both now subsidiaries of Watson Pharmaceuticals), and Goldline Labs (now a subsidiary of Teva Pharmaceuticals) essentially dropped out of the market after the 1990s.

Long-Term Medicaid Excess Payments Associated with the Alleged Conspiracy

Table 3 gives the estimated excess payments by Medicaid under 2 different counterfactual scenario assumptions regarding what the average Medicaid (pre-rebate) payment for a generic lorazepam claim would have been without the alleged conspiracy: (1) the average payment per claim in the 4 quarters prior to 1998 Q2 ($6.80) adjusted for the percentage change in average payment per claim for generic alprazolam (lorazepam's closest generic substitute) over the same time period and (2) the average payment per claim in the 4 quarters prior to 1998 Q2 ($6.80) adjusted for the rate of inflation (using the CPI for urban consumers, all goods). In 2009 dollars, estimated total excess Medicaid FFS payments over the full 12-year period are $624.9 million under the generic alprazolam counterfactual payment assumption. Under counterfactual scenario 2, the estimated total of excess Medicaid FFS payments over the full 12-year period is $657.4 million. If we were to assume an 11% manufacturer rebate on Medicaid spending for generic lorazepam over the 19-year period, the estimated excess payments are $556.1 million and $585.0 million under counterfactual

TABLE 3 Excess Medicaid Payments for Generic Lorazepam, 1998-2009

	Counterfactual Price Scenarios			
	Pre-1998 Generic Lorazepam Price + Adjustment Based on Alprazolam Price Change		Pre-1998 Generic Lorazepam Price + Adjustment Based on CPI for Urban Consumers, All Goods	
Year	Average Quarterly Counterfactual Price ($)[a]	Post-1997 Annual Excess Payments (2009$)[b]	Average Quarterly Counterfactual Price ($)[c]	Post-1997 Annual Excess Payments (2009$)[b]
1998	7.26	58,595,220	6.84	59,772,776
1999	8.16	85,569,975	6.97	90,212,046
2000	7.71	89,502,500	7.21	91,493,516
2001	9.77	77,144,827	7.41	88,068,972
2002	7.44	79,482,328	7.53	79,051,471
2003	8.76	64,925,731	7.70	70,262,051
2004	8.28	55,089,732	7.91	56,935,497
2005	8.32	47,003,530	8.17	47,718,330
2006	8.84	32,174,986	8.44	33,973,827
2007	10.38	22,012,671	8.68	27,873,844
2008	8.71	15,764,089	9.01	14,713,244
2009	8.89	-2,415,180	8.98	-2,717,548
12-year total Medicaid[d]		624,850,411		657,358,027

[a]For 1998 Q2, the counterfactual price was set at $6.80, the average per-claim payment for generic lorazepam across the previous 4 calendar quarters: 1997 Q2 ($6.72), 1997 Q3 ($6.79), 1997 Q4 ($6.65), and 1998 Q1 ($7.04). The counterfactual price for 1998 Q3 was computed as $6.80 times 1 plus the proportional change in the per-claim payment for generic alprazolam between 1998 Q2 and 1998 Q3. Each subsequent quarter's price was found similarly. The values shown in Table 3 are the averages of the quarterly counterfactual prices for the years 1998-2009 (average over 3 quarters in 1998 and over 4 quarters each year from 1999-2009).

[b]The estimate of annual post-1997 excess payments is the sum of 4 calendar quarters' post-1997 excess payments (except for 1998 when the sum is over 3 calendar quarters' excess payments). Quarterly post-1997 excess payments are estimated by multiplying the number of Medicaid-reimbursed generic lorazepam prescriptions during the quarter times the difference between the quarterly average payment for generic lorazepam and the quarterly assumed counterfactual price. Excess payment estimates were then inflated to 2009 dollars using the CPI for urban consumers, all goods. Note that values in Table 3 cannot be determined simply by multiplying number of prescription claims (Table 1) by the difference between actual lorazepam prices (Table 1) and the counterfactual prices (Table 3) because of the annual averages, rather than quarterly values, presented in the tables.

[c]For 1998 Q2, the counterfactual price was set at $6.80, the average per-claim payment for generic lorazepam across the previous 4 calendar quarters: 1997 Q2 through 1998 Q1. The counterfactual price for 1998 Q3 was computed as $6.80 times 1 plus the inflation rate from 1998 Q2 to 1998 Q3, found using the CPI for urban consumers, all goods. Each subsequent quarter's price was found similarly. The values shown in Table 3 are the averages of the quarterly counterfactual prices for the years 1998-2009 (average over 3 quarters in 1998 and over 4 quarters each year from 1999-2009).

[d]The 12-year total excess payments for Medicaid are found by summing the annual excess payments.

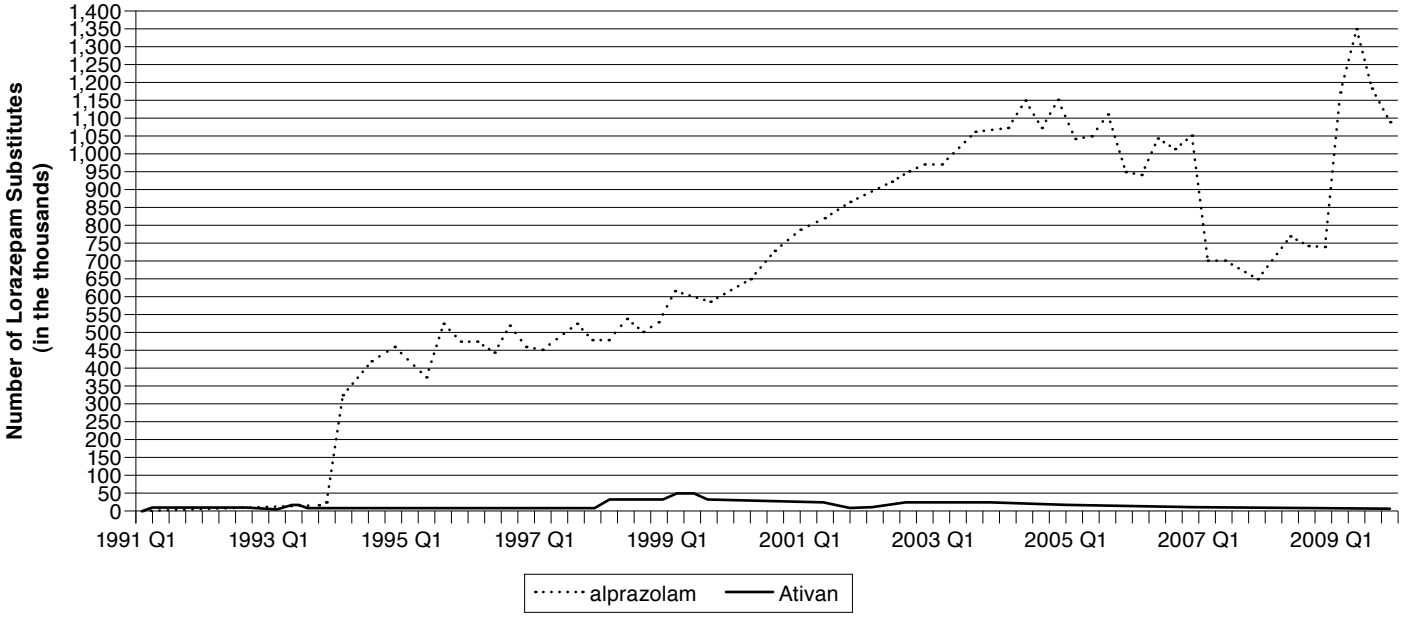
CPI = Consumer Price Index.

scenarios 1 and 2, respectively. These values are each 89% of the pre-rebate estimates.

For completeness, we also looked at the utilization and price trends for branded lorazepam and generic alprazolam, the 2 closest substitutes for generic lorazepam. Figures 1 and 2 show utilization and price trends, respectively. Whereas we might have expected the utilization of generic alprazolam to skyrocket following the steep rise in the price of generic lorazepam, that seems not to be the case (Figure 1). The steadily rising utilization trend for alprazolam remains undisturbed by changes in the generic lorazepam market. Interestingly, although the absolute number of claims for branded lorazepam remained tiny over the entire study period, we do observe a steep percentage rise in the utilization of branded lorazepam beginning in 1998 Q1. The number of prescriptions rose from 1,062 in 1997 Q4 to 26,122 in 1998 Q1 and to more than 40,000 in the first two quarters of 1999, representing approximately 5% of all lorazepam (brand plus generic) prescriptions for that 6-month period. Utilization remained in excess of 20,000 prescriptions per quarter until 2001 Q2. During 1999 Q1 and 1991 Q2, the average reimbursed amounts per prescription for branded lorazepam were $56.24 and $57.69, respectively, less than twice the $30 average price of lorazepam (without considering the potentially larger rebates for branded lorazepam), as state Medicaid programs adjusted their MACs.

The association of the alleged conspiracy with prices may be seen in Figure 2. Note that there were so few prescriptions of branded lorazepam (< 100 for some quarters) from 2007 Q1 through 2008 Q4, average price per prescription could not be reliably calculated, hence, there is a gap in the trend line between 2006 and 2009. Regardless, the branded lorazepam price trend seems unaffected by events in the generic lorazepam market in the late 1990s. The price of generic alprazolam declined from $38.16 in 1993 Q3 (the first quarter of generic entry in Medicaid following the patent expiration for branded alprazolam) to $6.98 in 1998 Q2. Payment per prescription then rose, following the alleged conspiracy in the generic lorazepam market, to $8.26 in 1998 Q4, then $9.18 in 1999 Q1, and

FIGURE 1 *Utilization of Closest Lorazepam Substitutes in Medicaid: 1991-2009*



$8.53 in 1999 Q2. Hence, the data suggest the possibility of a small impact on the price of generic alprazolam.

Discussion

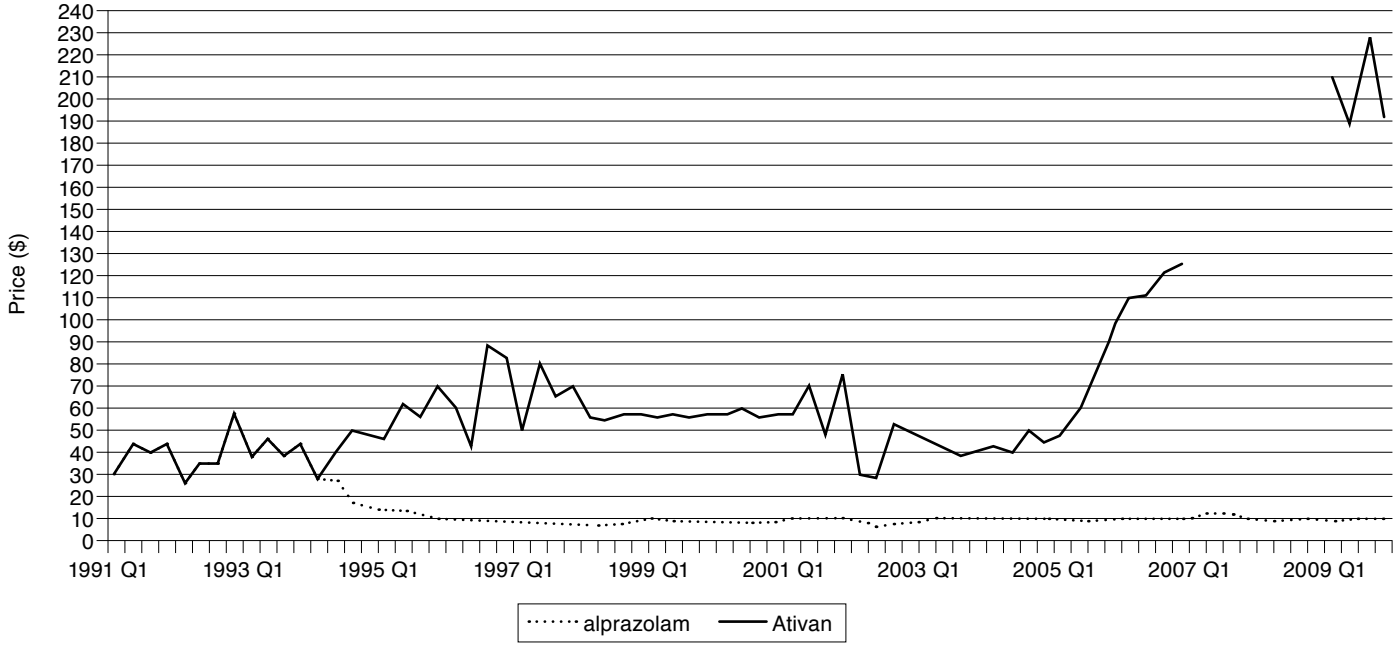
A long, rich literature has shown that, in general, across many different drug classes, as the number of generic entrants rises, the market price approaches the competitive price (or marginal cost).[26-29] With scores of generic manufacturers, from all over the world and of varying sizes, supplying many of the larger drug markets (e.g., fluoxetine, simvastatin, and risperidone), the expectation that pricing is competitive is a reasonable one.

With a small number of firms, however, competitive pricing should not be taken for granted. In the face of large potential monopoly profits, it is much more likely that implicit or explicit collusion will occur. With high enough seller concentration, firms are few enough to recognize their interdependence and, through such interdependence, "agree" on the profit-maximizing monopoly price.[18]

When it comes to the number of firms, how small is "small"? Searching for a critical concentration ratio has intrigued many scholars in industrial-organization economics over the years, although there seems to be no "one size fits all" that antitrust authorities can rely on for every market.[30-33] Moreover, the notion of a critical concentration ratio may be more realistic than assuming a smooth transition between monopoly and competitive pricing. In 1997, the year before the generic lorazepam price rise, CR_4 was 66.36. It jumped another 10 percentage points in 1998. At approximately $CR_4 = 70$ (the "critical concentration ratio"), the generic lorazepam oligopolists, through an alleged explicit collusive scheme plus alleged price-leadership behavior (other firms following Mylan's price increase), were able to increase price. Although consumers are no longer paying such high prices for generic lorazepam, the extremely high seller concentration that still existed in 2009 makes it more likely that another steep price rise could occur in the future than if the seller concentration had returned to its pre-1998 level.

Because of the nature of drug markets, if generic drug prices are high for any reason, most consumers cannot expect much relief in substitute markets. In the case of this class of psychotropic drugs without any direct-to-consumer advertising, patients are not very knowledgeable about alternatives. Meanwhile, the prescribing physicians are often unaware of the prices of available drugs.[34] Finally, without a body of solid comparative effectiveness research that can equate the efficacy and safety profiles of chemically distinct agents, payers (including Medicare, Medicaid, and private insurance companies) are reluctant to override a doctor's choice of medication. Although prior authorization schemes can be implemented, they are expensive to administer[35] and can inhibit access to medication.[6] In the case of the generic lorazepam market, comparative effectiveness studies of alprazolam versus lorazepam would have gone a long way to mitigate the burden of the alleged Mylan conspiracy. Payers would have felt comfortable enforcing a switch to the more reasonably priced generic alprazolam following the price jump in the generic lorazepam market.

FIGURE 2 Price-Per-Prescription of Closest Lorazepam Substitutes in Medicaid: 1991-2009



Empirical evidence strongly suggests substitution difficulty. Drug prices are not generally affected by either (a) the entry of new drugs in a therapeutic class or (b) the entry of a new class of drugs approved for the same indication.[8,9]

It is tempting to try to estimate the overall excess cost to U.S. payers. After all, pharmacies after the alleged price conspiracy were paying the same inflated prices for generic lorazepam regardless of ultimate payer. Although some uninsured individuals may have stopped purchasing the drug, it seems clear from Table 1, for the years in which we have utilization data for the United States, that national utilization of generic lorazepam rose over time, implying that at least most payers were covering the cost. Naïvely noticing that the ratio of total prescriptions for generic lorazepam to Medicaid-covered prescriptions ranged from 3.6-5.2 over the years, we would guess at an approximate $2.5 billion ($625 million × 4) total excess cost to U.S. payers.

Limitations

This study is limited primarily by the nature of Medicaid claims data. First, spending data are pre-rebate, and we do not have access to rebate information. The Medicaid Drug Rebate Program, established by the Omnibus Budget Reconciliation Act of 1990, requires a drug manufacturer to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services in order for states to receive federal funding for outpatient drugs dispensed to Medicaid patients.[36] Rebate percentages are based on average manufacturer prices (AMPs), the average price wholesalers pay manufacturers for drugs sold to retail pharmacies; the percentage is higher for innovator drugs than for noninnovator drugs. (For generic lorazepam, rebates can be assumed to have been 11% of AMP over the study period.[36]) In addition, a number of states have been collecting state-only supplemental rebates in conjunction with a PDL.[37] To the extent that we have been unable to account for generic lorazepam rebates, we have overstated the extent of excess Medicaid FFS payments. The extent of the overestimate is easily computed, however, as shown in the Results section, depending on one's assumption about Medicaid-captured rebates.

A second, fundamental limitation of this study is that it is not possible to know what Medicaid payment rates actually would have prevailed over the period 1998-2009 in the absence of the alleged conspiracy. Our estimates of excess Medicaid FFS payments rely on counterfactual scenarios projecting what Medicaid payments "would have been" under 2 different assumptions. The plausibility of our estimates of total excess Medicaid payments is entirely dependent on the plausibility of our counterfactual scenarios.

A third limitation of the study is that paid claims include not only drug ingredient cost but also fees associated with the claim. Moreover, although we have treated reimbursement per

claim as a reasonable proxy for price, prescriptions may vary in size, for example, a 2-week versus 30-day supply. To the extent that fees represent different percentages of the prescription cost over time or to the extent that the size distribution of prescriptions varies over time, our estimates may be biased.

Fourth, although we think that we have captured most of the outpatient prescriptions reimbursed for Medicaid beneficiaries, we realize that the database is not complete. The proportion of total Medicaid beneficiaries in managed care plans has risen significantly, from only 9.5% in 1991 to 40.1% in 1996[38] and 71.7% in 2009.[39] We did not determine the extent to which the national Medicaid FFS database that we used includes managed Medicaid pharmacy benefits that are carved out of managed care. Because the database includes only claims from Medicaid FFS, some of the trends observed in our results could be an artifact of a shrinking share of total Medicaid recipients in FFS plans.

Conclusions

Excess payments for generic lorazepam stemming from the alleged Mylan-supplier conspiracy in 1997 lasted for more than a decade. The $147 million (approximately $232 million in 2009 dollars) penalty was substantially less than our estimates of excess Medicaid payments over the period 1998-2009. Both competition policy makers and health policy makers need to be aware that generic markets are not necessarily competitive markets offering consumers and payers marginal-cost prices.

Authors

BOYANG BIAN, BPharm, MS, is a Doctoral Candidate; JEFF J. GUO, PhD, is Professor of Pharmacoeconomics & Pharmacoepidemiology; and JILL MARTIN BOONE, PharmD, is Professor of Pharmacy Practice, James L. Winkle College of Pharmacy, University of Cincinnati Academic Health Center, Cincinnati, Ohio. ELIZABETH GOREVSKI, PharmD, MS, is Clinical Research Pharmacist, Cincinnati Veterans Administration Medical Center, Cincinnati, Ohio; CHRISTINA M.L. KELTON, PhD, is Professor of Economics, Carl H. Lindner College of Business, and Adjunct Professor of Clinical Pharmacy, James L. Winkle College of Pharmacy, University of Cincinnati, Cincinnati, Ohio.

AUTHOR CORRESPONDENCE: Christina M.L. Kelton, PhD, Professor of Economics and Adjunct Professor of Clinical Pharmacy, University of Cincinnati, Carl H. Lindner College of Business, 414 Lindner Hall, 2925 Campus Green Dr., P.O. Box 210195, Cincinnati, Ohio, 45221-0195. Tel: 513.556.2983; E-mail: chris.kelton@uc.edu.

DISCLOSURES

This research had no external funding, and the authors report no conflicts of interest. Study concept and design were contributed equally by Bian, Gorevski, Kelton, and Boone. Bian had primary responsibility for data collection, with assistance from Guo. Data interpretation was primarily the work of Bian and Kelton, with assistance from Gorevski. The manuscript was written primarily by Kelton, with assistance from Gorevski and Bian and was revised by all authors but Boone.

ACKNOWLEDGMENTS

An earlier version of this study was presented as an unpublished poster at the Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research in Washington, D.C., June 2012. We would like to thank 4 anonymous referees for this journal, who significantly contributed both to the substance and the readability of the final draft of this article.

REFERENCES

1. Grabowski HG, Vernon JM. Effective patent life in pharmaceuticals. *Intl J Tech Mgmt*. 2000;19(1/2):98-120.

2. Cook A. How increased competition from generic drugs has affected prices and returns in the pharmaceutical industry. Congressional Budget Office Report. July 1998. Available at: http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/6xx/doc655/pharm.pdf. Accessed August 25, 2012.

3. Coster JM. Trends in generic drug reimbursement in Medicaid and Medicare. *US Pharm*. 2010;35(6; Generic Drug Review suppl):14-19. Available at: http://www.uspharmacist.com/content/s/127/c/21147/. Accessed August 25, 2012.

4. Gorevski E, Bian B, Kelton CM, Martin Boone JE, Guo JJ. Utilization, spending, and price trends for benzodiazepines in the US Medicaid program: 1991-2009. *Ann Pharmacother*. 2012;46(4):503-12.

5. U.S. Government Accountability Office. Drug pricing: research on savings from generic drug use. Letter to The Honorable Orrin G. Hatch. January 31, 2012. Available at: http://www.gao.gov/assets/590/588064.pdf. Accessed August 25, 2012.

6. Crowley JS, Ashner D, Elam L. Medicaid outpatient prescription drug benefits: findings from a national survey, 2003. Kaiser Commission on Medicaid and the Uninsured. December 2003. Available at: http://www.kff.org/medicaid/upload/Medicaid-Outpatient-Prescription-Drug-Benefits-Findings-from-a-National-Survey-2003.pdf. Accessed August 25, 2012.

7. Ferrand Y, Kelton CML, Guo JJ, Levy MS, Yu Y. Using time-series intervention analysis to understand U.S. Medicaid expenditures on antidepressant agents. *Res Social Adm Pharm*. 2011;7(1):64-80.

8. Guo JJ, Kelton CML. Competition between brand-name and generic drugs. In: Fulda TR, Wertheimer A, eds. *Handbook of Pharmaceutical Public Policy*. New York, NY: Haworth Press; 2007:395-416.

9. Guo JJ, Kelton CML, Pasquale MK, et al. Price and market-share competition of anti-ulcer gastric medications in the Ohio Medicaid market. *Intl J Pharm Med*. 2004;18(5):271-82.

10. U.S. Food and Drug Administration. Drugs@FDA. Ativan. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed August 25, 2012.

11. Drugs.com. Lorazepam tablets, USP CIV. Available at: http://www.drugs.com/pro/lorazepam.html. Accessed August 25, 2012.

12. U.S. Pharmacopeial Convention. *United States Pharmacopeia Dispensing Information: USP DI, Vol. 3*. Rockville, MD: USP; 1995.

13. Federal Trade Commission. FTC v. Mylan Laboratories, Inc., Cambrex Corporation, Profarmaco S.R.I., and Gyma Laboratories of America, Inc.: Amended complaint. February 8, 1999. Available at: http://www.ftc.gov/os/1999/02/mylanamencmp.htm. Accessed August 25, 2012.

14. Park DK, Wolfram R. The FTC's use of disgorgement in antitrust actions threatens to undermine the efficient enforcement of the federal antitrust law. *The Antitrust Source*. 2002;September:1-14. Available at: http://www.americanbar.org/content/dam/aba/publishing/antitrust_source/disgorgement.authcheckdam.pdf. Accessed August 25, 2012.

15. Centers for Medicare & Medicaid Services. Medicaid drug rebate program data: state utilization data. Updated August 14, 2012. Available at: http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Medicaid-Drug-Rebate-Program-Data.html. Accessed August 25, 2012.

16. The Lewin Group. Medicaid managed care cost savings—a synthesis of fourteen studies. Prepared for America's Health Insurance Plans. July 2004. Available at: http://www.ahip.org/Medicaid-Cost-Savings/. Accessed August 25, 2012.

17. Centers for Medicare & Medicaid Services. Medicaid state drug utilization data: web file structure and definitions, August 2009. Available at: http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Downloads/StateUtilizationDataSpecifications.pdf. Accessed August 25, 2012.

18. Samuelson WF, Marks SG. *Managerial Economics*, 7th ed. Hoboken, NJ: Wiley; 2012.

19. U.S. Department of Justice and the Federal Trade Commission. 1997 merger guidelines. Available at: http://www.justice.gov/atr/hmerger/11251.htm. Accessed August 25, 2012.

20. U.S. Department of Justice and the Federal Trade Commission. Horizontal merger guidelines. August 19, 2010. Available at: http://www.justice.gov/atr/public/guidelines/hmg-2010.html. Accessed August 25, 2012.

21. SDI Health LLC. 2010 top 200 generic drugs by total prescriptions: various years. Available at: http://drugtopics.modernmedicine.com/Pharmacy+Facts+&+Figures. Accessed August 25, 2012.

22. Centers for Medicare & Medicaid Services. Medicaid covered outpatient prescription drug reimbursement information by state: quarter ending March 2012. Available at: http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Downloads/StateReimbChart2Q2012.pdf. Accessed August 25, 2012.

23. Briesacher BA, Soumerai SB, Field TS, Fouayzi H, Gurwitz JH. Nursing home residents and enrollment in Medicare Part D. *J Am Geriatr Soc*. 2009;57(10):1902-07.

24. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers Criteria for potentially inappropriate medication use in older adults: results of a U.S. consensus panel of experts. *Arch Intern Med*. 2003;163(22):2716-24.

25. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ*. 2005;331(7526):1169-73.

26. Dusing ML, Guo JJ, Kelton CML, Pasquale MK. Competition and price discounts for a hospital buyer in the anti-infective pharmaceutical market. *J Pharm Fin Econ Pol*. 2005;14(2):59-85.

27. Frank RG, Salkever DS. Generic entry and the pricing of pharmaceuticals. *J Econ Mgmt Strategy*. 1997;6(1):75-90.

28. Reiffen D, Ward MR, Generic drug industry dynamics. *Rev Econ Stat*. 2005;87(1):37-49.

29. Caves RE, Whinston MD, Hurwitz MA. Patent expiration, entry, and competition in the U.S. pharmaceutical industry. *Brookings Papers: Microeconomics*. 1991;1991:1-66.

30. Rhoades SA, Cleaver JM. The nature of the concentration—price cost margin relationship for 352 manufacturing industries: 1967. *S Econ J*. 1973;40(1):90-102.

31. White LJ. Searching for the critical concentration ratio: an application of the "switching of regimes" technique. In: Goldfeld S, Quandt R, eds., *Studies in Nonlinear Estimation*. Cambridge, MA: Ballinger; 1976:61-76.

32. Geithman FE, Marvel HP, Weiss LW. Concentration, price, and critical concentration ratios. *Rev Econ Stat*. 1981;63(3):346-53.

33. Azzam AM, Rosenbaum DI, Weliwita A. Is there more than one critical concentration ratio? An empirical test for the Portland cement industry. *App Econ*. 1996;28:673-78.

34. Korn LM, Reichert S, Simon T, Halm EA. Improving physicians' knowledge of the costs of common medications and willingness to consider costs when prescribing. *J Gen Intern Med*. 2003;18(1):31-37.

35. Reissman D. Prior authorization: what does it really cost? *Health Care News*. December 1, 2001. Available at: http://www.heartland.org/healthpolicy-news.org/article/421/Prior_Authorization_What_Does_it_Really_Cost.html. Accessed August 25, 2012.

36. National Health Policy Forum. The Medicaid drug rebate program. April 13, 2009. Available at: http://www.nhpf.org/library/the-basics/Basics_MedicaidDrugRebate_04-13-09.pdf. Accessed August 25, 2012.

37. Bergman D, Kaye N, Hoadley J, Crowley J. State experience in creating effective P&T committees. National Academy for State Health Policy. March 2006. Available at: http://www.nashp.org/sites/default/files/medicaid_pandt.pdf. Accessed August 25, 2012.

38. Kaiser Commission on Medicaid and the Uninsured. Medicaid and managed care. December 2001. Available at: http://www.kff.org/Medicaid/upload/Medicaid-and-Managed-Care-Fact-Sheet.pdf. Accessed August 25, 2012.

39. Gifford K, Smith VK, Snipes D, Paradise J. A profile of Medicaid managed care programs in 2010: findings from a 50-state survey. Kaiser Commission on Medicaid and the Uninsured. September 2011. Available at: http://www.kff.org/medicaid/upload/8220-ES.pdf. Accessed August 25, 2012.

RESEARCH

Randomized Controlled Trial of Clinical Pharmacy Management of Patients with Type 2 Diabetes in an Outpatient Diabetes Clinic in Jordan

Anan Sadeq Jarab, PhD; Salam Ghazi Alqudah, BSc;
Tareq Lewis Mukattash, PhD; Ghassan Shattat, PhD; and Tariq Al-Qirim, PhD

ABSTRACT

BACKGROUND: Glycemic goals (hemoglobin A1c <7%) are often not achieved in patients with type 2 diabetes despite the availability of many effective treatments and the documented benefits of glycemic control in the reduction of long-term microvascular and macrovascular complications. Several studies have established the important positive effects of pharmacist-led management on achieving glycemic control and other clinical outcomes in patients with diabetes. Diabetes prevalence and mortality are increasing rapidly in Jordan. Nevertheless, clinical pharmacists in Jordan do not typically provide pharmaceutical care; instead, the principal responsibilities of pharmacists in Jordan are dispensing and marketing of medical products to physicians.

OBJECTIVE: To assess the primary clinical outcome of glycemic control (A1c) and secondary outcomes, including blood pressure, lipid values, self-reported medication adherence, and self-care activities for patients with type 2 diabetes in an outpatient diabetes clinic randomly assigned to either usual care or a pharmacist-led pharmaceutical care intervention program.

METHODS: Patients with type 2 diabetes attending an outpatient diabetes clinic of a large teaching hospital were recruited over a 4-month period from January through April 2011 and randomly assigned to intervention and usual care groups using the Minim software technique. The intervention group at baseline received face-to-face objective-directed education from a clinical pharmacist about type 2 diabetes, prescription medications, and necessary lifestyle changes, followed by 8 weekly telephone follow-up calls to discuss and review the prescribed treatment plan and to resolve any patient concerns. The primary outcome measure was glycemic control (A1c), and secondary measures included systolic and diastolic blood pressure, complete lipid profile (i.e., total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], serum triglycerides), and self-reported medication adherence (4-item Morisky Scale) and self-care activities (Summary of Diabetes Self-Care Activities questionnaire). Data were collected at baseline and at 6 months follow-up. Changes from baseline to follow-up were calculated for biomarker values, and between-group differences in the change amounts were tested using the *t* test for independent samples. A *P* value of <0.05 was considered statistically significant.

RESULTS: A total of 77 of 85 patients (90.6%) randomly assigned to the intervention group and 79 of 86 patients (91.9%) assigned to usual care had baseline and 6-month follow-up values. Compared with baseline values, patients in the intervention group had a mean reduction of 0.8% in A1c versus a mean increase of 0.1% from baseline in the usual care group ($P=0.019$). The intervention group compared with the usual care group had small but statistically significant improvements in the secondary measures of fasting blood glucose, systolic and diastolic blood pressure, total cholesterol, LDL-C, serum triglycerides, self-reported medication adherence, and self-care activities. Between-group differences in changes in the secondary measures of HDL-C and body mass index were not significant.

CONCLUSIONS: Patients with type 2 diabetes who received pharmacist-led pharmaceutical care in an outpatient diabetes clinic experienced reduction in A1c at 6 months compared with essentially no change in the usual care group. Six of 8 secondary biomarkers were improved in the intervention group compared with usual care.

J Manag Care Pharm. 2012;18(7):516-26

What is already known about this subject

- Improving glycemic control is the key to reducing microvascular and macrovascular complications associated with type 2 diabetes mellitus. Epidemiological analysis of the United Kingdom Prospective Diabetes Study (UKPDS) showed that for each 1% reduction in hemoglobin A1C, there was a corresponding 21% reduction in any endpoint related to diabetes, with a 14% reduction for myocardial infarction, 12% reduction in stroke, and a 37% reduction for microvascular complications (Stratton et al., 2000).
- Randomized controlled trials (RCTs) of pharmacist interventions in disease management of type 2 diabetes have shown significant reductions in A1c compared with control group patients in usual care. Al Mazroui et al. (2009) found that 117 patients who received clinical pharmacist interventions had a significant reduction in mean A1c values from 8.5% to 6.9% compared with 117 control group patients who had approximately constant mean A1c values at baseline and 12-month assessments (8.4% and 8.3%, respectively). An RCT by Choe et al. (2005) reported a reduction in mean A1c values from 10.1% to 8.0% in 41 intervention patients who received clinical pharmacy services compared with 39 control group patients who showed a reduction in A1c values from 10.2% to 9.3% ($P=0.03$).
- Self-care activities that help to control blood glucose levels and avoid diabetes-related complications are vital in diabetes treatment. Doucette et al. (2009) indicated in an RCT that a pharmacist-provided diabetes care service led to significant improvement in dietary self-management and other self-care activities in patients with diabetes.

What this study adds

- In this RCT, a comprehensive clinical pharmacy service consisting of patient education on type 2 diabetes, prescription therapy, and medication adherence over a 6-month intervention period was significantly associated with improved glycemic control and other cardiovascular risk factors, including systolic and diastolic blood pressure (BP) and lipid values. After 6 months follow-up, mean [95% CI] reductions were significantly greater in pharmaceutical care patients (n = 77) than usual care patients (n = 79) for A1c (-0.8% [-1.6 to 0.1] vs. +0.1 [-0.4 to 0.7]); fasting blood glucose (-2.3 millimoles per litre [mmol/L] [-5.7 to 1.1] vs. +0.9 [-0.8 to 2.8]); systolic BP (-5.8 millimeters of mercury [mm Hg] [-8.2 to -3.2] vs. +1.1 [0.1 to 2.4]); diastolic BP (-7.1 mm Hg [-9.8 to -4.2] vs. +1.8 [-1.1 to 4.8]); total cholesterol (-0.7 mmol/L [-1.7 to 0.3] vs. +0.1 [-3.1 to 3.8]); LDL-C (-0.6 mmol/L [-1.7 to 0.6] vs. 0.0 [-0.4 to 0.4]); and serum triglycerides (-0.5 mmol/L [-2.8 to 2.1] vs. +0.2 [-0.7 to 1.1]). This study also indicated statistically significant differences in favor of the intervention group compared with the control group in the proportion of patients who achieved therapeutic goals for A1c (23.4% vs. 15.2%, $P = 0.031$); BP (80.5% vs. 46.8%, $P = 0.012$); and LDL-C (45.5% vs. 30.4%, $P = 0.018$) over the 6-month study period.
- Compared with the usual care group, intervention patients who received the clinical pharmacy service showed significant improvement in self-reported medication adherence and lifestyle changes that represent the cornerstone in the management of type 2 diabetes.
- The current study is the first RCT to evaluate the effects of clinical pharmacy service on biomarker values and health behavior in patients with type 2 diabetes in Jordan. Improved biomarkers and patient-reported outcomes in the current study provide evidence about the importance of clinical pharmacist involvement in the care for patients with diabetes in Jordan.

Type 2 diabetes results from a progressive insulin secretory defect with reduced sensitivity to the effects of existing insulin.[1] The disease is characterized by fasting and post-prandial hyperglycemia and relative insulin insufficiency. If left untreated, poor control of blood glucose may cause long-term microvascular and macrovascular complications, such as nephropathy, neuropathy, retinopathy, and cardiovascular disease (CVD).[2] Type 2 diabetes is an epidemic disease, and its prevalence is growing at an alarming rate in both developed and developing countries.[3] The prevalence of type 2 diabetes worldwide has increased 5-fold during the last 15 years.[4] It has been estimated that 200 million people had type 2 diabetes in 2010, and the number is expected to reach 300 million by the year 2025.[4]

The prevalence of diabetes in Jordan is among the highest in the world, making it a particularly alarming health problem there.[5] Among Jordanian adults, diabetes prevalence increased from 6.3% in 2002 to 7.4% in 2004.[6] A cross-sectional study of a random sample of 1,121 Jordanians aged 25 years or older in 2008 revealed an "age-standardized prevalence" of 17.1%, a 31.5% increase in the prevalence of diabetes compared with a similar survey conducted in 1994.[7] Furthermore, World Health Organization (WHO) data indicates that the proportion of deaths attributable to diabetes in Jordan increased from 1% in 2002[8] to 7% in 2010.[9] Beside diabetes prevalence, the lack of knowledge of diabetes and of its management in the general population is rapidly becoming one of the most challenging health problems worldwide, particularly in developing countries such as Jordan.[7]

Management of type 2 diabetes is complex and requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications.[1,10] Several observational studies have shown that intensive glycemic control leads to improved cardiovascular and microvascular outcomes.[11-13] Results from randomized controlled trials (RCTs) have demonstrated that tight glycemic control—hemoglobin A1c less than 7%—correlates with a reduction in the risk of microvascular complications in patients with type 2 diabetes.[14,15] The evidence that tight glycemic control leads to significant reduction in CVD outcomes is controversial. However, long-term follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) suggests that treatment to an A1c target of less than 7% soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular diseases.[11] These findings led the American Diabetes Association (ADA) to recommend an A1c level of less than 7% as a goal of optimal blood glucose control for patients with diabetes.[16] However, these glycemic goals are often not achieved despite the availability of many effective treatments and the documented benefits of blood glucose control.[17,18]

Clinical pharmacists can play a vital role in improving diabetes management by providing pharmaceutical care programs and prudent pharmacological therapy,[19] with an emphasis on the importance of adherence to treatment recommendations,[20] taking into account the importance of patients' participation in designing, implementing, and monitoring therapeutic plans to produce optimal therapeutic outomes.[20,21]

Several RCTs have reported that clinical pharmacist-led management programs improved glycemic control and various other clinical outcomes in patients with diabetes.[22-29] For example, Scott et al. (2006) reported that patients with type 2 diabetes who received pharmacist-managed diabetes care (n = 76) demonstrated improved glycosylated A1c values, systolic blood pressure, and low-density lipoprotein cholesterol (LDL-C) levels and met treatment goals more often than patients receiving standard care (n = 73).[27]

Study Objective

The objective of the present study was to evaluate the impact of a clinical pharmacist-led pharmaceutical care program on different clinical outcomes and self-management behavior in outpatients with type 2 diabetes in Jordan. It was important to study pharmaceutical care in Jordan because of the increasing prevalence and mortality of diabetes and the extremely limited application of effective clinical pharmacy services for patients with diabetes in Jordan.

Methods

Study Design, Setting, and Subjects

The effectiveness of the pharmaceutical care intervention was assessed in an RCT with a 6-month follow-up of patients with type 2 diabetes who visited an outpatient diabetes clinic at the 762-bed Royal Medical Services (RMS) Hospital, one of the largest hospitals in Jordan. The diabetes clinic at the RMS Hospital provides usual care services to more than 100 patients daily with regular follow-up clinic visits every 3 or 6 months, depending on the glycemic control for each patient. Patients were included in the study if they were aged 18 years or older, treated at RMS Hospital and diagnosed with type 2 diabetes at least 1 year previously, took at least 1 prescribed medication for diabetes, and had an A1c level exceeding 7.5%. Patients were excluded from the study if they were diagnosed with convulsive disorder, diabetic proliferative retinopathy, or diabetic neuropathy as reported in their medical files.

Patient Recruitment and Randomization

During an outpatient diabetes clinic visit, those patients who met the inclusion criteria and had their A1c, blood pressure, lipid measures (total cholesterol, LDL-C, HDL-C, and triglycerides), and other laboratory tests measured were informed verbally about the study by the research pharmacist (Alqudah) and were provided with an information sheet. The patients were asked to sign a consent form if they were willing to participate in the study. Study participants were randomly assigned to intervention and control groups via a minimization technique using Minim software (available for free download).[30] The patients were recruited over a period of 4 months from January through April 2011, and the last follow-up was performed on October 27, 2011. The study received approval from the Institutional Review Board, King Hussein Hospital, Royal Medical Services, Jordan.

Description of Pharmacist Intervention Versus Usual Care

Following randomization and the baseline assessment, the clinical pharmacist ensured that intervention patients were receiving evidence-based antidiabetic therapy and adjunct therapy, including treatment for dyslipidemia and hypertension. Clinical pharmacist recommendations, such as simplification of dosage regimens or more intensive management of blood glucose and blood pressure, were discussed with the physician when necessary.

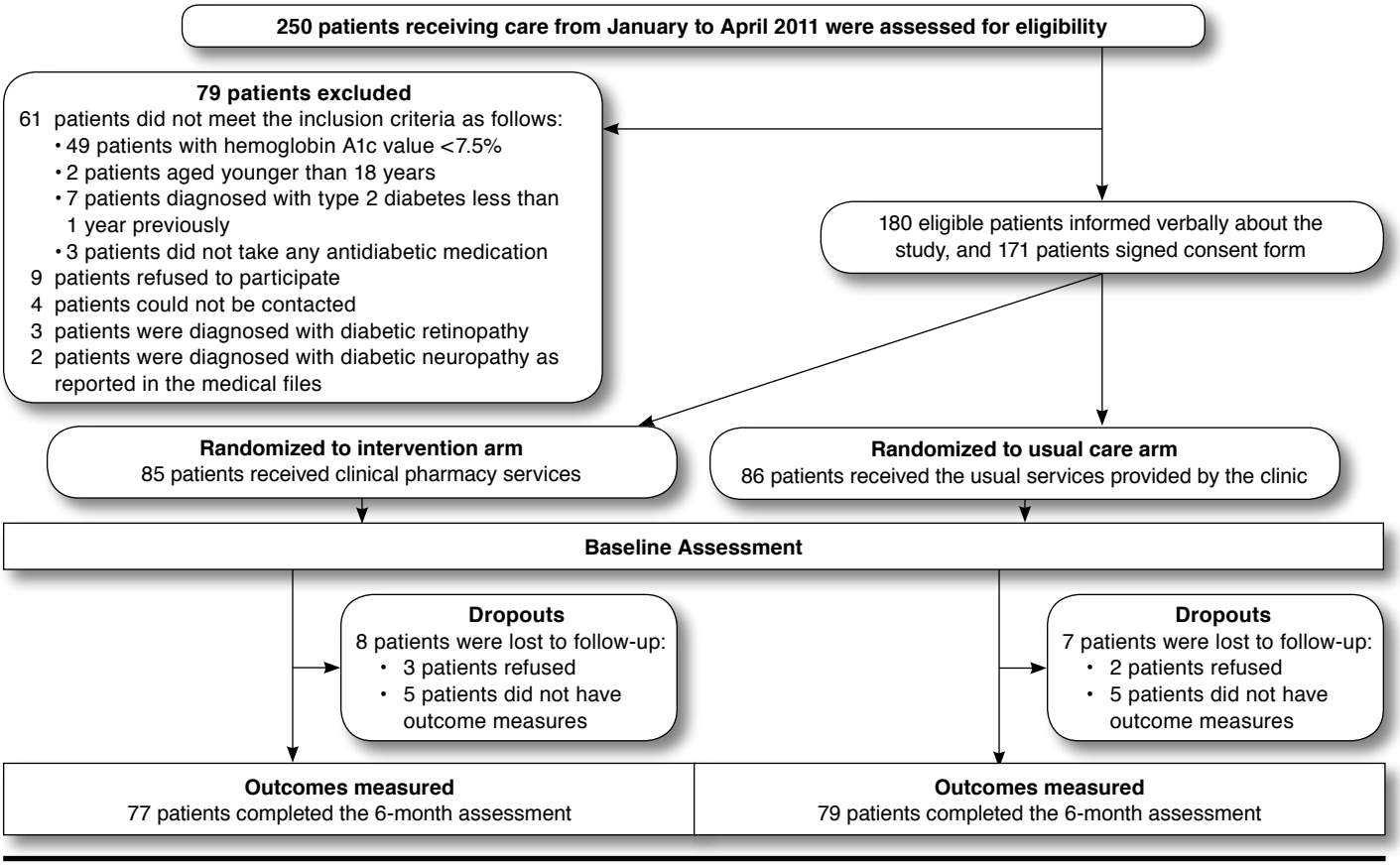
After the patient meeting with the physician, the clinical pharmacist provided, in a separate room at the outpatient clinic, a structured patient education and discussion about type 2 diabetes, risks for and types of complications from diabetes, prescribed drug therapy, proper dosage, possible side effects, and the importance of medication adherence. The clinical pharmacist also emphasized lifestyle management as follows: patients were encouraged to (a) change unhealthy dietary habits that adversely influence blood glucose, blood pressure, and lipid levels; (b) perform regular physical activity that fits with their daily schedule; and (c) monitor and record their blood glucose levels. Using a motivational interviewing technique, advice was provided to patients with a positive smoking history, and patients were referred to a special smoking cessation program run within the hospital when necessary. Diabetes-specific biomarker targets (e.g., A1c < 7%, blood pressure < 130/80 millimeters of mercury [mm Hg], and LDL < 2.6 millimoles per liter [mmol/L],[31] were specified for each intervention patient. A special booklet on diabetes medications and necessary lifestyle changes (e.g., physical activity and meal planning) was prepared to assist in the educational session, and patients were given a copy to take home. Finally, 8 weekly telephone calls were made by the clinical pharmacist to each intervention patient to discuss and review the prescribed therapy, to emphasize the importance of adherence to treatment plan, and to answer patient questions or address patient concerns. The average length of each call was 20 minutes.

Patients in the usual care group did not receive clinical pharmacist intervention or education on disease, medications, or necessary self-care activities and did not receive the 8 weekly telephone follow-up calls from the clinical pharmacist. These patients did not usually receive telephonic or mailed reminders for their upcoming appointments. Patients in the usual care group did, however, receive the usual care provided by the medical and nursing staff, which included patient assessment, a 3- or 6-month review at which blood glucose and blood pressure were measured, advice on self-monitoring of blood glucose (SMBG), and nutrition counseling.

Study Instruments

Self-Reported Medication Adherence (Morisky Scale). This simple, validated 4-question survey assessed the likelihood that patients take their medications as prescribed.[32] The questions were as follows: Do you forget to take your medications? Are you careless about time of taking your medications? Do you stop taking your medications when you feel better? Do you stop taking your medications when you feel worse? To score the questionnaire, each "yes" response is given a score of 1, and each "no" response is given a score of 0 (range 0 to 4). According to the Morisky classification, adherence is divided

FIGURE 1 Study Design Flowchart



into 3 groups: high for those scoring 0, medium for those scoring 1 or 2, and low for those scoring 3 or 4, when scoring one point for each "yes" answer. For the purpose of the present analysis, the patients were divided into 2 groups: those scoring 0 were considered adherent, and those scoring 1-4 were deemed nonadherent.

Summary of Diabetes Self-Care Activities (SDSCA) Questionnaire. The SDSCA is a comprehensive, well-validated, self-report measure of self-care behaviors in patients with diabetes.[33] This instrument is multidimensional, and each of its domains was assessed and scored separately. The instrument asks patients to recall their self-care behaviors during the previous 7 days for 5 domains: diet (4 questions, e.g., How many of the last 7 days have you followed a healthful eating plan?); exercise (2 questions, e.g., On how many of the last 7 days did you participate in at least 30 minutes of physical activity?); SMBG (2 questions, e.g., On how many of the last 7 days did you test your blood sugar the number of times recommended by your health care provider?); foot care (2 questions, e.g., On how many of the last 7 days did you check your feet?); and smoking (1 question, Have you smoked a cigarette, even 1 puff, during the last 7 days?).

The English versions of the Morisky Scale for medication adherence[32] and the SDSCA[33] questionnaire for self-care activities used in the present study were translated into Arabic as follows: a forward translation of the original questionnaire from English into Arabic was performed by 2 qualified independent, native linguistic expert translators. A backward translation from Arabic into English was carried out by 2 different translators. Finally, both translations were compared and found to match the original English copy of the questionnaire. Furthermore, a panel of 4 experts (2 clinical pharmacists and 2 diabetes medicine specialists) examined the research instrument for face and content validity. Pilot work was performed, and questions were adjusted as appropriate before moving to the main study.

Sample Size

The primary outcome measure was a reduction in A1c (intervention vs. control) at the end of the 6-month study period.

A sample size calculation, based on published data on the variability (standard deviation [SD] = 2.2%) of A1c in patients with type 2 diabetes,[34] indicated that to detect an absolute difference of more than 1% in A1c, with $\alpha = 0.05$ and a power of 90%, a sample size of 104 patients in each of the control and intervention groups was required.

Baseline Assessments

After randomization, baseline data for each patient were collected by the researcher pharmacist using a custom-designed questionnaire, medical charts, and hospital computers. The collected data included demographic measures, disease characteristics, prescribed and nonprescribed medications, and medication regimen details. The patients also completed the Morisky Scale[32] and the SDSCA questionnaire.[33]

Follow-Up Assessments

Except for demographic data, baseline data collection measures, including all laboratory and questionnaire data, were repeated by the research pharmacist (Alqudah) with the assistance of Jarab during scheduled diabetes clinic visits 6 months after the initial visit for each patient (e.g., a patient recruited in April 2011 was followed up in October 2011). The pharmacist (Alqudah) called each patient in the intervention group 1 week prior to each upcoming appointment to remind and confirm the scheduled visit. The primary outcome measure was A1c. All other data collected, including systolic and diastolic blood pressure, serum lipid values (total cholesterol, LDL-C, HDL-C, and serum triglycerides), body mass index (BMI), medication adherence, and levels of self-care activities, formed secondary outcome measures.

Data Analysis

Data collected at baseline and at the 6-month assessments were coded and entered into SPSS software, version 17 (IBM SPSS, Armonk, NY) for statistical analysis. Data were examined using Pearson chi-square analysis for categorical variables. For continuous variables, normality of data was tested first using the Kolmogorov-Smirnov and the Shapiro-Wilk statistical tests. Significance in those tests indicated that the continuous variable was not normally distributed. The Mann-Whitney *U* test was performed for the non-normally distributed variables, which were represented as median values. The *t* test for independent samples was performed for the normally distributed variables, which were represented as mean values. A *P* value of < 0.05 was considered statistically significant.

Results

A total of 171 type 2 diabetes patients (85 intervention; 86 usual care) attending an outpatient diabetes clinic were recruited into the study. During the study period, 8 patients from the intervention group and 7 patients from the usual care group dropped out from the study (Figure 1). Therefore, a total of 156 patients (77 intervention; 79 usual care) completed the 6-month study period.

TABLE 1 Baseline Characteristics of the Study Participants

Characteristics	Intervention (n = 85)	Usual Care n = (86)	*P* Value
Age in years, mean [SD]	63.4 [10.1]	65.3 [9.2]	0.215[a]
Female % (n)	42.4 (36)	44.2 (38)	0.832[b]
Duration of diabetes (years), mean [SD]	9.7 [7.4]	10.1 [7.7]	0.717[a]
Education % (n)			0.627[b]
University	24.7 (21)	26.7 (23)	
Secondary/high school	75.3 (64)	73.3 (63)	
Marital status % (n)			0.481[b]
Married	78.8 (67)	74.4 (64)	
Single, divorced, or separated	21.2 (18)	25.6 (22)	
Monthly income % (n)			0.092[b]
Less than 500 JD	69.4 (59)	60.5 (52)	
500-1,000 JD	21.2 (18)	22.1 (19)	
More than 1,000 JD	9.4 (8)	17.4 (15)	

[a]P value from t test for independent samples.
[b]P value from Pearson chi-square test.
JD = Jordanian dinar (approximately $1.41 U.S.); SD = standard deviation.

Patients' Characteristics at Baseline

The age, gender, duration of diabetes, marital status, educational level, and monthly income attained by the 2 groups are represented in Table 1. Statistical analyses indicated no significant differences between the 2 groups on these measures.

Biomedical Outcomes

A1c (Primary Outcome Measure). At the baseline assessment, the A1c values were similar for the intervention and usual care groups. Intervention patients who received clinical pharmacy services showed a mean reduction in A1c of 0.8% over 6 months, while the usual care group had a mean increase of 0.1% in A1c compared with baseline ($P = 0.019$; Table 2). The proportion of patients who achieved the ADA recommendation of A1c less than 7%[1] was significantly higher in the intervention group (23.4%) compared with the usual care group (15.2%) at the 6-month assessment ($P = 0.031$). Compared with baseline values, the intervention patients showed a mean reduction of 2.3 mmol/L, while usual care patients had a mean increase of 0.9 mmol/L in fasting blood glucose (FBG) at the 6-month assessment ($P = 0.014$; Table 2).

Systolic and Diastolic Blood Pressure. Statistically significant differences in mean reduction of both systolic ($P = 0.035$) and diastolic ($P = 0.026$) blood pressure were found between the 2 groups at the end of the study (Table 2). The proportion of patients who achieved target systolic and diastolic blood

TABLE 2 Key Biomarker Values at Baseline and 6 Months for Intervention Versus Usual Care

Outcome	Intervention (n=77)		Usual Care (n=79)		*P* Value (Baseline)[c]	*P* Value (Change)[d]
	Baseline[a]	Change at 6 Months[b]	Baseline[a]	Change at 6 Months[b]		
% A1c	8.5 (6.9 to 10.3)	–0.8 (–1.6 to 0.1)	8.4 (6.6 to 10.2)	+0.1 (–0.4 to 0.7)	0.838	0.019
FBG (mmol/L)	12.5 (9.6 to 14.7)	–2.3 (–5.7 to 1.1)	11.7 (6.5 to 16.1)	+0.9 (–0.8 to 2.8)	0.324	0.014
Systolic BP (mm Hg)	132 (123 to 144)	–5.8 (–8.2 to –3.2)	134 (125 to 144)	+1.1 (0.1 to 2.4)	0.611	0.035
Diastolic BP (mm Hg)	85 (74 to 96)	–7.1 (–9.8 to –4.2)	85 (81 to 89)	+1.8 (–1.1 to 4.8)	0.962	0.026
Serum cholesterol (mmol/L)	4.7 (3.4 to 5.4)	–0.7 (–1.7 to 0.3)	4.7 (3.9 to 5.7)	+0.1 (–3.1 to 3.8)	0.748	0.040
LDL-C (mmol/L)	2.1 (0.9 to 3.0)	–0.6 (–1.7 to 0.6)	2.2 (1.0 to 3.2)	0.0 (–0.4 to 0.4)	0.567	0.031
HDL-C (mmol/L)	1.3 (0.5 to 2.0)	–0.15 (–2.0 to 1.8)	1.3 (0.9 to 1.6)	0.0 (–0.7 to 0.9)	0.893	0.728
Serum triglycerides (mmol/L)	1.9 (0.4 to 3.1)	–0.5 (–2.8 to 2.1)	2.0 (0.8 to 3.3)	+0.2 (–0.7 to 1.1)	0.651	0.017
Body mass index (kg per m^2)	32.4 (21.2 to 39.6)	–0.5 (–1.9 to 2.0)	32.8 (27.7 to 38.4)	+0.4 (–0.7 to 1.9)	0.794	0.189

[a]*Baseline values are presented as median (IQR).*

[b]*Changes over 6 months are shown as the mean difference (95% confidence interval).*

[c]*P values from Mann-Whitney U test for the between-group comparisons of baseline values.*

[d]*P values from t test for independent samples for the between-group comparisons of baseline to follow-up change amounts.*

A1c = glycosylated hemoglobin; BP = blood pressure; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; kg per m^2 = kilograms per squared meter; LDL-C = low-density lipoprotein cholesterol; mm Hg = millimeters of mercury; mmol/L = millimoles per liter.

pressure values (< 130/80 mm Hg)[31,35] was significantly higher in the intervention group (80.5%) compared with the usual care group (46.8%) at the 6-month assessment ($P = 0.012$; Table 3).

Lipid Values. Compared with baseline values, the intervention patients showed a mean reduction of 0.7, 0.6, and 0.5 mmol/L in total cholesterol, LDL-C, and triglycerides levels, respectively, while usual care patients had a constant LDL-C and a mean increase of 0.1 mmol/L in total cholesterol and 0.2 mmol/L in triglycerides levels at the 6-month assessment ($P = 0.040$, 0.031, and 0.17 for total cholesterol, LDL-C, and triglycerides changes, respectively). Results indicated no significant improvement in HDL-C levels (intervention vs. usual care) over the 6-month study period ($P = 0.728$). Furthermore, a significantly greater proportion of intervention patients (53.2%) than usual care patients (30.4%) achieved the LDL-C target (< 2.6 mmol/L)[31,36] at the 6-month assessment ($P = 0.018$; Table 3).

Body Mass Index. Although intervention patients illustrated a reduction in BMI while usual care patients showed an increase in BMI values over the 6-month study period, this difference (intervention vs. usual care) did not reach statistical significance ($P = 0.189$; Table 2).

Self-Reported Adherence with the Prescribed Medications. Except for the significant increase in statin prescriptions in the intervention group patients at the 6-month assessment ($P = 0.038$), results indicated no significant differences between the intervention group and the usual care group in the usage of key medications at baseline and 6-month assessments (Table 3). Furthermore, the Mann-Whitney *U* test revealed no significant differences in the total number of prescribed medications between the 2 groups. Pearson chi-square analysis revealed a significantly lower proportion of nonadherent patients in the intervention group (28.6%) compared with the usual care group (64.6%) at the 6-month assessment ($P = 0.003$; Table 3).

Summary of Diabetes Self-Care Activities Questionnaire. Except for the foot care and smoking domains, the intervention group patients reported significantly better self-care activities, including diet ($P = 0.041$), exercise ($P = 0.025$), and SMBG ($P = 0.007$), compared with the usual care group at 6 months follow-up (Table 3). Each score included in the table is the mean value of the answer to the questions included in each domain (e.g., the diet domain score was calculated as the sum of scores on questions about diet, divided by 4 because there were 4 questions for that domain).

Discussion

Besides being the first study to assess the impact of a clinical pharmacy service on patients with type 2 diabetes in Jordan, this study intervention utilized the positive features of published single-interventional approaches and combined them into a structured diabetes care program. Although the benefits of clinical pharmacy services in the present study cannot be assessed in relation to the individual contributions of these intervention elements, they reflect strategies that have been used successfully in other contexts.[22,37]

The role of clinical pharmacists in Jordan has been expanding very slowly during the last 10 years to include more clinically oriented responsibilities. The slow progression of pharmaceutical care in Jordan may be attributed to several barriers to this concept; examples of these barriers include physicians' negative attitudes toward expanding the pharmacist's role in

TABLE 3 Baseline and Follow-Up Assessments of Study Outcomes for Intervention Versus Usual Care

Outcome	Baseline					6 Months Follow-up				
	Intervention n = 85		Usual Care n = 86		*P* Value[a]	Intervention n = 77		Usual Care n = 79		*P* Value[a]
Number of medications[b]	8	(7-9)	8	(7-10)	0.615	7	(6-8)	8	(6-10)	0.375
Number of antidiabetic medications[b]	2	(1-3)	2	(1-3)	0.591	2	(1-4)	2	(1-3)	0.213
Patients on insulin therapy[c]	65.9%	(56)	69.8%	(60)	0.475	79.2%	(61)	78.5%	(62)	0.881
Patients taking antihypertensive therapy[c]	82.4%	(70)	82.6%	(69)	0.814	89.6%	(69)	87.3%	(69)	0.782
Patients taking statin therapy[c]	62.4%	(53)	64.0%	(55)	0.364	81.8%	(63)	67.1%	(53)	0.038
Patients who achieved target A1c < 7%[c]	0.0		0.0		1.0	23.4%		15.2%		0.031
Patients who achieved target BP < 130/80 mm Hg[c]	45.9%	(39)	48.8%	(42)	0.743	80.5%	(62)	46.8%	(37)	0.012
Patients who achieved LDL-C target < 2.6 mmol/L[c]	29.4%	(25)	27.9%	(24)	0.562	54.5%	(42)	30.4%	(24)	0.018
Patients who self-reported medication nonadherence[c]	74.1%	(63)	70.9%	(61)	0.724	28.6%	(22)	64.6%	(51)	0.003
Domains of the SDSCA questionnaire										
Total diet score[b]	4.2	(1.8-6.4)	4.0	(3.1-5.0)	0.682	4.7	(2.5-7.1)	3.8	(2.8-4.8)	0.041
Physical activity score[b]	2.3	(1.1-4.1)	2.5	(0.5-4.7)	0.725	3.7	(3.0-4.5)	2.7	(0.9-3.9)	0.025
SMBG score[b]	4.5	(3.6-5.4)	4.8	(3.6-5.2)	0.647	5.3	(2.2-7.6)	4.0	(0.5-7.9)	0.007
Foot care score[b]	3.0	(2.2-4.0)	3.0	(2.0-4.0)	0.916	3.5	(1.8-5.5)	3.0	(1.0-5.2)	0.172
Current smokers	54.1%	(46)	45.3%	(39)	0.162	53.2%	(41)	46.8%	(37)	0.331

[a]*P values from Pearson chi-square test for categorical variables and Mann-Whitney U test for continuous variables.*
[b]*Values expressed as median (interquartile range).*
[c]*Values expressed as % (n).*
A1c = glycosylated hemoglobin; BP = blood pressure; LDL-C = low-density lipoprotein cholesterol; mm Hg = millimeters of mercury; mmol/L = millimoles per liter; SDSCA = Summary of Diabetes Self-Care Activities; SMBG = self-monitoring of blood glucose.

the patient care process[38] and the lack of effective pharmaceutical care training.[39] With all of the existing barriers, our study demonstrated the importance of the clinical pharmacist's role in improving clinical outcomes in patients with type 2 diabetes in Jordan.

A clinical pharmacist intervention that consisted of optimizing pharmacotherapy, individualized self-management education, adherence support, and regular telephone follow-up resulted in significant improvement in A1c, the primary outcome measure in this study.

A community-based RCT by Clifford et al. (2005) with an intervention strategy similar to that used in the present study (i.e., individualized education on a patient-specific medication profile along with regular telephone follow-up) for patients with type 2 diabetes indicated that A1c was decreased by a mean of 0.5% in the intervention group, whereas there was no change in the control group over a 12-month follow-up period.[22] An RCT by Choe et al. (2005) reported a reduction in mean A1c values from 10.1% to 8.0% in 41 intervention patients with type 2 diabetes who received a clinical pharmacy intervention similar to the one used in the present study (i.e., modification of pharmacotherapy and self-management diabetes education along with telephone follow-up) compared with 39 control group patients who showed a reduction in A1c values from 10.2% to 9.3% (*P* value for between-group difference in change amount = 0.03).[24] Krass et al. (2007) found in a pharmacy-randomized RCT that patients with type 2 diabetes who received education on diabetes management along with adherence support showed significantly greater reduction in mean A1c compared with patients who did not receive the service.[23] In an RCT conducted in patients aged 18 years or older with A1c exceeding 9.0%, Jameson and Baty (2010) found that a pharmacist collaborative practice program led to a significantly higher proportion of patients in the intervention group improving their A1c values by at least 1% relative to the control group (67.3% vs. 41.2%).[29]

An important finding in the present study was that significantly more patients in the intervention group (23.4%) than in the control group (15.2%) achieved the ADA target goal for A1c of less than 7% at the 6-month assessment. Corresponding data from the RCT by Al Mazroui et al. (2009) indicated that 45.4% of patients in the intervention group and 30.3% in the control group achieved the ADA target at a 12-month follow-up assessment ($P < 0.021$).[28]

Taken together with the results of the present study, it is clear that pharmaceutical care can result in significant improvements in glycemic control in multiple settings. Epidemiological analysis (UKPDS) links a 1% A1c reduction to an estimated 14% reduction in the risk of myocardial infarction and an estimated 12% reduction in the risk of stroke.[11] The intervention group in the present study experienced a 0.8% mean reduction in A1c.

The improvements in A1c in the present study may be due to the integrated clinical pharmacist intervention with regard

to optimizing the prescribed pharmacotherapy, providing individualized education on various self-care activities, improving adherence to prescribed medication, and regular telephone follow-up.

The present study indicated significant improvement in FBG values in patients who received pharmaceutical care when compared with usual care patients over the 6-month study period. This finding is consistent with findings from Al Mazroui et al.[28] who reported a significant decrease in FBG in patients who received pharmaceutical care intervention at the end of a 12-month follow-up period. The Fremantle Diabetes Study (FDS) also showed a greater reduction in FBG in intervention patients than in control patients over a 12-month study period.[22]

Consistent with earlier studies, the clinical pharmacy service in the present study yielded significant improvement in both systolic and diastolic blood pressure.[22,28,40] Improvement in blood pressure was also demonstrated by the significantly higher proportion of intervention patients who achieved target systolic and diastolic blood pressure values (< 130/80 mm Hg) compared with the control group at the end of the study. Since patients in both groups were prescribed similar antihypertensive medications, this finding may be due to comprehensive education of patients and the associated improvements in lifestyle behaviors and medication adherence observed in the intervention group. Epidemiological studies suggest that the risk of cardiovascular events increases by 20% with every 10 mm Hg increase in systolic blood pressure.[41] Although the decline in systolic blood pressure in the intervention patients in the present study was less than 10 mm Hg, it may still have a positive impact on cardiovascular risk.[22,42]

The present study found significant between-group differences in measures of lipid control and in the proportion of patients who achieved target LDL-C values (< 2.6 mmol/L). Consistent with findings from the current study, earlier studies found that a pharmacist-based management program for patients with type 2 diabetes was associated with significant improvements in serum triglycerides,[28,43-46] total cholesterol,[25,28] and LDL-C levels.[24,27,28,47] Analysis of UKPDS data by Turner et al. (1998) indicated that the risk of either angina pectoris or myocardial infarction increases by 1.57 for every 1 mmol/L increase in LDL-C level, and patients with LDL-C levels higher than 3.9 mmol/L were 2.3 times as likely to develop coronary artery disease than those with LDL-C levels less than 3 mmol/L.[48]

The significant improvement in LDL-C, triglycerides, and total serum cholesterol levels observed in the present study could be due to the clinical pharmacist input and the significant increase in the number of intervention patients who were prescribed statin therapy when compared with the control group patients at the 6-month assessment. The improved adherence to medication and lifestyle advice may have contributed to improving the lipid profile. The present study did not find significant improvement in HDL-C levels or BMI. However, only 1 study of which we are aware demonstrated a favorable increase in HDL-C, and 1 study showed a significant reduction in BMI levels as a result of pharmacist-provided diabetes management.[22,43]

Although medication adherence was assessed by an instrument that has not been validated for use in our setting, especially in the format that uses fewer items (e.g., the 4-item instead of 8-item version of the Morisky scale), this instrument has been validated and was found to be reliable and widely used in a variety of medication adherence studies.[49-53] Furthermore, Kripilani et al. (2009) used the Morisky Scale as a "gold standard" against which to test a new adherence measurement instrument.[54] Research has indicated that adherence to medication in type 2 diabetes is poor and is considered as one of the main barriers to the benefit of optimal diabetes care and a major cause of unnecessary hospitalization.[55,56] Consistent with findings from earlier research,[28] patients who received the clinical pharmacy service in the present study demonstrated significantly better self-reported medication adherence compared with the control group patients.

The significant improvement in dietary habits in intervention patients at the end of the present study is consistent with findings from earlier research. Doucette et al. (2009) reported in an RCT that pharmacists were effective at increasing the number of days per week that patients spent engaging in healthy diet and diabetes self-care activities.[57] On the other hand, patients who received the clinical pharmacy service in the present study had significantly better self-reported physical activity than did patients in usual care. Evidence of the beneficial effects of exercise on blood glucose control in patients with type 2 diabetes exists in the literature.[58,59] The significant improvement in dietary and physical activity behaviors seen in the intervention patients in this study is likely due to the robust content of the educational material that determined types and proportions of healthy diet and encouraged the patients to perform regular, individualized physical activity. The reported significant improvement in SMBG in the intervention patients was not surprising and could be attributed to the provision by the clinical pharmacist of high-quality information about the blood glucose values indicative of hyperglycemia and hypoglycemia and about how to respond appropriately to these results. Foot care was not significantly improved in the intervention patients at the end of the study. Similar findings were reported by Sadur et al. (1999).[60] Therefore, foot care is an area where considerable scope for further improvements is required. The present study also did not show significant improvement in smoking behavior; this may be a result of the minimal cessation counseling offered by our intervention and the lack of

focus on this area. Therefore, more intensive smoking intervention that utilizes the transtheoretical model of change and assesses patient readiness to stop smoking may lead to better results in smoking cessation behavior.

Limitations

First, this study used a patient-reported measure of medical adherence, and the results may be affected by social desirability and recall bias. Second, although the study outcomes were statistically more favorable in the intervention group compared with usual care, the study was underpowered because the trial enrolled a small number of patients due to limited availability of a single investigator. Third, our study assessed outcomes after only 6 months, and longer follow-up is necessary to determine if the short-term outcomes are sustained from the clinical pharmacist interventions in this hospital-based diabetes clinic. Fourth, this study assessed only intermediate clinical outcomes and did not examine either humanistic-service outcomes or program costs for the clinical pharmacy interventions.

Conclusions

The present study found that, compared with usual care, a clinical pharmacy service for patients with type 2 diabetes may improve biomarker values, including A1c, blood pressure, and lipid profile, in addition to self-reported medication adherence and self-care activities. Future research with a larger sample size, conducted over a period of follow-up longer than 6 months, is needed to confirm the effects of this clinical pharmacy service and to identify the most effective elements of the service model.

Authors

ANAN SADEQ JARAB, PhD, is Assistant Professor; GHASSAN SHATTAT, PhD, is Associate Professor; and TARIQ AL-QIRIM, PhD, is Associate Professor, AIZaytoonah University of Jordan, Amman, Jordan. SALAM GHAZI ALQUDAH, BSc, is Captain Pharmacist, Jordanian Royal Medical Services Hospital, Amman, Jordan. TAREQ LEWIS MUKATTASH, PhD, is Assistant Professor, Jordan University of Science and Technology, Irbid, Jordan.

AUTHOR CORRESPONDENCE: Anan Sadeq Jarab, PhD, AIZaytoonah University of Jordan, Pharmacy, P.O. Box 130, Amman, Jordan 11733. Tel.: 00962776337513; E-mail: anansalam10@yahoo.com.

DISCLOSURES

All authors certify that there was no external funding for this research article and report no financial or other potential conflicts of interest related to the subject of this article.

Concept and design were performed primarily by Jarab with the assistance of Mukattash. The data were collected primarily by Alqudah and Jarab and interpreted primarily by Jarab and Shattat. The manuscript was written primarily by Jarab and Mukattash and revised primarily by Jarab and Al-Qirim.

ACKNOWLEDGMENTS

The authors thank Maher Khdour, PhD; Firas AlHajji, PhD; Fares Haddad, MD, JMB; and Luay AlEssa, MD, PhD, for reviewing the study survey instrument for validity.

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care*. 2012;35(Suppl 1):S11-S63. Available at: http://care.diabetesjournals.org/content/35/Supplement_1/S11.full.pdf+htm. Accessed August 19, 2012.

2. Kelly C, Rodgers P. Implementation and evaluation of a pharmacist-managed diabetes service. *J Manag Care Pharm*. 2000;6(6):488-93. Available at: http://www.amcp.org/data/jmcp/research_v6_488-493.pdf.

3. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27(5):1047-53. Available at: http://www.who.int/diabetes/facts/en/diabcare0504.pdf. Accessed August 19, 2012.

4. Waly MI, Essa MM, Ali A, Al-Shuaibi YM, Al-Farsi YM. The global burden of Type 2 diabetes: a review. *Int J Biol Med Res*. 2010;1(4):326-29. Available at: http://www.biomedscidirect.com/journalfiles/IJBMRF201046/the_global_burden_of_type_2_diabetes_a_review.pdf. Accessed August 19, 2012.

5. Ajlouni K, Jaddou H, Batieha A. Diabetes and impaired glucose tolerance in Jordan: prevalence and associated risk factors. *J Intern Med*. 1998;244(4):317-23. Available at: http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2796.1998.00369.x/pdf. Accessed August 19, 2012.

6. Centers for Disease Control and Prevention (CDC). Assessing risk factors for chronic disease—Jordan, 2004. *MMWR Morb Mortal Wkly Rep*. 2006;55(23):653-55. Available at: http://www.cdc.gov/mmwR/preview/mmwrhtml/mm5523a3.htm. Accessed August 19, 2012.

7. Ajlouni K, Khader YS, Batieha A, Ajlouni H, El-Khateeb M. An increase in prevalence of diabetes mellitus in Jordan over 10 years. *J Diabetes Complications*. 2008;22(5):317-24.

8. World Health Organization. Facing the facts: the impact of chronic disease in Jordan. Available at: http://www.who.int/chp/chronic_disease_report/media/impact/jordan.pdf. Accessed August 19, 2012.

9. World Health Organization. Noncommunicable diseases: country profiles 2011. Available at: http://www.who.int/nmh/publications/ncd_profiles_report.pdf. Accessed August 19, 2012.

10. Norris SL, Lau J, Smith SJ. Self-management educations for adults with type 2 diabetes: a meta-analysis of the effect on glycaemic control. *Diabetes Care*. 2002;25(7):1159-71. Available at: http://care.diabetesjournals.org/content/25/7/1159.full.pdf+html. Accessed August 19, 2012.

11. Stratton IM, Alder AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405-12. Available at: http://www.bmj.com/content/321/7258/405.pdf%2Bhtml. Accessed August 19, 2012.

12. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ*. 2001;322:15-18. Available at: http://www.bmj.com/content/322/7277/15.pdf%2Bhtml. Accessed August 19, 2012.

13. Standl E, Balletshofer B, Dahl B, et al. Predictors of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. *Diabetologia*. 1996;39(12):1540-45.

14. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-53.

15. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-72. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa0802987. Accessed August 19, 2012.

16. Genuth S, Eastman R, Kahn R, Klein R, Lachin J; American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. *Diabetes Care*. 2003;26(Suppl 1):S28-S32. Available at: http://care.diabetesjournals.org/content/26/suppl_1/s28.full.pdf+html. Accessed August 19, 2012.

17. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2004;27(Suppl 1):S15-S35. Available at: http://care.diabetesjournals.org/content/27/suppl_1/s15.full.pdf+html. Accessed August 19, 2012.

18. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA*. 2004;291(3):335-42. Available at: http://jama.jamanetwork.com/article.aspx?articleid=198035. Accessed August 19, 2012.

19. McClean MT, McElnay JC, Andrews J. The importance of patient education and patient involvement in the treatment of diabetes. *Pharm J*. 2000;265:108-10.

20. Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. *Am J Med*. 2005;118(Suppl 5A):S27-S34.

21. Armour CL, Taylor SJ, Hourihan F. Implementation and evaluation of Australian pharmacists' diabetes care services. *J Am Pharm Assoc (2003)*. 2004;44(4):455-66.

22. Clifford RM, Davis WA, Batty KT, Davis TM. Effect of a pharmaceutical care program on vascular risk factors in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care*. 2005;28(4):771-76. Available at: http://care.diabetesjournals.org/content/28/4/771.full.pdf+html. Accessed August 19, 2012.

23. Krass I, Armour CL, Mitchell B, et al. The Pharmacy Diabetes Care Program: assessment of a community pharmacy diabetes service model in Australia. *Diabet Med*. 2007;24(6):677-83.

24. Choe HM, Mitrovich S, Dubay D, Hayward RA, Krein SL, Vijan S. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomized controlled trial. *Am J Manag Care*. 2005;11(4):253-60. Available at: http://www.ajmc.com/publications/issue/2005/2005-04-vol11-n4/Apr05-2017p0253-0260/. Accessed August 19, 2012.

25. Fornos JA, Andrés NF, Andrés JC, Guerra MM, Egea B. A pharmacotherapy follow-up program in patients with type-2 diabetes in community pharmacies in Spain. *Pharm World Sci*. 2006;28(2):65-72.

26. Odegard PS, Goo A, Hummel J, Williams KL, Gray SL. Caring for poorly controlled diabetes mellitus: a randomized pharmacist intervention. *Ann Pharmacother.* 2005;39(3):433-40.

27. Scott DM, Boyd ST, Stephan M, Augustine SC, Reardon TP. Outcomes of pharmacist-managed diabetes care services in a community health center. *Am J Health Syst Pharm*. 2006;63(21):2116-22.

28. Al Mazroui NR, Kamal MM, Ghabash NM, Yacout TA, Kole PL, McElnay JC. Influence of pharmaceutical care on health outcomes in patients with Type 2 diabetes mellitus. *Br J Clin Pharmacol*. 2009;67(5):547-57. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2686072/pdf/bcp0067-0547.pdf. Accessed August 19, 2012.

29. Jameson JP, Baty PJ. Pharmacist collaborative management of poorly controlled diabetes mellitus: a randomized controlled trial. *Am J Manag Care*. 2010;16(4):250-55. Available at: http://www.ajmc.com/publications/issue/2010/2010-04-vol16-n04/AJMC_10apr_Jameson_250to255/3. Accessed August 19, 2012.

30. Evans S, Royston P, Day S. Minim: allocation by minimisation in clinical trials. 2004. Available from: http://www-users.york.ac.uk/~mb55/guide/minim.htm. Accessed August 19, 2012.

31. American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care*. 2010;33(Suppl 1):S11-S61. Available at: http://care.diabetesjournals.org/content/33/Supplement_1/S11.full.pdf+html. Accessed August 19, 2012.

32. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986;24(1):67-74.

33. Toobert DJ, Hampson SE, Glasgow RE. The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. *Diabetes Care*. 2000;23(7):943-50. Available at: http://care.diabetesjournals.org/content/23/7/943.full.pdf+html. Accessed August 19, 2012.

34. Kinmonth AL, Woodcock A, Griffin S, Spiegal N, Campbell MJ. Randomised controlled trial of patient-centred care of diabetes in general practice: impact on current wellbeing and future disease risk. The Diabetes Care from Diagnosis Research Team. *BMJ*. 1998;317(7167):1202-08. Available at: www.bmj.com/highwire/filestream/382276/field_highwire_article_pdf/0.pdf. Accessed August 19, 2012.

35. Chobanian AV, Bakris GL, Black HR, et al.; the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-52. Available at: http://hyper.ahajournals.org/content/42/6/1206.full.pdf+html. Accessed August 19, 2012.

36. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-21. Available at: http://circ.ahajournals.org/content/106/25/3143.full.pdf. Accessed August 19, 2012.

37. Kennie NR, Schuster BG, Einarson TR. Critical analysis of the pharmaceutical care research literature. *Ann Pharmacother.* 1998;32(1):17-26.

38. AbuRuz SM, Al-Ghazawi MA, Bulatova N, Jarab AS, Alawwa IA, Al-Saleh A. Expectations and experiences of physicians regarding pharmaceutical care and the expanding role of pharmacists in Jordan. *JJPS*. 2012;5(1):74-86. Available at: http://journals.ju.edu.jo/JJPS/article/viewFile/2768/2462. Accessed August 19, 2012.

39. Aburuz S, Al-Ghazawi M, Snyder A. Pharmaceutical care in a community-based practice setting in Jordan: where are we now with our attitudes and perceived barriers? *Int J Pharm Pract*. 2012;20(2):71-79.

40. Pei-Xi Zhao, Chao Wang, Li Qin, et al. Effect of clinical pharmacist's pharmaceutical care intervention to control hypertensive outpatients in China. *Afr J Pharm Pharmacol*. 2012;6(1):48-56. Available at: http://www.academicjournals.org/ajpp/PDF/pdf2012/8%20Jan/Zhao%20et%20al.pdf. Accessed August 19, 2012.

41. Gerstein HC, Malmberg K, Capes S, Yusuf S. Cardiovascular diseases. In: Gerstein HC, Haynes RB, eds. *Evidence-Based Diabetes Care*. Hamilton, Ontario: BC Decker; 2001:488-514.

42. Adler AI, Stratton IM, Neil HA. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*. 2000;321(7258):412-19. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC27455/pdf/412.pdf. Accessed August 19, 2012.

43. Johnson CL, Nicholas A, Divine H, Perrier DG, Blumenschein K, Steinke DT. Outcomes from DiabetesCARE: a pharmacist-provided diabetes management service. *J Am Pharm Assoc (2003).* 2008;48(6):722-30.

44. Leal S, Glover JJ, Herrier RN, Felix A. Improving quality of care in diabetes through a comprehensive pharmacist-based disease management program. *Diabetes Care.* 2004;27(12):2983-84. Available at: http://care.diabetesjournals.org/content/27/12/2983.full.pdf+html. Accessed August 19, 2012.

45. McCord AD. Clinical impact of a pharmacist-managed diabetes mellitus drug therapy management service. *Pharmacotherapy.* 2006;26(2):248-53.

46. Morello CM, Zadvorny EB, Cording MA, Suemoto RT, Skog J, Harari A. Development and clinical outcomes of pharmacist-managed diabetes care clinics. *Am J Health Syst Pharm.* 2006;63(14):1325-31.

47. Nau DP, Ponte CD. Effects of a community pharmacist-based diabetes patient management program on intermediate clinical outcome measures. *J Manag Care Pharm.* 2002;8(1):48-53. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=6505.

48. Turner RC, Millns H, Neil HA. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ.* 1998;316(7134):823-28. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC28484. Accessed August 19, 2012.

49. Krapek K, King K, Warren SS, et al. Medication adherence and associated hemoglobin A1c in type 2 diabetes. *Ann Pharmacother.* 2004;38(9):1357-62.

50. Venturini F, Nichol MB, Sung JC, Bailey KL, Cody M, McCombs JS. Compliance with sulfonylureas in a health maintenance organization: a pharmacy record-based study. *Ann Pharmacother.* 1999;33(3):281-88.

51. George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. *Br J Clin Pharmacol.* 2000;50(2):166-71. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2014396/pdf/bcp0050-0166.pdf. Accessed August 19, 2012.

52. Patel RP, Taylor SD. Factors affecting medication adherence in hypertensive patients. *Ann Pharmacother.* 2002;36(1):40-45.

53. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res.* 1999;47(6):555-67.

54. Kripalani S, Risser J, Gatti ME, Jacobson TA. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value Health.* 2009;12(1):118-23.

55. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA.* 2002;288(22):2868-79. Available at: http://www.safetynetinstitute.org/content/Upload/AssetMgmt/Site/resources/chroniccare/InterventionsPatientAdherence.pdf. Accessed August 19, 2012.

56. Irons BK, Lenz RJ, Anderson SL, Wharton BL, Habeger B, Anderson HG. A retrospective cohort analysis of the clinical effectiveness of a physician-pharmacist collaborative drug therapy management diabetes clinic. *Pharmacotherapy.* 2002;22(10):1294-1300.

57. Doucette WR, Witry MJ, Farris KB, McDonough RP. Community pharmacist-provided extended diabetes care. *Ann Pharmacother.* 2009;43(5):882-89.

58. Deakin T, McShane CE, Cade JE, Williams RD. Group based training for self-management strategies in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005;(2)CD003417.

59. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports.* 2006;16(Suppl 1):S3-S63.

60. Sadur CN, Moline N, Costa M, et al. Diabetes management in a health maintenance organization: efficacy of care management using cluster visits. *Diabetes Care.* 1999;22(12):2011-17. Available at: http://care.diabetesjournals.org/content/22/12/2011.long. Accessed August 19, 2012.

SUBJECT REVIEW

Dosing Frequency and Medication Adherence in Chronic Disease

Craig I. Coleman, PharmD; Brendan Limone, PharmD; Diana M. Sobieraj, PharmD; Soyon Lee, PharmD; Matthew S. Roberts, BS; Rajbir Kaur, PharmD; and Tawfikul Alam, MD

ABSTRACT

BACKGROUND: Prior research has shown a decrease in medication adherence as dosing frequency increases; however, meta-analyses have not been able to demonstrate a significant inverse relationship between dosing frequency and adherence when comparing twice-daily versus once-daily dosing.

OBJECTIVE: To determine the effect of scheduled dosing frequency on medication adherence in patients with chronic diseases.

METHODS: A systematic literature search of MEDLINE and Embase from January 1986 to December 2011 and a hand search of references were performed to identify eligible studies. Randomized and observational studies were included if they utilized a prospective design, assessed adult patients with chronic diseases, evaluated scheduled oral medications taken 1 to 4 times daily, and measured medication adherence for at least 1 month using an electronic monitoring device. Manual searches of reference sections of identified studies and systematic reviews were also performed to find other potentially relevant articles. Standard definitions for medication taking, regimen, and timing adherence were used and evaluated. Studies were pooled using a multivariate linear mixed-model method to conduct meta-regression accounting for both random and fixed effects, weighted by the inverse of the variance of medication adherence.

RESULTS: Fifty-one studies, comprising 65, 76, and 47 dosing frequency arms for the taking, regimen, and timing adherence endpoints were included. Unadjusted adherence estimates were highest when the least stringent definition, taking adherence, was used (range for dosing frequencies: 80.1%-93.0%) and lowest when the most stringent definition, timing adherence, was used (range for dosing frequencies: 18.8%-76.9%). In multivariate meta-regression analyses, the adjusted weighted mean percentage adherence rates for all regimens dosed more frequently than once per day were significantly lower compared with once-daily regimens (for 2-times, 3-times, and 4-times daily regimens, respectively: differences for taking adherence: –6.7%, –13.5%, and –19.2%; regimen adherence: –13.1%, –24.9%, and –23.1%; and timing adherence: –26.7%, –39.0%, and –54.2%).

CONCLUSION: Patients with chronic diseases appear to be more adherent with once-daily compared with more frequently scheduled medication regimens. The use of more stringent definitions of adherence magnified these findings.

J Manag Care Pharm. 2012;18(7):527-39

What is already known about this subject

- Many chronic diseases require that patients take 1 or more maintenance medications, often taken more than once daily. Medication nonadherence is associated with suboptimal health outcomes and increased health care costs. Previous research suggests that a substantial inverse relationship between dosing frequency and medication adherence may exist; however, differences between once- and twice-daily regimens or twice- and 3-times daily regimens have not been demonstrated.
- An outdated meta-analysis by Claxton et al. (2001) explored the effect of medication dosing frequency on medication adherence, including studies published through the year 2000. Its limitations stem from a suboptimal statistical meta-analytic technique, averaging the mean adherence rates for the included studies, as well as from including a highly heterogeneous group of acute and chronic disease studies utilizing various dosage forms. While this meta-analysis showed higher adherence for once-daily dosing compared with 3- or 4-times daily dosing, it did not show a difference between once- and twice-daily dosing.
- No meta-analysis has demonstrated a significant inverse relationship between dosing frequency and medication adherence when comparing once- and twice-daily dosing.

What this study adds

- The present study employed a methodologically sound analysis utilizing a multivariate linear mixed-model method to conduct meta-regression accounting for both random and fixed effects, weighted by the inverse of the variance of medication adherence. Fixed effects were assumed for study-level factors, including dosing frequency, disease state, study design, country in which study was conducted, participant's awareness of electronic monitoring, duration of adherence monitoring, and year of publication.
- In multivariate meta-regression analyses, the adjusted weighted mean percentage adherence rates for twice-daily, 3-times daily, and 4-times daily dosing regimens, respectively, were significantly lower compared with once-daily regimens (differences for taking adherence: –6.7%, –13.5%, –19.2%; regimen adherence: –13.1%, –24.9%, –23.1%; and timing adherence: –26.7%, –39.0%, –54.2%). Using the more stringent definition of timing adherence, differences between once-daily and multiple doses were magnified.

Chronic disease is the primary cause of morbidity and mortality in the United States.[1] Many chronic diseases require patients to take 1 or more maintenance medications, often more than once daily. Prior research suggests that an inverse relationship between dosing frequency and medication adherence may exist.[2,3]

In 2009, Siani et al. published a systematic review that included specific quiescent chronic disease states: hypertension, dyslipidemia, type 2 diabetes mellitus, asthma, seizure disorder, congestive heart failure, migraine headaches, and stable angina.[2] Twenty studies published through August 2007 were included, but the authors did not attempt to statistically pool data from these studies. The results of included studies were generally favorable for less frequent dosing regimens, with 15 of 20 studies showing a statistically significant inverse relationship between dosing frequency and adherence. However, the authors noted that there are few data on adherence to more frequent dosing regimens (3- and 4-times daily), and most included studies had small sample sizes, making it extremely challenging to draw any statistical conclusions. In addition, higher dosing frequencies such as 3-times daily and 4-times daily were reported only in a few identified studies.[2]

An outdated meta-analysis by Claxton et al. (2001) explored the effect of medication dosing frequency on medication adherence including studies published up to the year 2000; however, the researchers averaged the mean adherence rates of all the included studies rather than using proper meta-analytic techniques.[3] Moreover, Claxton et al. pooled a heterogeneous group of studies, including those examining adherence in acute and chronic conditions and evaluating oral, injectable, and inhaled medications, without adjusting for these confounders.[4] While the analysis found adherence to be significantly higher for once-daily dosing compared with 3- or 4-times daily dosing, it did not demonstrate a statistically significant difference in adherence between once- and twice-daily regimens.[3] With the inclusion of studies published in the last decade as well as the use of stronger meta-analytic techniques, it seems prudent to re-explore the relationship between dosing frequency and medication adherence.

The primary objective of the current study was to conduct a methodologically sound systematic review and meta-regression analysis to evaluate the association of scheduled medication dosing frequency (1 to 4 times daily) with medication adherence in patients with chronic diseases.

Methods

Study Identification

We conducted a literature search in the bibliographic databases MEDLINE and Embase from 1986 (the year the first electronic medication monitoring device became available) through December 2011 using the search strategies detailed in the Appendix. We limited the results of this search to controlled trials or systematic reviews published in English. Manual searches of reference sections of included studies as well as systematic reviews were performed to identify other potentially relevant articles.

Medication adherence can be measured through various means, including patient self-report, analysis of prescription refill records, measurement of serum drug levels, pill counts, and electronic monitors, such as medication event monitoring systems (MEMS; manufactured by AARDEX Group Ltd., Sion, Switzerland).[5] No one method is without limitation; however, electronic monitors are commonly considered to provide the most accurate information for measuring adherence. These electronic devices are capable of taking into account both the number and time of pill container openings, allowing noninvasive assessment of more complex adherence definitions such as taking adherence and regimen adherence. For this reason, the search was limited to studies monitoring adherence via electronic monitoring methods. In order to find other potentially relevant articles, we manually searched the reference sections of included studies and systematic reviews as well as bibliographies obtained from the AARDEX website (http://www.aardex-group.com and http://www.iadherence.org/publication.adx).

Study Selection

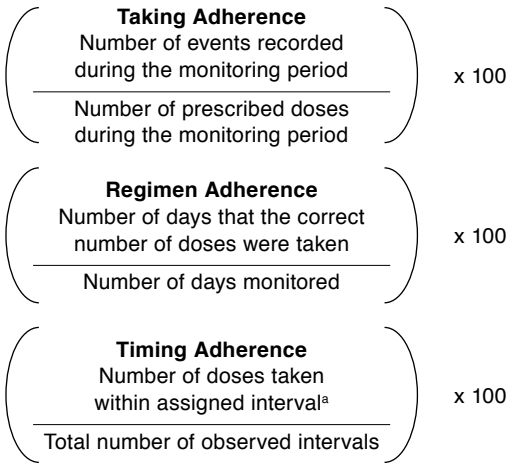
The following inclusion criteria were applied to identified articles: (a) prospective study design or systematic review with or without meta-analysis, (b) adult patient population with 1 or more chronic diseases, (c) scheduled oral medication intervention to be taken 1 to 4 times daily, (d) follow-up for 1 or more months, and (e) electronic monitoring of adherence reported. For studies that randomized patients to 1 or more interventions specifically designed to enhance adherence (other than electronic monitoring itself), only the control arms were included. An *a priori* decision to exclude studies that evaluated human immunodeficiency virus (HIV), psychiatric illness, cancer, or treatment to prevent organ rejection was made because medication adherence in these populations is not likely representative of the average chronic disease population.

Data Extraction

Identified articles were independently reviewed by 2 investigators (Roberts and Sobieraj) with disagreements resolved by a third (Coleman). The following data were extracted from each of the 51 included studies: (a) patient demographics, (b) study design, (c) country in which study was conducted, (d) chronic disease being studied, (e) whether patients were blinded to electronic monitoring, (f) frequency of dosing regimens, (g) duration of follow-up, and (h) patient adherence data. When necessary, authors were contacted via e-mail for clarification or additional data.

Three definitions commonly reported in the literature were used to measure adherence: taking, regimen, and timing

FIGURE 1 *Calculation of 3 Adherence Measures*



[a]*Assigned intervals varied among studies.*

adherence (Figure 1).[2,3,6] Taking adherence was defined as the number of openings divided by the prescribed number of doses. Regimen adherence was defined as the percentage of days with the appropriate number of doses taken, putting importance on the correct number of cap openings per day (and not allowing extra cap openings on one day to compensate for missed openings on another day). Timing adherence, the most stringent definition of adherence commonly used in the medical literature, was defined as the percentage of doses taken within assigned intervals. This latter adherence definition may be particularly important for drugs that should be administered at specific times of day for pharmacokinetic reasons (e.g., those that should or should not be administered with meals due to effects on bioavailability); to improve tolerability (e.g., thiazides should not administered before bedtime to prevent frequent waking to urinate); or to maintain efficacy (e.g., administering nitrates on a schedule that assures a nitrate-free interval and maintaining continuous dopaminergic stimulation and modulating end-of-dose failure with levodopa in Parkinson's disease).[3,7-9]

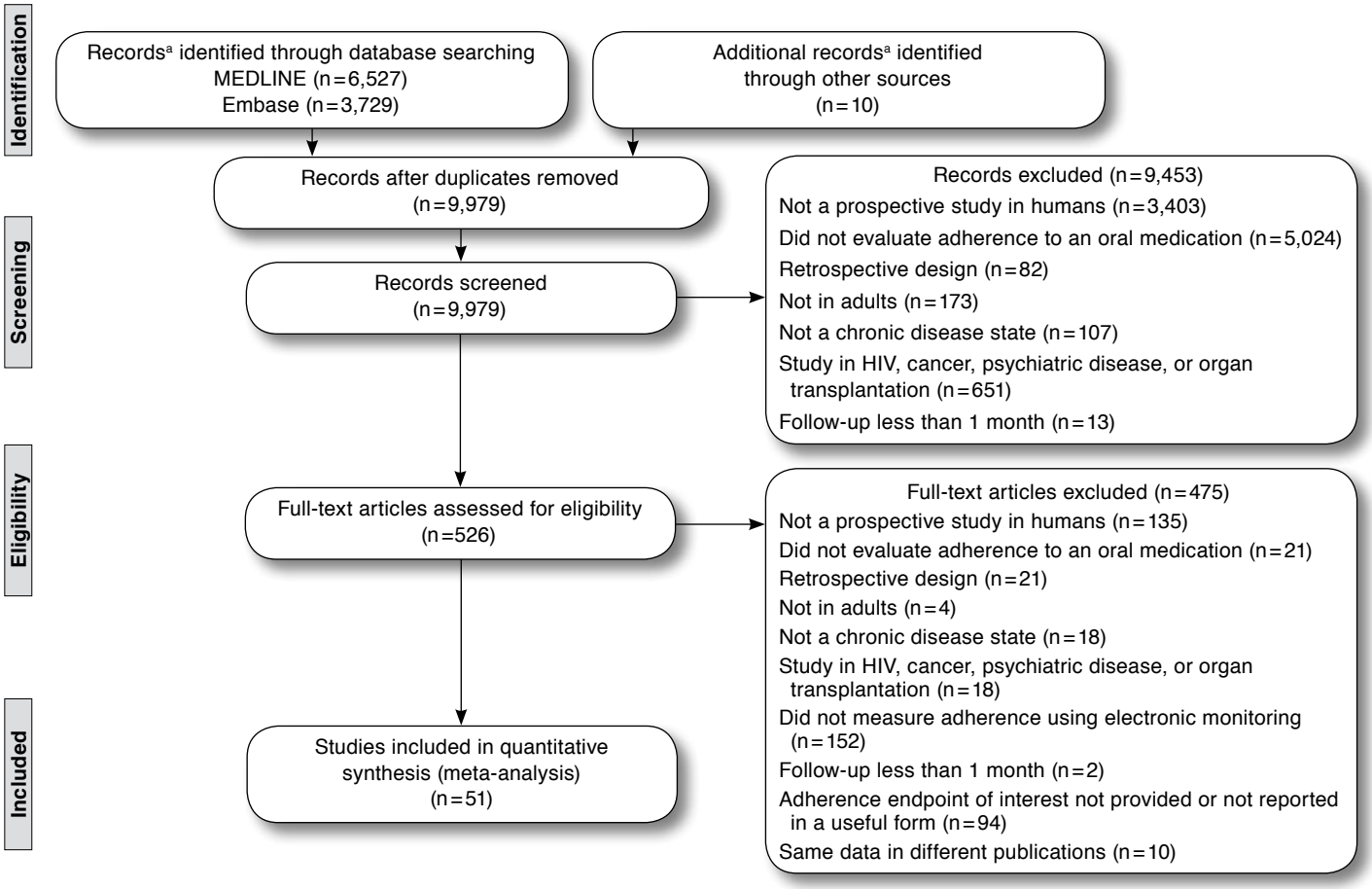
Data Synthesis

Individual arms from included studies were categorized into the 4 dosing frequencies evaluated (1 to 4 times daily) and pooled using meta-analytic methods within each frequency. In order to determine how each dosing frequency as well as other pertinent study characteristics were associated with medication adherence, both traditional random-effects meta-analyses and meta-regression analyses were conducted. A multivariate linear mixed-model method was used to conduct meta-regression accounting for both random and fixed effects.[4] Fixed effects were assumed for study-level factors, including dosing frequency, disease state, study design, country in which study was conducted, participant's awareness of electronic monitoring, duration of adherence monitoring, and year of publication. Both the traditional meta-analyses and the multivariate analyses were weighted by the inverse of the variance of medication adherence. Statistical analysis was performed using StatsDirect version 2.7.6 (StatsDirect Ltd., Cheshire, England) and SAS (PROC MIXED), version 9.1 (SAS Institute Inc., Cary, NC).

Results

The initial systematic literature search yielded 9,979 nonduplicate citations (Figure 2), and after screening, 526 of these citations were reviewed at the full-text level. Of these, 475 were excluded for various reasons, most commonly because the publication was not a report of a prospective study in humans or did not measure adherence using an electronic monitoring device. A total of 51 unique studies were identified for inclusion (Table 1).[6,10-59] From these, 65, 76, and 47 separate dosing frequency arms were available for the taking, regimen, and timing adherence endpoints, respectively (Table 2). Included studies were published between 1987 and 2011, with approximately one-half (n = 25) published in the last decade. The studies enrolled between 4 and 501 patients and followed them for no less than 28 days and up to 365 days; 20% of studies (n = 10) followed patients for 168 days (six 28-day periods) or more. Only 15.7% of study reports (n = 8) explicitly stated that they blinded patients to the electronic monitoring device. Nineteen of the 51 studies (37.3%) were conducted in the United States, with the remainder conducted in various European countries. A majority (29 of 51) of studies were conducted in patient populations with cardiovascular diseases (most commonly hypertension but also hyperlipidemia, heart failure, stable angina, and anticoagulation). Other disease states included neurologic (epilepsy, migraine, and Parkinson's disease), type 2 diabetes mellitus (T2DM), asthma, and other/mixed (psoriasis, vitamin deficiency, osteoporosis, autoimmune disease, and gout). Drugs monitored were either specific therapies (e.g., warfarin for anticoagulation), pharmacologic classes (e.g., beta-blockers for heart failure), or broader categories (e.g., antihypertensive agents, anti-Parkinson's drugs). With the exception of epilepsy and asthma studies, which enrolled younger adults, the mean/median age of study populations was between 50 and 70 years. In most studies, the proportions of men and women were approximately equal, except for 1 study enrolling only women with osteopenia and 4 studies that enrolled only men (studies of hypertension [n = 2], T2DM [n = 1], and hyperlipidemia [n = 1]). All studies collected adherence data prospectively, with 8 studies randomizing patients according to dosing frequency, 17 studies presenting a *post hoc* observational analysis of randomized data, and the remaining 26 using an observational study design.

FIGURE 2 *Flow Diagram for Study Inclusion*



[a]Records include titles and full abstracts; abstracts were not available for all titles.
HIV = human immunodeficiency virus.

In traditional random-effects meta-analysis of each of the 3 adherence definitions, weighted mean adherence rates were notably lower for regimens taken more than once per day than for once-daily regimens (Table 3). Unadjusted adherence rates were highest when taking adherence, the least stringent measure, was evaluated (range for dosing frequencies: 80.1% to 93.0%) and lowest when timing adherence, the most stringent, was evaluated (range for dosing frequencies: 18.8% to 76.9%).

Upon adjustment using multivariate meta-regression, these findings remained consistent and were statistically significant (Table 4). The adjusted differences in adherence across frequencies (once daily vs. others) were again most profound when evaluating timing adherence, followed by regimen and taking adherence. Compared with once-daily regimens (n = 2,006 patients), taking adherence was 6.7%, 13.5%, and 19.2% lower in twice- (n = 1,259), 3-times (n = 362), and 4-times (n = 57) daily regimens, respectively. Regimen adherence was 13.1%, 24.9%, and 23.1% lower in twice- (n = 826), 3-times (n = 321), and 4-times (n = 86) daily regimens, respectively, compared with once-daily regimens (n = 2,118). Finally, compared with once-daily regimens (n = 936), timing adherence was 26.7%, 39.0%, and 54.2% lower for twice- (n = 650), 3-times (n = 343), and 4-times (n = 109) daily regimens, respectively.

Few study-level factors were found to have statistically significant effects on medication adherence in meta-regression analysis (Table 4). A statistically significant decrease in taking adherence was found in studies that blinded patients to electronic monitoring (–10.1%) or when follow-up was 168 days or longer (–8.7%). Blinding to electronic monitoring was also found to decrease regimen adherence to a statistically significant level (–12.4%), as was asthma as the target disease state (–21.0%) compared with cardiovascular disease (reference

TABLE 1 *Characteristics of Included Studies*

First Author, Year	Study Design	Disease State	Mean Age (Years)	Percent Male (%)	Drug Class	Blinded to EM?	Dosing Frequencies (n =)	Mean Duration of Follow-Up (Days)	Country
Clerisme-Beaty, 2011[10] (Standard education arms only)	O/R	Poorly controlled asthma	~35	25	Montelukast and placebo	NR	QD (n = 25) QD (n = 23)	28	United States
Doró, 2011[11]	O	HTN	61	45	Antihypertensives	NR	QD (n = 15) BID (n = 9) TID (n = 5)	89	Hungary
Favrat, 2011[12]	O/R	Vitamin deficiency	~69	46	Vitamin B12	NR	QD (n = 47)	28	Switzerland
Kronish, 2010[13]	O	CAD	59	53	Aspirin	No	QD (n = 105)	84	United States
Platt, 2010[14]	O	Anticoagulation	55	65	Warfarin	No	QD (n = 114)	141 (median)	United States
Stilley, 2010[15]	O/R	Hyperlipidemia	46	54	Lovastatin/placebo	No	QD (n = 157)	168	United States
Grosset, 2009[16]	O	Parkinson's disease	65	71	Antiparkinson agents	NR	QD (n = 57) BID (n = 44) TID (n = 113) QID (n = 57)	28 (median)	European countries
Udelson, 2009[17]	R	HF	~65	73	Beta-blockers	No	QD (n = 135) BID (n = 135) BID (n = 131)	140	United States
Yentzer, 2008[18]	O	Psoriasis	50	63	Acitretin	NR	QD (n = 22)	84	United States
Kardas, 2007[19]	R	Stable angina	57	41	Beta-blockers	No	QD (n = 47) BID (n = 49)	66	Poland
Rand, 2007[20]	O/R	Asthma	35	30	Montelukast/placebo	NR	QD (n = 346)	84	United States
Grosset, 2007[21] (Pre-intervention phase only)	O/R	Parkinson's disease	~61-65	38	Antiparkinson agents	NR	QD (n = 34) BID (n = 15) TID (n = 68) QID (n = 28)	84	United Kingdom
Márquez-Contreras, 2006[22] (Standard education arm only)	O/R	HTN	59	50	Antihypertensives	NR	QD (n = 100)	184	Spain
Charpentier, 2005[23]	R	T2DM	56	61	Sulfonylureas	NR	QD (n = 100) BID (n = 33) TID (n = 68)	187	France
Kardas, 2005[24]	R	T2DM	~61	46	Sulfonylureas	No	QD (n = 49) BID (n = 48)	121-123	Poland
Tu, 2005[25]	O/R	HF	62	31	Metoprolol	NR	BID (n = 80)	180-360	United States
Buelow, 2004[26]	O	Epilepsy	38	36	Antiepileptics	NR	BID (n = 15) TID (n = 4) QID (n = 2)	28[a]	United States
Clowes, 2004[27] ("No monitoring" arm only)	O/R	Osteopenia	62	0	Raloxifene	Yes	QD (n = 24)	336	United Kingdom
Girvin, 2004[30]	O/R	HTN	NR	NR	Antihypertensives	No	QD (n = 23)	84	United Kingdom
Kardas, 2004[28]	R	Stable angina	64	41	Isosorbide mononitrate	No	QD (n = 50) BID (n = 50)	62-64	Poland
de Klerk, 2003[29]	O	RA, PMR, gout	~63	43	RA, PMR, and gout drugs	No	QD (n = 17) QD (n = 12) QD (n = 17) BID (n = 20) BID (n = 25) TID (n = 13)	210	Netherlands
Hamilton, 2003[31]	O/R	HTN	58	51	Potassium/placebo	No	TID (n = 106) TID (n = 106)	28	United States
Laporte, 2003[32] (Standard education arms only)	O/R	Anticoagulation	67	41	Vitamin K antagonists	Yes	QD (n = 42)	83 (median)	France
Bohachick, 2002[6]	O	HF	56	70	ACE inhibitors	No	QD (n = 69) BID (n = 74) TID (n = 26)	84	United States
Winkler, 2002[33]	O	T2DM	69	68	Sulfonylureas	Yes	QD (n = 11) BID (n = 7)	54	Switzerland
Chung, 2000[34]	O	Asthma	29	56	Zafirlukast	Yes	BID (n = 47)	84	United Kingdom
Schwed, 1999[36]	O	Primary type II hyperlipidemia	57	100	Fluvastatin	No	QD (n = 39)	28	Switzerland

TABLE 1 Characteristics of Included Studies *(continued)*

First Author, Year	Study Design	Disease State	Mean Age (Years)	Percent Male (%)	Drug Class	Blinded to EM?	Dosing Frequencies (n=)	Mean Duration of Follow-Up (Days)	Country
Waeber, 1999a[37]	O/R	HTN	61	60	Aspirin/placebo	No	QD (n=501)	365	European countries
Waeber, 1999b[38]	O	HTN	79	63	Antihypertensives	No	QD (n=35)	84	Switzerland
Girvin, 1998[35]	R	HTN	62	64	Enalapril	NR	QD (n=25)[b] BID (n=25)[b]	112	United Kingdom
Mulleners, 1998[39]	O	Migraine	NR	26	Beta-blockers, pizotifen, or methysergide	Yes	QD (n=11) BID (n=11) TID (n=7)	54	United Kingdom
Rivers, 1998[40]	O	Epilepsy	34	67	Antiepileptics	No	BID (n=5)	84	United Kingdom
Leenen, 1997[41]	R	HTN	55	62	CCBs	No	QD (n=103) BID (n=82)	140	Canada
Paes, 1997[42]	O	T2DM	~69	40	Oral antidiabetic drugs	Yes	QD (n=40) BID (n=36) TID (n=15)	155	Netherlands
Vrijens, 1997[43]	O/R	HTN	NR	NR	Enalapril	NR	QD (n=127)	42	Belgium
de Klerk, 1996[44]	O/R	Ankylosing spondylitis	NR	NR	NSAIDs	No	QD (n=65)	225	Netherlands
Mallion, 1996[45]	O	HTN	58	58	Trandolapril	No	QD (n=501)	32	France
Mason, 1996a[46]	O	T2DM	68	100	Sulfonylureas	NR	QD (n=40) BID (n=30)	NR	United States
Mason, 1996b[47]	O	Anticoagulation	65	NR	Warfarin	Yes	QD (n=20)	60	United States
Straka, 1996[48]	O	Ischemic heart disease	67	37	Isosorbide dinitrate	No	TID (n=68)[c]	28	United States
Cramer, 1995[49]	O	Epilepsy	NR	NR	Antiepileptics	NR	BID (n=66) BID (n=66) TID (n=36) QID (n=23)	189	Canada
Brun, 1994[50]	R	Stable angina	~64	65	Isosorbide mononitrate	No	QD (n=16) BID (n=15)	78-79	Sweden
Kruse, 1994[51]	O	HTN	62	54	Antihypertensives	No	QD (n=15) BID (n=9)	214	Germany
Steiner, 1994[52]	O	Migraine	45	22	Pizotifen	Yes	TID (n=4)	56	United Kingdom
Kruse, 1993[53]	O/R	Familial hyper-cholesterolemia	~47	71	Lovastatin and placebo	No	QD (n=12)[b] QD (n=12)[b] QD (n=12)[b] QD (n=12)[b]	28	Germany
Rudd, 1993[54]	O	Chronic cardiovascular conditions	54	68	Cardiovascular medications	NR	QD (n=20) BID (n=8) TID (n=2)	84	United States
Rudd, 1992[55]	O/R	HTN	57	67	CCB or ACE inhibitor	No	BID (n=18)	147	United States
Eisen, 1990[56]	O/R	HTN	61 (median)	100	Antihypertensives	No	QD (n=45) BID (n=40) TID (n=20)	140	United States
Kruse, 1990[57]	O	Various chronic diseases	50	58	Antiepileptics, cardiac glycosides, lipid-lowering drugs, antidiabetic agents, diuretics, beta-blocker, aspirin, or theophylline	Mixed[d]	QD (n=12) BID (n=5) BID (n=4) TID (n=4) TID (n=4)	42	Germany
Cramer, 1989[58]	O	Epilepsy	NR	50	Antiepileptics	No	QD (n=3) BID (n=12) TID (n=7) QID (n=4)	132	United States
Eisen, 1987[59]	O	HTN	61 (median)	100	Thiazide diuretics	No	QD (n=24)	103	United States

[a]*Twenty-eight-day follow-up requested of study participants.*
[b]*Crossover study.*
[c]*TID regimen with a 10-hour nitrate-free period.*
[d]*Twenty-one patients were blinded to MEMS; 10 patients were not.*

ACE inhibitors = angiotensin-converting enzyme inhibitors; BID = twice daily; CAD = coronary artery disease; CCB = calcium channel blocker; EM = electronic monitoring; HF = heart failure; HTN = hypertension; MEMS = Medication Event Monitoring System; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; O = observational; O/R = observational analysis of data obtained from a randomized controlled trial; PMR = polymyalgia rheumatica; QD = once daily; QID = 4 times daily; R = randomized; RA = rheumatoid arthritis; T2DM = type 2 diabetes mellitus; TID = 3 times daily.

TABLE 2 *Taking, Regimen, and Timing Adherence Data for Included Studies*

Study, Year	Taking Adherence Mean (±SE) Percentage				Regimen Adherence Mean (±SE) Percentage				Timing Adherence Mean (±SE) Percentage			
	QD	BID	TID	QID	QD	BID	TID	QID	QD	BID	TID	QID
Clerisme-Beaty, 2011[10]	—	—	—	—	47.8±2.3 52.0±2.2	—	—	—	—	—	—	—
Doró, 2011[11]	98.4±0.8	92.9±2.8	88.4±6.0	—	—	—	—	—	91.1±2.4	60.4±11.7	54.3±10.0	—
Favrat, 2011[12]	98.6±1.6	—	—	—	93.1±1.9	—	—	—	89.8±2.6	—	—	—
Kronish,2010[13]	—	—	—	—	87.0±1.6	—	—	—	—	—	—	—
Platt, 2010[14]	—	—	—	—	78.8±1.8	—	—	—	—	—	—	—
Stilley, 2010[15]	81.1±2.1	—	—	—	70.7±2.0	—	—	—	—	—	—	—
Grosset, 2009[16]	101.3±2.0	97.3±2.4	92.1±1.7	84.4±3.0	92.0±2.0	75.4±3.9	77.4±2.4	56.4±4.3	87.1±2.8	29.1±7.3	26.2±1.7	12.0±2.0
Udelson, 2009[17]	88.2±2.1	89.3±1.8 87.1±2.2	—	—	—	—	—	—	—	—	—	—
Yentzer, 2008[18]	—	—	—	—	78.8±3.4	—	—	—	—	—	—	—
Kardas, 2007[19]	86.5±3.1	76.1±3.8	—	—	84.4±3.2	64.0±4.5	—	—	58.6±4.7	42.0±4.0	—	—
Rand, 2007[20]	—	—	—	—	77.5±1.2	—	—	—	—	—	—	—
Grosset, 2007[21]	—	—	—	—	—	—	—	—	76.4±3.8	28.5±7.2	22.2±2.4	13.7±1.3
Márquez-Contreras, 2006[22]	87.7±2.4	—	—	—	83.7±2.3	—	—	—	79.9±2.8	—	—	—
Charpentier, 2005[23]	87.0±1.6	84.0±2.6	79.0±2.1	—	87.0±1.6	—	—	—	—	—	—	—
Kardas, 2005[24]	93.5±2.0	87.2±3.0	—	—	86.3±2.2	66.9±4.2	—	—	62.0±3.2	43.2±3.8	—	—
Tu, 2005[25]	—	63.0±3.8	—	—	—	—	—	—	—	32.7±3.5	—	—
Beulow, 2004[26]	—	—	—	—	—	58.3±10.2	31.8±19.0	91.5±6.9	—	—	—	—
Clowes, 2004[27]	74.0±8.0	—	—	—	—	—	—	—	—	—	—	—
Girvin, 2004[30]	96.8±1.3	—	—	—	—	—	—	—	79.6±2.1	—	—	—
Kardas, 2004[28]	88.9±2.3	73.8±3.6	—	—	85.5±2.3	59.5±4.7	—	—	59.1±3.9	49.4±4.0	—	—
de Klerk, 2003[29]	96.0±3.3 65.0±8.4 84.0±4.1	82.0±3.8 72.0±6.1	77.0±8.2	—	88.0±2.3 44.0±9.2 74.0±5.6	68.0±5.9 55.0±5.9	67.0±10.2	—	—	—	—	—
Hamilton, 2003[31]	—	—	63.0±2.6	—	—	—	—	—	—	—	58.4±2.6	—
Laporte, 2003[32]	—	—	—	—	80.7±3.0	—	—	—	—	—	—	—
Bohachick, 2002[6]	97.6±1.5	93.1±1.5	88.9±2.7	—	90.1±2.0	83.8±2.8	68.4±5.8	—	87.9±2.3	69.7±3.5	52.6±5.3	—
Winkler, 2002[33]	101.0±1.4	82.9±10.7	—	—	93.6±1.7	63.4±12.1	—	—	—	—	—	—
Chung, 2000[34]	—	80.0±3.5	—	—	—	—	—	—	—	64.0±3.8	—	—
Schwed, 1999[36]	94.3±1.5	—	—	—	88.1±2.4	—	—	—	88.2±2.1	—	—	—
Waeber, 1999a[37]	—	—	—	—	78.2±1.1	—	—	—	—	—	—	—
Waeber, 1999b[38]	—	—	—	—	80.8±3.5	—	—	—	—	—	—	—
Girvin, 1998[35]	101.2±1.2	90.1±2.4	—	—	92.2±1.6	72.6±3.7	—	—	76.2±2.7	29.6±3.4	—	—
Mulleners, 1998[39]	—	—	—	—	79.8±5.2	60.0±9.0	54.2±10.6	—	—	—	—	—
Rivers, 1998[40]	—	—	—	—	—	88.6±5.5	—	—	—	—	—	—
Leenen, 1997[41]	94.0±1.0	91.0±2.0	—	—	90.0±2.0	82.0±2.0	—	—	86.0±2.0	76.0±2.0	—	—
Paes, 1997[42]	98.7±3.0	83.1±4.3	65.8±8.5	—	79.1±3.0	65.6±4.5	38.1±8.6	—	77.7±3.4	40.7±4.9	5.3±1.5	—
Vrijens, 1997[43]	94.3±1.0	—	—	—	—	—	—	—	—	—	—	—
de Klerk, 1996[44]	—	—	—	—	78.0±3.1	—	—	—	—	—	—	—
Mallion, 1996[45]	90.8±0.9	—	—	—	—	—	—	—	—	—	—	—
Mason, 1996a[46]	—	—	—	—	89.6±2.1	81.3±4.3	—	—	—	—	—	—
Mason, 1996b[47]	—	—	—	—	86.0±3.8	—	—	—	—	—	—	—
Straka 1996[48]	—	—	—	—	—	—	66.0±3.5	—	—	—	—	—
Cramer, 1995[49]	—	—	—	—	—	89.0±0.9 86.0±1.4	80.0±3.0	80.0±4.8	—	66.0±3.0 59.0±3.2	40.0±3.2	33.0±3.8
Brun, 1994[50]	99.0±0.9	95.0±3.1	—	—	98.0±0.8	87.8±6.1	—	—	58.0±14.7	48.8±9.6	—	—
Kruse, 1994[51]	88.8±4.6	87.9±6.9	—	—	84.8±5.9	79.8±8.2	—	—	—	—	—	—
Steiner, 1994[52]	—	—	—	—	—	—	58.4±14.5	—	—	—	32.8±6.7	—
Kruse, 1993[53]	92.0±4.5 90.4±5.4 95.3±2.0 88.7±3.3	—	—	—	—	—	—	—	67.3±8.4 60.9±9.6 66.8±7.6 62.2±7.3	—	—	—
Rudd, 1993[54]	81.8±5.3	75.9±12.7	72.4±19.8	—	—	—	—	—	—	—	—	—
Rudd, 1992[55]	—	84.4±4.2	—	—	—	60.5±4.7	—	—	—	46.3±4.3	—	—
Eisen, 1990[56]	96.0±1.0	93.0±1.9	83.8±3.4	—	83.6±3.0	74.9±3.2	59.0±6.8	—	—	—	—	—
Kruse, 1990[57]	77.1±6.4	—	—	—	76.5±4.6	61.4±12.4 85.0±5.3	54.0±7.3 46.6±5.4	—	—	—	—	—
Cramer, 1989[58]	—	—	—	—	87.0±6.4	81.0±4.9	77.0±4.5	39.0±12.0	—	—	—	—
Eisen, 1987[59]	97.0±1.6	—	—	—	—	—	—	—	84.0±3.1	—	—	—

BID = twice daily; QD = once daily; QID = 4 times daily; SE = standard error; TID = 3 times daily; — = data not available.

TABLE 3 *Traditional Meta-Analysis of Dosing Frequency Analyses of Taking, Regimen, and Timing Adherence*[a]

Frequency of Dosing	N (%) Groups [N of Patients] in Taking Adherence Analysis	Taking Adherence[b] (95% CI)	N (%) Groups [N of Patients] in Regimen Adherence Analysis	Regimen Adherence[c] (95% CI)	N (%) Groups [N of Patients] in Timing Adherence Analysis	Timing Adherence[d] (95% CI)
Once daily	33 (50.8) [n = 2,006]	93.0 (91.2-94.7)	35 (46.1) [n = 2,118]	81.8 (77.9-85.7)	20 (42.6) [n = 936]	76.9 (72.5-81.3)
Twice daily	22 (33.8) [n = 1,259]	85.6 (82.5-88.8)	24 (31.6) [n = 826]	74.2 (70.0-78.5)	16 (34.0) [n = 650]	59.3 (40.6-58.0)
Three times daily	9 (13.8) [n = 362]	80.1 (72.0-88.2)	13 (17.1) [n = 321]	62.8 (55.4-70.1)	8 (17.0) [n = 343]	35.9 (21.8-50.1)
Four times daily	1 (1.5) [n = 57]	84.4 (78.5-90.3)	4 (5.3) [n = 86]	68.2 (48.9-87.4)	3 (6.4) [n = 109]	18.8 (10.1-27.5)

[a]*Weighted by the inverse of the variance of medication adherence.*
[b]*Taking adherence was defined as the number of openings divided by the prescribed number of doses.*
[c]*Regimen adherence was defined as the percentage of days with the appropriate number of doses taken.*
[d]*Timing adherence was defined as the percentage of near optimal interadministration intervals.*
CI = confidence interval.

TABLE 4 *Results of Meta-Regression Analyses of Taking, Regimen, and Timing Adherence*[a]

Study-Level Factor	Adjusted Difference in Taking Adherence[b] (95% CI)	Adjusted Difference in Regimen Adherence[c] (95% CI)	Adjusted Difference in Timing Adherence[d] (95% CI)
Frequency of dosing			
Once daily	Referent	Referent	Referent
Twice daily	–6.7 (–11.0 to –2.4)	–13.1 (–19.6 to –6.6)	–26.7 (–35.8 to –17.8)
Three times daily	–13.5 (–19.4 to –7.6)	–24.9 (–33.1 to –16.7)	–39.0 (–51.2 to –26.8)
Four times daily	–19.2 (–36.3 to –2.1)	–23.1 (–37.0 to –9.2)	–54.2 (–71.8 to –36.6)
Year of publication			
After 2000	–0.8 (–5.1 to 3.5)	–4.6 (–10.3 to 1.1)	–0.7 (–9.3 to 7.9)
2000 or prior	Referent	Referent	Referent
Country			
United States	–3.2 (–8.1 to 1.7)	–4.5 (–12.3 to 3.3)	6.5 (–4.9 to 17.9)
Not United States	Referent	Referent	Referent
Study design			
Randomized	–2.8 (–8.1 to 2.5)	–3.1 (–13.3 to 7.1)	–13.1 (–24.4 to –1.3)
O/R	–2.5 (–7.4 to 2.4)	–4.2 (–13.2 to 4.8)	–14.7 (–24.1 to –5.3)
Observational	Referent	Referent	Referent
Blinded to EM			
Yes	–10.1 (–18.7 to –1.5)	–12.4 (–21.8 to –3.0)	–11.7 (–33.1 to 9.7)
No/Indeterminate	Referent	Referent	Referent
Disease state			
Cardiovascular	Referent	Referent	Referent
Neurologic	7.7 (–2.3 to 17.7)	1.5 (–7.3 to 10.3)	–7.4 (–19.2 to 4.4)
Type 2 diabetes	4.5 (–3.3 to 12.3)	0.0 (–9.4 to 9.4)	–8.2 (–25.1 to 8.7)
Asthma	–0.1 (–17.0 to 17.2)	–21.0 (–36.4 to –5.1)	17.5 (–14.3 to 49.3)
Other/mixed	–2.9 (–10.5 to 4.7)	–7.6 (–16.8 to 1.6)	20.2 (–6.1 to 46.5)
Follow-up at least 168 days			
Yes	–8.7 (–14.4 to –3.0)	–2.6 (–10.8 to 5.6)	4.6 (–7.9 to 17.1)
No	Referent	Referent	Referent

[a]*Results from a multiple-linear, mixed-method model controlling for the study-level factors shown in the table.*
[b]*Taking adherence was defined as the number of openings divided by the prescribed number of doses.*
[c]*Regimen adherence was defined as the percentage of days with the appropriate number of doses taken.*
[d]*Timing adherence was defined as the percentage of near optimal interadministration intervals.*
CI = confidence interval; EM = electronic monitoring; O/R = observational analysis of data obtained from a randomized controlled trial.

group). Neither randomization by dosing frequency nor *post hoc* observational analysis of randomized trial data were significant predictors of taking or regimen adherence compared with observational analysis (reference group); however, randomized design was associated with reduced timing adherence.

Discussion

This meta-analysis found that patients with chronic diseases are most adherent to medication regimens that require them to take drugs once daily compared with more frequent dosing regimens based on electronic measurement of adherence.

Specifically, twice-daily, 3-times daily, and 4-times daily dosing regimens had progressively lower weighted mean adherence rates compared with once-daily regimens, a finding that was robust to multiple adherence definitions. While timing adherence may not be clinically important for every drug, the consistent finding that more frequent dosing was associated with decreased adherence across all the definitions lends credence to our results.

However, even the use of once-daily regimens did not guarantee perfect adherence (76.9% to 93.0%); therefore, one can conclude that frequency is not the only modifier of adherence. Other factors that were independently negatively associated with medication-taking adherence included blinding to electronic monitoring and longer follow-up periods. In addition, regimen adherence was statistically significantly lower when the chronic disease studied was asthma compared with cardiovascular disease. Typically, adherence rates increase when patients know they are being watched, and as expected, patients blinded to electronic monitoring demonstrated decreased adherence in this analysis. The finding that longer follow-up periods led to decreased adherence was expected, as adherence rates in chronic conditions typically drop off most significantly after 6 months.[5] The reduced adherence rate in studies of asthma is difficult to explain as there were only 3 studies, and all 3 included only second-line therapies. One may speculate that patients may have been nonadherent due to lack of efficacy or that the disease state itself has an impact on adherence; however, more data are needed to draw an accurate conclusion. Timing adherence was also decreased when researchers used a randomized trial design.

Claxton et al., who produced the most recent meta-analysis of the effect of dosing frequency on adherence, used methods to statistically pool data from included trials to evaluate taking adherence across multiple dose frequencies.[3] They found that taking adherence was significantly higher with once-daily compared with 3-times or 4-times daily regimens (79%, 65%, and 51%, respectively; $P<0.001$) and with twice-daily compared with 4-times daily regimens (69% vs. 51%; $P=0.001$). However, the researchers found no significant differences between the once-daily and twice-daily or twice-daily and 3-times daily treatment regimens after Bonferroni adjustment of P values.

A lack of data may have prohibited Claxton et al. from achieving enough statistical power to detect a true difference. This problem was a primary reason for conducting the present study, as an additional 26 studies published after the study by Claxton et al. were included. Also of concern was the method by which Claxton et al. performed their statistical analysis. According to the Cochrane Handbook for Systematic Reviews, when conducting a meta-analysis, studies should be weighted based upon the inverses of their variances; in other words, studies with more precise estimates have a larger impact on the final results.[60] Claxton et al. instead calculated simple averages of the mean adherence rates of all the included studies. This approach may have been reasonable at the time but is an imperfect technique by today's standards.

Similar to the current analysis, Claxton et al. included a heterogeneous patient population. However, Claxton et al. included both acute and chronic diseases along with various dosage forms (e.g., oral, inhaled, topical, and ophthalmic) in the analysis. Such heterogeneous disease states and dosage forms likely had a major confounding effect on their results. Without correction for this heterogeneity, application of the results remains challenging. The present study addressed these issues by excluding studies of nonoral dosage forms and acute disease states as well as attempting to correct for confounding through statistical techniques. Both traditional random-effects meta-analysis (which assumes that studies are estimating different but related effects and therefore makes an adjustment to the studies' weighting based upon the extent of variation or heterogeneity between them [often measured by the Cochrane Q or I2 statistic]) and multivariate mixed-linear model meta-regression analysis were conducted.[60] Meta-regression was used to adjust for the potential confounding effect of other study-level characteristics.

It is estimated that almost 90% of Americans aged 60 years or older take at least 1 prescription medication, typically on a scheduled basis.[61] Despite evidence for an association between medication adherence and improved quality of life, medication adherence rates for patients with chronic conditions are estimated at only 50%-60%.[62-67] The effectiveness of prescription drugs for chronic diseases is likely diminished when patient adherence is suboptimal; thus, it is not surprising that poor medication adherence has been associated with higher morbidity, mortality, and health care costs.[68-74] Of note, it is thought that 33%-69% of medication-related hospital admissions in the United States are the result of poor medication adherence, with a total estimated price tag of more than $100 billion per year.[68,69,75,76] Consequently, it would seem prudent to take reasonable steps to improve patient medication adherence, such as the selection of drugs with less frequent daily dosing, while at the same time remembering to consider whether any additional costs will be outweighed by the benefits.

Limitations

There are some limitations to the meta-analysis that should be noted. First, much of the published medication adherence literature involves studies of small sample sizes and in populations with differing disease states. In an attempt to overcome these obstacles, we conducted a multivariate meta-regression analysis to adjust for multiple study-level characteristics.[4] However, it is unlikely we were able to adjust for all important sources of heterogeneity between studies, and we cannot rule out the presence of residual confounding. These realities have made it more difficult to draw firm conclusions regarding the

association between dosing frequency and medication adherence.

Second, monitoring adherence via electronic devices may not be considered a "real-world" process; however, these devices do provide the most detailed data on adherence. Patient self-reports often suffer from erroneous accounts of taken or missed doses, while blood-level monitoring may indicate only whether a patient took the most recent doses. Prescription refills also provide questionable adherence information because they do not indicate the timing of intake, whereas electronic monitoring devices are able to provide those data.[3]

A third limitation is the small sample sizes of the 4-times daily groups. It is unlikely that there will be a time when a physician must choose between once-daily and 4-times daily medications; however, including 4-times daily groups in the analysis at the very least verifies the notion that there is an inverse relationship between dosing frequency and medication adherence. Fourth, there is also concern that the exclusion of studies with suboptimal reporting could have affected the present study results. Through the literature search, a number of studies were identified that could have provided useful data for this analysis but had to be excluded due to their failure to report a measure of statistical variance (a standard deviation, standard error, or confidence interval). Despite great effort in contacting the corresponding authors to obtain the information that would have allowed us to include these studies, not all authors responded to the requests.

Conclusion

Although the heterogeneous population precludes the ability to draw firm conclusions regarding specific diseases and adherence rates, this analysis demonstrated an inverse relationship between medication adherence and dosing frequency in patients with chronic disease.

Authors

CRAIG I. COLEMAN, PharmD, is Associate Professor of Pharmacy Practice, and DIANA M. SOBIERAJ, PharmD, is Assistant Professor of Pharmacy Practice, University of Connecticut, Hartford, Connecticut. BRENDAN LIMONE, PharmD, is Health Economics and Outcomes Research Fellow; SOYON LEE, PharmD, is Health Economics and Outcomes Research Fellow; MATTHEW S. ROBERTS, BS, is Research Scientist; RAJBIR KAUR, PharmD, is Health Economics and Outcomes Research Fellow; and TAWFIKUL ALAM, MD, is Research Scientist, Hartford Hospital, Hartford, Connecticut.

AUTHOR CORRESPONDENCE: Craig I. Coleman, PharmD, Associate Professor of Pharmacy Practice, University of Connecticut School of Pharmacy, 80 Seymour St., Hartford, CT 06102-5037. Tel.: 860.545.2096; Fax: 860.545.2277; E-mail: ccolema@harthosp.org.

DISCLOSURES

The first author has received significant grant funding and has participated on a speaker board for Janssen Pharmaceuticals. The remaining authors report no financial or other conflicts of interest. This research was supported by a grant from Janssen Scientific Affairs. The authors of this report take full responsibility for the integrity, accuracy, and content of the report. The funding source had no role in the design and conduct of the study, data collection, management, analysis, and interpretation of the data, or preparation of the manuscript. The funding source reviewed and approved the final manuscript.

Concept and design were performed by Coleman and Sobieraj. The data were collected by Alam, Kaur, Lee, and Roberts. Data analysis was performed by Coleman, Limone, and Sobieraj. The manuscript was written primarily by Coleman, Sobieraj, and Roberts and was revised primarily by Coleman and Limone.

ACKNOWLEDGMENTS

The authors would like to thank study authors Drs. Karina W. Davidson, Peter Doró, Richard Eastell, Bernard Favrat, Katherine Grosset, Ian Kronish, and Paul Vaucher for providing additional data from their studies needed to conduct this analysis.

REFERENCES

1. Centers for Disease Control and Prevention. Chronic disease prevention and health promotion. Available at: http://www.cdc.gov/nccdphp/. Accessed July 27, 2012.

2. Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. *Am J Manag Care*. 2009;15(6):e22-33. Available at: http://www.ajmc.com/articles/AJMC_09JunSaini_Xclusiv_e22to33. Accessed July 27, 2012.

3. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23(8):1296-310.

4. Kalaian HA, Raudenbush SW. A multivariate mixed linear model for meta-analysis. *Psychological Methods.* 1996;1(3):227-35.

5. Osterberg L, Blaske T. Adherence to medication. *New Engl J Med.* 2005;353(5):487-97.

6. Bohachick P, Burke LE, Sereika S, Murali S, Dunbar-Jacob J. Adherence to angiotensin-converting enzyme inhibitor therapy for heart failure. *Prog Cardiovasc Nurs.* 2002;17(4):160-66.

7. Mevacor (Lovastatin). Merck & Co., Inc. February 2012. Available at: http://www.merck.com/product/usa/pi_circulars/m/mevacor/mevacor_pi.pdf. Accessed July 27, 2012.

8. Chase TN. The significance of continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Drugs.* 1998;55(Suppl 1):S1-S9.

9. Amsterdam EA. Rationale for intermittent nitrate therapy. *Am J Cardiol.* 1992;70(17):55G-59G.

10. Clerisme-Beaty EM, Bartlett SJ, Teague WG, et al. The Madison Avenue effect: how drug presentation style influences adherence and outcome in patients with asthma. *J Allergy Clin Immunol.* 2011;127(2):406-11. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3050545/?tool=pubmed. Accessed July 27, 2012.

11. Doró P, Benko R, Czakó A, Matuz M, Thurzó F, Soós G. Optimal recall period in assessing the adherence to antihypertensive therapy: a pilot study. *Int J Clin Pharm.* 2011;33(4):690-95.

12. Favrat B, Vaucher P, Herzig L, et al. Oral vitamin B12 for patients suspected of subtle cobalamin deficiency: a multicentre pragmatic randomised controlled trial. *BMC Fam Pract.* 2011;12:2. Available at: http://www.biomedcentral.com/1471-2296/12/2. Accessed July 27, 2012.

13. Kronish IM, Rieckmann N, Shimbo D, Burg M, Davidson KW. Aspirin adherence, aspirin dosage, and C-reactive protein in the first 3 months after acute coronary syndrome. *Am J Cardiol.* 2010;106(8):1090-94. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2967432/?tool=pubmed. Accessed July 27, 2012.

14. Platt AB, Localio AR, Brensinger CM, et al. Can we predict daily adherence to warfarin? Results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) Study. *Chest*. 2010;137(4):883-89. Available at: http://chestjournal.chestpubs.org/content/137/4/883.long. Accessed July 27, 2012.

15. Stilley CS, Bender CM, Dunbar-Jacob J, Sereika S, Ryan CM. The impact of cognitive function on medication management: three studies. *Health Psychol.* 2010;29(1):50-55. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2807986/?tool=pubmed. Accessed July 27, 2012.

16. Grosset D, Antonini A, Canesi M, et al. Adherence to antiparkinson medication in a multicenter European study. *Mov Discord*. 2009;24(6):826-32.

17. Udelson JE, Pressler SJ, Sackner-Bernstein J, et al. Adherence with once daily versus twice daily carvedilol in patients with heart failure: the Compliance And Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol CR and Twice-Daily Immediate-Release Carvedilol IR in Patients with Heart Failure (CASPER) Trial. *J Card Fail*. 2009;15(5):385-93.

18. Yentzer BA, Yelverton CB, Pearce DJ, et al. Adherence to acitretin and home narrowband ultraviolet B phototherapy in patients with psoriasis. *J Am Acad Dermatol.* 2008;59(4):577-81.

19. Kardas P. Compliance, clinical outcome, and quality of life of patients with stable angina pectoris receiving once-daily betaxolol versus twice daily metoprolol: a randomized controlled trial. *Vasc Health Risk Manag.* 2007;3(2):235-42. Available at: http://www.dovepress.com/articles.php?article_id=1478. Accessed July 27, 2012.

20. Rand C, Bilderback A, Schiller K, Edelman JM, Hustad CM, Zeiger RS; MIAMI Study Research Group. Adherence with montelukast or fluticasone in a long-term clinical trial: results from the mild asthma montelukast versus inhaled corticosteroid trial. *J Allergy Clin Immunol*. 2007;119(4):916-23.

21. Grosset KA, Grosset DG. Effect of educational intervention on medication timing in Parkinson's disease: a randomized controlled trial. *BMC Neurol.* 2007;7:20. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1931606/pdf/1471-2377-7-20.pdf. Accessed July 27, 2012.

22. Márquez-Contreras E, Martell-Claros N, Gil-Guillén V, et al.; Compliance Group of the Spanish Society of Hypertension (SEE). Efficacy of a home blood pressure monitoring programme on therapeutic compliance in hypertension: the EAPACUM-HTA study. *J Hypertens.* 2006;24(1):169-75.

23. Charpentier G, Fleury F, Dubroca I, Vaur L, Clerson P. Electronic pill-boxes in the evaluation of oral hypoglycemic agent compliance. *Diabetes Metab.* 2005;31(2):189-95.

24. Kardas P. The DIACOM study (effect of DosIng frequency of oral Antidiabetic agents on the COMpliance and biochemical control of type 2 diabetes). *Diabetes Obes Metab.* 2005;(6):722-28.

25. Tu W, Morris AB, Li J, et al. Association between adherence measurements of metoprolol and health care utilization in older patients with heart failure. *Clin Pharmacol Ther.* 2005;77(3):189-201. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2577028/?tool=pubmed. Accessed July 27, 2012.

26. Buelow JM, Smith MC. Medication management by the person with epilepsy: perception versus reality. *Epilepsy Behav.* 2004;5(3):401-06.

27. Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. *J Clin Endocrinol Metab.* 2004;89(3):1117-23. Available at: http://jcem.endojournals.org/content/89/3/1117.long. Accessed July 27, 2012.

28. Kardas P; COMPASS Investigators. Comparison of once daily versus twice daily oral nitrates in stable angina pectoris. *Am J Cardiol.* 2004;94(2):213-16.

29. de Klerk E, van der Heijde D, Landewé R, van der Tempel H, Urquhart J, van der Linden S. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. *J Rheumatol*. 2003;30(1):44-54. Erratum in: *J Rheumatol.* 2003;30(2):423.

30. Girvin BG, Johnston GD. Comparison of the effects of a 7-day period of non-compliance on blood pressure control using three different antihypertensive agents. *J Hypertens.* 2004;22(7):1409-14.

31. Hamilton GA. Measuring adherence in a hypertension clinical trial. *Eur J Cardiovasc Nurs.* 2003;2(3):219-28.

32. Laporte S, Quenet S, Buchmüller-Cordier A, et al. Compliance and stability of INR of two oral anticoagulants with different half-lives: a randomised trial. *Thromb Haemost.* 2003;89(3):458-67.

33. Winkler A, Teuscher AU, Mueller B, Diem P. Monitoring adherence to prescribed medication in type 2 diabetic patients treated with sulfonylureas. *Swiss Med Wkly.* 2002;132(27-28):379-85. Available at: http://www.smw.ch/for-readers/archive/backlinks/?url=/docs/archive200x/2002/27/smw-10036.html. Acessed July 27, 2012.

34. Chung KF, Naya I. Compliance with an oral asthma medication: a pilot study using an electronic monitoring device. *Respir Med*. 2000;94(9):852-58.

35. Girvin B, Johnston GD. A randomized comparison of a conventional dose, a low dose and alternate-day dosing of bendrofluazide in hypertensive patients. *J Hypertens.* 1998;16(7):1049-54.

36. Schwed A, Fallab CL, Burnier M, et al. Electronic monitoring of compliance to lipid-lowering therapy in clinical practice. *J Clin Pharmacol.* 1999;39(4):402-09.

37. Waeber B, Leonetti G, Kolloch R, McInnes GT. Compliance with aspirin or placebo in the Hypertension Optimal Treatment (HOT) study. *J Hypertens.* 1999;17(7):1041-45.

38. Waeber B, Vetter W, Darioli R, Keller U, Brunner HR. Improved blood pressure control by monitoring compliance with antihypertensive therapy. *Int J Clin Pract.* 1999;53(1):37-38.

39. Mulleners WM, Whitmarsh TE, Steiner TJ. Noncompliance may render migraine prophylaxis useless, but once-daily regimens are better. *Cephalalgia.* 1998;18(1):52-56.

40. Rivers PH, Ardagh-Walter N, Wright EC. Measurement of anticonvulsant adherence behaviour in the community using a Medication Events Monitoring System (MEMS). *Health Care Anal.* 1998;6(4):308-16.

41. Leenen FH, Wilson TW, Bolli P, et al. Patterns of compliance with once versus twice daily antihypertensive drug therapy in primary care: a randomized clinical trial using electronic monitoring. *Can J Cardiol.* 1997;13(10):914-20.

42. Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. *Diabetes Care.* 1997;20(10):1512-17.

43. Vrijens B, Goetghebeur E. Comparing compliance patterns between randomized treatments. *Control Clin Trials.* 1997;18(3):187-203.

44. de Klerk E, van der Linden SJ. Compliance monitoring of NSAID drug therapy in ankylosing spondylitis, experiences with an electronic monitoring device. *Br J Rheumatol*. 1996;35(1):60-65. Available at: http://rheumatology.oxfordjournals.org/content/35/1/60.long. Accessed July 27, 2012.

45. Mallion JM, Dutrey-Dupagne C, Vaur L, et al. Benefits of electronic pill-boxes in evaluating treatment compliance of patients with mild to moderate hypertension. *J Hypertens.* 1996;14(1):137-44.

46. Mason BL, Matsuyama JR, Jue SG. Microprocessor-assessed adherence with once- or twice-a-day dosing with Sulfonylurea—no difference. *West J Med.* 1996;164(2):182. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1303401/?tool=pubmed. Accessed July 27, 2012.

47. Mason B. Anticoagulant clinic warfarin adherence rates and assessment. *J Pharm Technol.* 1996;12(3):97-101.

48. Straka RJ, Fish JT, Benson SR, Suh JT. Magnitude and nature of noncompliance with treatment using isosorbide dinitrate in patients with ischemic heart disease. *J Clin Pharmacol.* 1996;36(7):587-94.

49. Cramer J, Vachon L, Desforges C, Sussman NM. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. *Epilepsia*. 1995;36(11):1111-17.

50. Brun J. Patient compliance with once-daily and twice-daily oral formulations of 5-isosorbide mononitrate: a comparative study. *J Int Med Res*. 1994;22(5):266-72. Erratum in: *J Int Med Res*. 1994;22(6):350.

51. Kruse W, Rampmaier J, Ullrich G, Weber E. Patterns of drug compliance with medications to be taken once and twice daily assessed by continuous electronic monitoring in primary care. *Int J Clin Pharmacol Ther*. 1994;32(9):452-57.

52. Steiner TJ, Catarci T, Hering R, Whitmarsh T, Couturier EG. If migraine prophylaxis does not work, think about compliance. *Cephalalgia*. 1994;14(6):463-64.

53. Kruse W, Nikolaus T, Rampmaier J, Weber E, Schlierf G. Actual versus prescribed timing of lovastatin doses assessed by electronic compliance monitoring. *Eur J Clin Pharmacol*. 1993;45(3):211-15.

54. Rudd P, Ramesh J, Bryant-Kosling C, Guerrero D. Gaps in cardiovascular medication taking: the tip of the iceberg. *J Gen Intern Med*. 1993;8(12):659-66.

55. Rudd P, Ahmed S, Zachary V, Barton C, Bonduelle D. Compliance with medication timing: implications from medication trial for drug development and clinical practice. *J Clin Res Pharmacoepidemiol*. 1992;6(1):15-27.

56. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med*. 1990;150(9):1881-84.

57. Kruse W, Weber E. Dynamics of drug regimen compliance—its assessment by microprocessor-based monitoring. *Eur J Clin Pharmacol*. 1990;38(6):561-65.

58. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA*. 1989;261(22):3273-77.

59. Eisen SA, Woodward RS, Miller D, Spitznagel E, Windham CA. The effect of medication compliance on the control of hypertension. *J Gen Intern Med*. 1987;2(5):298-305.

60. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. The Cochrane Collaboration. March 2011. Available at: www.cochrane-handbook.org. Accessed July 27, 2011.

61. Butler RJ, Davis TK, Johnson WG, Gardner HH. Effects of nonadherence with prescription drugs among older adults. *Am J Manag Care*. 2011;17(2):153-60. Available at: http://www.ajmc.com/publications/issue/2011/2011-2-vol17-n2/AJMC_11feb_Butler_153to160/. Accessed July 27, 2012.

62. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA*. 2002;288(4):455-61.

63. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA*. 1998;279(18):1458-62.

64. Feldman R, Bacher M, Campbell N, Drover A, Chockalingam A. Adherence to pharmacologic management of hypertension. *Can J Public Health*. 1998;89(5):I16-18.

65. Flack J, Novikov SV, Ferrario CM. Benefits of adherence to anti-hypertensive drug therapy. *Eur Heart J*. 1996;17(Suppl A):S16-S20. Available at: http://eurheartj.oxfordjournals.org/content/17/suppl_A/16.long. Accessed July 30, 2012.

66. Mallion JM, Baguet JP, Siche JP, Tremel F, de Gaudemaris R. Compliance, electronic monitoring and antihypertensive drugs. *J Hypertens Suppl*. 1998;16(1):S75-S79.

67. Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet*. 1996;348(9024):383-86.

68. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. *Ann Pharmacother*. 2002;36(9):1331-36.

69. Senst BL, Achusim LE, Genest RP, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. *Am J Health Syst Pharm*. 2001;58(12):1126-32.

70. New England Healthcare Institute. Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease. August 12, 2009. Available at: http://www.nehi.net/publications/44/thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease. Accessed July 30, 2012.

71. Rodgers PT, Ruffin DM. Medication nonadherence—Part I: The health and humanistic consequences. *Manag Care Interface*. 1998;11(8):58-60.

72. Schiff GD, Fung S, Speroff T, McNutt RA. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. *Am J Med*. 2003;114(8):625-30.

73. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med*. 2006;166(17):1836-41.

74. Sullivan SD, Krelig DH, Hazlet TK. Noncompliance with medication regimens and subsequent hospitalization: a literature analysis and cost of hospitalization estimate. *J Res Pharmaceut Econ*. 1990;2(2):19-33.

75. Berg JS, Dischler J, Wagner DJ, Raia JJ, Palmer-Shevlin N. Medication compliance: a healthcare problem. *Ann Pharmacother*. 1993;27(9 Suppl):S1-S24.

76. Levy G, Zamacona MK, Jusko WJ. Developing compliance instructions for drug labeling. *Clin Pharmacol Ther*. 2000;68(6):586-91.

APPENDIX Search Strategy for MEDLINE and Embase

#1 'patient compliance'/exp OR 'patient compliance' OR 'medication adherence'/exp OR 'medication adherence' OR adhere* OR comply OR complian* OR non?adhere* OR non?complian*

#2 medication* AND event AND monitor* AND systems* OR 'mems'/exp OR mems OR electronic AND monitor* OR adhere* AND monitor* OR 'microprocessor'/exp OR microprocessor

#3 'pill'/exp OR pill AND box* OR 'pill'/exp OR pill AND container* OR 'medication'/exp OR medication AND vial OR 'pill'/exp OR pill AND vial OR pillbox*

#4 electronic OR electronically

#5 #2 OR #3

#6 #4 AND #5

#7 #1 AND #6

Editors' note to online readers: All *JMCP* articles contain hyperlinks to the source documents for free-access references. These hyperlinks are embedded in the reference numbers cited in the text as well as in the list of references at the end of each article.

Abstracts from Professional Poster Presentations at AMCP's 2012 Educational Conference

The following poster presentations have been prepared for the Academy of Managed Care Pharmacy's 2012 Educational Conference, October 3-5, 2012, in Cincinnati, Ohio. Poster presentations are selected by the Program Planning and Development Committee from proposals that are submitted to the AMCP. Authors of posters are responsible for the accuracy and completeness of the data presented in the posters and in the abstracts published here. For more information about the studies described below, please contact the corresponding authors, indicated by an asterisk (*), whose addresses are listed in full. The names of the individuals who are scheduled to present at the meeting are shown in bold.

A Suboxone-Opioid Program: Members Identified for Intervention and Success

Johnson MT,* *Friedmann Y, Smith L, Thayer R. Aetna Inc., 151 Farmington Ave., Hartford, CT 06156; JohnsonMT@aetna.com, 740.549.6529*

BACKGROUND: According to the journal *Drug and Alcohol Dependence*, the risk of death for those dependent on opioids is 5.71 times higher than healthy individuals in the population of the same age, gender, and race. A Suboxone-opioid monitoring program launched June 2010. This patient safety program notifies Suboxone prescribers via letter about overlapping Suboxone and opioid and/or tramadol pharmacy claims. A Suboxone prior authorization is required. The prior authorization criteria confirms an opioid dependence diagnosis, enrollment in a drug addiction treatment program, and verifies that the Suboxone prescriber has an "X" DEA number. Once the Suboxone prior authorization is completed, members receive an approval letter informing them not to fill opioids/tramadol ongoing.

OBJECTIVE: To reduce prescription drug misuse and abuse while helping ensure safe and appropriate Suboxone use.

METHODS: A retrospective programming application runs weekdays to identify fully insured commercial members who have Suboxone pharmacy claims and concurrent opioid and/or tramadol pharmacy claims. Once an overlap is identified, a letter is generated and mailed to the Suboxone prescriber. Within 2 weeks following the mailing, a pharmacist makes an outbound phone call to the Suboxone prescriber. The pharmacist makes sure the Suboxone prescriber received the letter and, if needed, answers questions and/or provides additional information. The Suboxone prescriber is encouraged to discuss the opioid/tramadol fill with the member. As of May 1, 2012, if ongoing opioid/tramadol use is identified as misuse, future coverage for opioid/tramadol pharmacy claims is denied.

RESULTS: Letters were mailed to 2,224 Suboxone prescribers, of which 1,320 were male and 904 were female. The member age bracket with the highest number of letters mailed was aged 30-34 years. Florida was the state where the highest member percentage (16.9%) resided followed by California (14.7%), Texas (10.6%), Pennsylvania (9.5%), and New Jersey (9.1%). The Suboxone-opioid program identified members belonging to 1,503 unique plan sponsors. Success was defined by members stopping opioid/tramadol use within the post-analysis period, which was 4 months. The start period was the date the letter was mailed plus 15 days to allow time for the Suboxone prescriber to receive the letter. The end date was the last day of the fourth month after the letter was mailed or the next letter mailed, whichever came first.

CONCLUSIONS: There were 1,243 members who successfully stopped opioid/tramadol use in the post-analysis period. The successful member population was 57% male and 43% female. Overall, after Suboxone-opioid program letters were mailed and phone calls were completed, 53% males and 60% females within the post-analysis period obtained success stopping opioid/tramadol use. While there were more letter and phone outreaches completed on males than females, the success rate was higher for females. The overall success rate of the Suboxone-opioid program for males and females from June 2010 to April 2012 was 56%. Identifying gender, age, residence, and plan sponsor will assist with targeting behavioral health and educational programming to help the opioid-dependent member population.

SPONSORSHIP: This research was conducted by Aetna Inc., Hartford, CT, without external funding.

Acute Coronary Syndrome (ACS): Mortality and Morbidity Following a Diagnosis of ACS

Vanderpoel J, *Schein JR, Heubner B, Arneson T, Crivera C,* Damaraju C, Herzog CA. Janssen Scientific Affairs, LLC, 1000 US-202, Raritan, NJ 08869; ccrivera@its.jnj.com, 908.218.7046*

BACKGROUND: Acute coronary syndrome (ACS) encompasses acute myocardial infarction (AMI; either ST elevation or non-ST elevation MI) or unstable angina. Recently, the adequacy of current treatment strategies has come into question, given the excess burden of illness associated with ACS treated in accordance with accepted clinical practice guidelines.

OBJECTIVE: To document the rate at which patients develop additional cardiovascular comorbidities over a 3-year period following their index ACS events.

METHODS: The 5% Medicare database was used to identify patients with a hospitalization claim containing a code for AMI (410, 410.X, 410.X0, or 410.X1) or unstable angina (411 or 411.X) during 2005-2006. Patients with no documented evidence of prior ACS, atrial fibrillation (AF), or heart failure (HF), indicated by at least 1 Part A inpatient claim or 2 Part A outpatient or Part B claims, in the year prior to ACS and who survived the hospitalization were included. Kaplan-Meier methods were used to estimate the probability of patients experiencing the composite endpoint of AF, HF, or death. A Cox proportional hazards model was developed to examine factors associated with subsequent AF, HF, or death.

RESULTS: Of 19,427 Medicare patients with a new diagnosis of ACS, 6,800 (35%) developed AF, HF, or both within 3 years. Of these patients, 14% developed AF alone, 66% developed HF alone, and 20% developed both AF and HF. Based on Kaplan-Meier methods, 29% of patients with newly diagnosed ACS and no prior AF or HF would be expected to develop AF, HF, or die within 1 year; by 3 years after the diagnosis of ACS, 45% would be expected to develop AF, HF, or die. From the Cox model, the following risk factors contributing significantly ($P<0.0001$) to the development of any of these 3 outcomes were identified: chronic kidney disease (HR=1.57, 95% CI=1.48-1.66), liver disease (HR=1.44, 95% CI=1.22-1.70), chronic obstructive pulmonary disease (HR=1.42, 95% CI=1.36-1.49), venous thromboembolism (HR=1.38, 95% CI=1.22-1.57), and diabetes (HR=1.26, 95% CI=1.20-1.32).

CONCLUSIONS: ACS is a red flag for the development of additional cardiovascular disease and mortality, especially in patients with chronic diseases such as diabetes and chronic kidney disease.

SPONSORSHIP: This research was conducted by Janssen Scientific Affairs, LLC, Raritan, NJ, without external funding.

Adherence Measurement for Long-Acting Injectable Antipsychotics: An Empirical Analysis of Days Supply and Quantity Fields on Prescription Claims

Dickson M, ***Durkin M****,* Kozma C, Paris A. Janssen Scientific Affairs, LLC, 1125 Trenton-Harbourton Rd., Titusville, NJ 08560; Mdurkin@its.jnj.com, 609.730.2867*

BACKGROUND: Administrative claims data are increasingly being relied upon for quality measures, including measures of adherence to treatment. Calculation of adherence using administrative claims data is dependent on the accuracy of the days supply field on prescription claims. Little has been published on the validity of days supply for long-acting injectable antipsychotics (LAI) and the implications for adherence measurement.

OBJECTIVE: To investigate the effect of using raw unadjusted days supply data versus validated days supply data in adherence calculation for LAIs.

METHODS: The analysis used LAI prescription claims from August 1, 2009, through July 31, 2011, from a large national administrative claims database. Claims for products dispensed in multidose vials were excluded because the number of doses per container cannot be determined from these administrative claims. Days supply from claims for single-dose LAIs were validated from multiple perspectives, including an examination of the ratio of reported days supply to quantity dispensed and a comparison of reported days supply to a days supply value calculated from quantity dispensed and package insert (PI) recommendations. In cases where the observed quantity dispensed field value for liquid vial products represented product volume in mL, it was replaced by a quantity in number of product units. The percent of claims excluded as unverifiable was calculated at the product and strength within product levels. Adherence, as measured by proportion of days covered (PDC) over 1 year from the date of a patient's first observed LAI prescription, was compared between raw unadjusted claims and validated claims. PDCs were calculated for individual products and for strengths within product.

RESULTS: There were 894,846 LAI antipsychotic claims in the database. Claims for multidose vials of fluphenazine (n = 142,084) and of haloperidol decanoate (n = 95,399) were excluded. The final analytic sample included 657,363 single-dose LAI claims for the following products: haloperidol decanoate (1 mL), paliperidone palmitate, risperidone microspheres, and olanzapine pamoate. Replacing mL quantity dispensed values with the appropriate unit quantity allowed re-inclusion of >80% of the claims with observed liquid volume quantities that were initially excluded. A strict requirement of days supply in accordance to PI would eliminate from 16% to 85% of claims, varying by product. The elimination of unverified claims reduced the sample available for adherence calculation from 25%-85% at the product level. At the product level, differences between the PDC calculated for all available raw claims and for the sample of validated claims ranged from <1% to 16%.

CONCLUSIONS: The number of claims excluded and the magnitude of effect on calculated adherence varied by product and within product, by strength. The observed use of volume in mL rather than product units in the quantity dispensed field for liquid vial products should be addressed to accurately analyze adherence for LAIs. The issue of adherence calculation for multidose vial products remains a concern but was beyond the scope of this research.

SPONSORSHIP: This research was conducted by Janssen Scientific Affairs, LLC, Titusville, NJ, without external funding.

Adherence to Proposed ACR Treatment Guidelines for Gout

Singh J, Hagerty D, Mischler R,* ***Morlock R****. UAB, 510 20th St. South, Box 805B, Birmingham, AL 35242; jasvinder.md@gmail.com, 651.454.1231*

BACKGROUND: Although gout is a relatively common condition, treatment is often not ideal, with many patients continuing to experience multiple flares and some developing complications associated with the disease. To improve patient care, the American College of Rheumatology (ACR) recently proposed a draft set of recommendations for treating patients with gout.

OBJECTIVE: To assess the percentage of patients who meet the recently proposed treatment guidelines in a cohort of patients using xanthine oxidase (XO) inhibitor therapy.

METHODS: Data were assessed from a quantitative survey of U.S. physicians about gout disease management and oversampling for rheumatologists. Laboratory and clinical data were confirmed through chart audits using a structured case report form. The sample was restricted to patients treated with allopurinol or febuxostat. Type and initial allopurinol/febuxostat dose, presence of kidney disease, use of prophylactic medication, serum uric acid (sUA) level, physician type (rheumatologist vs. primary care physician [PCP]), and patient sociodemographic factors were recorded/abstracted. Descriptive statistics were used to describe the number of patients initiating urate-lowering therapy (ULT) with anti-inflammatory prophylactic medication, titration of allopurinol, having a follow-up sUA and achieving sUA <6 mg per dL within 12 months of treatment initiation. Results are presented overall and by physician type.

RESULTS: The sample included 125 rheumatologists and 124 PCPs. Of the 1,245 patients with gout, 858 (69%) were treated with an XO inhibitor: 621 (72.4%) were treated with allopurinol and 237 (27.6%) were treated with febuxostat. Rheumatologists managed the care for 500 (58.3%) patients, and PCPs managed the care for 358 (41.7%) patients. Rheumatologists used an anti-inflammatory prophylactic treatment (nonsteroidal anti-inflammatory drugs [NSAIDs]/colchicine/corticosteroids) in 67% of cases, and only 37% of cases treated by PCPs received prophylactic therapy. A follow-up sUA assessment in the 1 year following the allopurinol/febuxostat initiation was done in 68% and 53% of patients managed by rheumatologists and PCPs, respectively. Rheumatologists were more likely to start with a lower dose of allopurinol (185 mg) versus PCPs (208 mg; $P<0.01$), and only 8% of patients treated by a PCP and 29% of patients treated by rheumatologists were titrated above 300 mg of allopurinol ($P<0.01$). Within 12 months of the allopurinol/febuxostat treatment, only 50% of patients managed by rheumatologists and 36% of patients managed by PCPs achieved an sUA of <6 mg per dL (among those who had an sUA level checked). There was no statistically significant difference between allopurinol (45%) and febuxostat (41%) in the proportion of patients reaching the sUA target ($P=0.26$).

CONCLUSIONS: Adherence to draft ACR guidelines vary by physician type with no more than 50% of patients achieving sUA <6 mg per dL within 12 months of XO therapy. Significant opportunities exist to improve care for all patients regardless of physician specialty, including use of prophylactic treatment, dose titration of ULT, and/or effective treatment strategies to bring patients to sUA goal.

SPONSORSHIP: This research was funded by Ardea Inc., San Diego, CA.

Association Between Pregabalin Access Restrictions and Pain-Related Health Care Utilization and Expenditures in Medicare Supplemental Health Plans

Johnston SS, Udall M, **Alvir J**, McMorrow D, Chu B, Fowler R, Mullins D. Truven Health Analytics, 4301 Connecticut Ave., N.W., Ste. 330, Washington, DC 20008; stephen.johnston@truvenheatlh.com, 202.340.9248*

BACKGROUND: Prior studies of pregabalin prior authorization programs in Medicaid and commercial health plans (Margolis et al., 2009; 2010) have, respectively, provided evidence associating pregabalin access restrictions with either increased or insignificantly affected pain-related health care utilization and expenditures in patients with painful diabetic peripheral neuropathy (pDPN) or post-herpetic neuralgia (PHN).

OBJECTIVE: To examine the association between pain-related health care utilization and expenditures and pregabalin prior authorization (PA) or step therapy (ST) access restrictions in patients with pDPN, PHN, or fibromyalgia (FM), with Medicare supplemental insurance.

METHODS: Retrospective, cross-sectional study using data from a large Medicare supplemental health care claims database. Selected patients were aged 65 or older, continuously enrolled in a single prescription carrier throughout calendar years 2008 (baseline) and 2009 (follow-up), had ≥1 medical claim with an ICD-9-CM diagnosis code for DPN, PHN, or FM, followed within 60 days by a medication or pain intervention procedure used in treating pDPN, PHN, or FM during 2008-2009. Patients were classified based on their prescription carriers' pregabalin access policies during 2008-2009: PA required (PA group); ST required (ST group); unrestricted access (unrestricted group). Follow-up period pain-related health care utilization and expenditures in the PA and ST groups were compared with the unrestricted group using generalized linear models adjusted for baseline demographics and clinical characteristics. PHN patients were combined with pDPN patients due to low sample size.

RESULTS: The pDPN/PHN sample comprised 24,362 patients with pDPN only, 4,327 with PHN only, and 1,615 with both pDPN and PHN: 2,277 in the PA group, 1,478 in the ST group, and 26,513 in the unrestricted group. The FM sample comprised 25,246 patients: 1,917 in the PA group, 1,830 in the ST group, and 21,499 in the unrestricted group. In the pDPN/PHN sample, when compared with the unrestricted group: adjusted odds of pregabalin use were significantly lower in the PA group OR=0.589, 95% CI=0.496-0.700, $P<0.001$) and insignificantly higher in the ST group (OR=1.122, 95% CI=0.963-1.307, $P=0.140$); adjusted pain-related expenditures were significantly lower in the PA group (predicted cost difference=−$533, cost ratio=0.716, 95% CI=0.653-0.784, $P<0.001$) and insignificantly higher in the step therapy group (predicted cost difference=$74, cost ratio=1.039, 95% CI= 0.944-1.145, $P=0.431$). In the FM sample, when compared with the unrestricted group: adjusted odds of pregabalin use were significantly lower in the PA group (OR=0.675, 95% CI=0.553-0.824, $P<0.001$) and the ST group (OR=0.774, 95% CI=0.644-0.930, $P=0.006$); adjusted pain-related expenditures were insignificantly lower in the PA group (predicted cost difference=−$65, cost ratio=0.960, 95% CI=0.795-1.160, $P=0.674$) and insignificantly higher in the step therapy group (predicted cost difference=$60, cost ratio=1.037, 95% CI=0.964-1.115, $P=0.331$).

CONCLUSIONS: In general congruence with prior research, pregabalin access restrictions were, in most cases, associated with lower odds of pregabalin use but not overall savings on pain-related health care expenditures. This study's methodology was limited by its cross-sectional design, which is less internally valid for policy evaluation than the difference-in-difference designs employed by the 2 prior studies of pregabalin access restrictions.

SPONSORSHIP: This research was funded by Pfizer Inc., New York, NY.

Cardiovascular Events and LDL Cholesterol Lowering Associated with High-Potency Statin Therapies in a Real-World Setting

***Barron J**,* DeVries A, White J. HealthCore, Inc., 800 Delaware Ave., 5th Fl., Wilmington, DE 19801; jbarron@healthcore.com, 302.230.2113*

BACKGROUND: To our knowledge, no single study has evaluated differences in cardiovascular event rates among the 3 most commonly used statins within the same real-world population. With generic compounds projected to capture 95% of the statin market share, questions arise as to whether branded statins offer clinical benefits over available generics.

OBJECTIVE: To assess the real-world outcomes on cardiovascular events following initiation of therapy with 3 commonly prescribed high-potency statins and 1 statin/cholesterol absorption inhibitor combination by identifying potential differences in cardiovascular event rates and risk of event by type of statin, and to measure the effect of specific statin therapies on the reduction of low-density lipoprotein cholesterol (LDL-C) levels.

METHODS: The dataset for this observational, retrospective, administrative claims analysis was created using pharmacy and medical claims, and laboratory results from 13 geographically distributed major U.S. health plans. Patients aged 18-63 years who were taking statin therapy were divided into primary (no documented cardiovascular events 12 months pre-index) and secondary (≥1 documented cardiovascular event 12 months pre-index) prevention. The primary outcome measure was the occurrence of a cardiovascular event (i.e., myocardial infarction, coronary heart disease, coronary artery bypass graft, angioplasty, angina/ischemic heart disease, cerebrovascular disease, transient ischemic attack, aortic aneurysm, or congestive heart failure). LDL-C level was measured pre-index to establish a baseline value and again 28 days post-index for the LDL-C reduction analysis, a secondary endpoint.

RESULTS: For the primary prevention group (214,066 patients), cardiovascular event rates were 0.9% rosuvastatin, 1.0% atorvastatin, 0.9% simvastatin, 0.9% simvastatin/ezetimibe. All statins reduced LDL-C levels by approximately one-third: 32.3% rosuvastatin, 33.9% atorvastatin, 33.9% simvastatin, 28.4% simvastatin/ezetimibe. For the group as a whole, the average pre-index LDL-C level was 146 mg per dL, which fell to 91.9 mg per dL post-index. In the secondary prevention group (22,594 patients), 6.2% (1,410 patients) experienced a cardiovascular event: 6.1% rosuvastatin, 6.2% atorvastatin, 6.3% simvastatin, 5.5% simvastatin/ezetimibe. Changes in LDL-C levels were similar for all statin treatment groups, decreasing by 28.2% for rosuvastatin, 27.9% for atorvastatin, 28.3% for simvastatin, and 24.3% for simvastatin/ezetimibe. The average LDL-C levels fell from 128.5 mg per dL at baseline to 85.1 mg per dL post-index. All post-index LDL-C levels were below recommended target levels. Choice of statin therapy used was not associated with a difference in cardiovascular events in either the primary or secondary prevention groups (table).

CONCLUSIONS: Despite differences in the potential LDL-C lowering effect of rosuvastatin, atorvastatin, simvastatin, and simvastatin/ezetimibe, we found no significant differences in cardiovascular event rates or changes in LDL-C levels in our real-world population, suggesting a classwide effect of statins when used at equivalent LDL-lowering doses. These data provide important information regarding expected clinically meaningful outcomes from these high-potency therapies as they are used in real-world practice.

SPONSORSHIP: This research was funded by WellPoint, Inc., Indianapolis, IN, and HealthCore, Inc., Wilmington, DE.

TABLE Cardiovascular Events and LDL

Factor	Hazard Ratio	95% CI	*P* Value
Primary prevention group			
Atorvastatin	0.96	0.789-1.168	0.68
Rosuvastatin	1.075	0.729-1.585	0.72
Simvastatin/ezetimibe	1.284	0.761-2.168	0.35
Secondary prevention group			
Atorvastatin	0.967	0.735-1.274	0.81
Rosuvastatin	0.908	0.589-1.399	0.66
Simvastatin/ezetimibe	1.074	0.588-1.960	0.82

Referent: simvastatin.
CI = confidence interval; LDL = low-density lipoprotein.

Comorbidity Burden, Health Care Resource Utilization, and Health Care Costs Among Medicare Advantage Members with Alzheimer's Disease

*Suehs BT, Davis CD, **Shah SN**,* Alvir J, Joshi AV, van Amerongen D, Patel NC. Pfizer Inc., 235 E. 42nd St., New York, NY 10017; sonali.shah@pfizer.com, 212.733.3292*

BACKGROUND: The prevalence of Alzheimer's disease (AD) in the United States was estimated at 5.4 million individuals in 2011. Based on future expectations around the growing aged population, AD represents a serious public health issue.

OBJECTIVE: To examine and compare comorbidity burden, health care resource utilization (HCRU), and associated costs in the Medicare population of newly diagnosed AD members versus non-AD members (controls).

METHODS: This was a retrospective cohort study utilizing Humana Medicare Advantage Prescription Drug plan (MAPD) member claims data collected between January 1, 2007, and June 30, 2011. Members newly diagnosed with AD and with 36 months of continuous enrollment (12-month pre-index, 24-month post-index) were matched 1:2 to non-AD controls on age, gender, race/ethnicity, geographic region, and plan year of enrollment. Comorbidity burden (RxRisk-V score, Charlson Comorbidity Index score [CCI]), HCRU (outpatient, inpatient, emergency department, home health service, skilled nursing facility), and associated health care costs were compared between cohorts.

RESULTS: A total of 3,374 members with AD were identified and matched to 6,748 non-AD controls. The mean age (SD) of members diagnosed with AD was 79.4 (±7.9) years, and 62.5% (n = 2,108) were female. Comorbidity burden and health care costs are summarized in the table. Pre-index comorbidity burden was similar between-groups when measured using the RxRisk-V ($P = 0.058$), while the pre-index CCI was higher among AD members ($P < 0.001$). AD members displayed greater comorbidity burden than their non-AD counterparts on both measures during post-index years 1 and 2 (all between-group $P < 0.001$). HCRU was significantly higher for AD members during the pre-index period, and post-index years 1 and 2 (all $P < 0.001$). Similarly, mean annual per member total health care costs and medical costs were significantly higher for the AD cohort compared with the non-AD cohort during all time frames examined (all $P < 0.001$). While pharmacy costs were greater among AD members during each year of post-index follow-up ($P < 0.001$), there was no difference during the pre-index period ($P = 0.254$).

CONCLUSIONS: Members diagnosed with AD demonstrated greater comorbidity burden, health care resource utilization, and direct health care costs compared with matched non-AD controls. These findings demonstrate the significant clinical and financial impact associated with AD in a Medicare population.

TABLE Mean Per-Member Health Care Costs and Mean (SD) Comorbidity Index Scores During Pre-Index Year, Post-Index Year 1, and Post-Index Year 2 for Members Diagnosed with AD and Matched Non-AD Controls[a]

	AD Members (n = 3,374)			Non-AD Controls (n = 6,748)		
	Pre-Index	Year 1	Year 2	Pre-Index	Year 1	Year 2
Health care costs						
Total health care costs ($)	9,517	14,066	11,740	6,605	6,968	6,982
Total medical costs ($)	7,799	11,449	9,006	4,953	5,313	5,349
Total pharmacy costs ($)	1,718	2,616	2,734	1,651	1,655	1,633
Comorbidity burden						
RxRisk-V score	4.48 (3.23)	5.05 (3.34)	5.03 (3.35)	4.36 (2.89)	4.60 (2.97)	4.77 (3.03)
Deyo-Charlson score	1.41 (1.85)	1.90 (2.11)	1.83 (2.13)	1.15 (1.71)	1.35 (1.88)	1.50 (2.01)

[a]*All between-group differences at individual time points are statistically significant (t test of means, $P < 0.001$), with exception of RxRisk-V score ($P = 0.058$) and pharmacy costs ($P = 0.254$) during the pre-index period. All costs are adjusted to 2011 dollars based on the medical care component of the Consumer Price Index.*
AD = Alzheimer's disease; SD = standard deviation.

SPONSORSHIP: This research was conducted by Pfizer Inc., New York, NY; Humana Inc., Cincinnati, OH; and Competitive Health Analytics, Inc., Louisville, KY.

Comparison of Compliance with Fingolimod and Other First-Line Disease-Modifying Treatments Among Patients with Multiple Sclerosis

*Abouzaid S, Wu N, Wu Y, **Kim E**,* Boulanger L, Brandes D. Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936; edward.kim@novartis.com, 862.778.7583*

BACKGROUND: Disease-modifying therapies (DMTs) are used to treat multiple sclerosis (MS) by decreasing the number and severity of relapses and delaying progression of the disease. Adherence to DMTs is essential for the reduction of MS relapses and progression. Patients with lower adherence rates experience more inpatient visits and higher MS-related medical costs. Fingolimod, the first oral DMT approved by the FDA, may improve the access to and compliance with MS treatment when compared with injectable DMTs.

OBJECTIVE: To compare compliance with fingolimod and other first-line DMTs indicated for the treatment of MS.

METHODS: Using pharmacy claims from Medco Health Solutions, Inc., patients who initiated 1 of the DMTs between October 2010 and February 2011 were identified: fingolimod (Gilenya), interferon beta-1b (Betaseron, Extavia), subcutaneous interferon beta-1a (Rebif), glatiramer acetate (Copaxone), and intramuscular interferon beta-1a (Avonex). Initiation was defined as no prescription fill for the same medication in the prior 12 months. Patients who filled only 1 prescription of the index DMT were excluded because they may have terminated the treatment due to intolerance or adverse effects. Compliance with the index DMT was measured via proportion of days covered (PDC) and

medication possession ratio (MPR) based on prescriptions filled during the 12 months after the second dispense of the index medication. Logistic regression models were estimated to compare patient compliance with different DMT treatments.

RESULTS: Of the 1,891 MS patients who initiated DMT, 13.1% initiated fingolimod, 10.7% interferon beta-1b, 20.0% intramuscular interferon beta-1a, 18.8% subcutaneous interferon beta-1a, and 37.4% glatiramer acetate. Patients initiating fingolimod had the highest MPR and PDC values among the DMT cohorts in both experienced DMT users (fingolimod: mean MPR=0.92, 90.5% with MPR≥0.8; mean PDC=0.83, 73.7% with PDC≥0.8) and naïve users (fingolimod: mean MPR=0.90, 87.4% with MPR≥0.8; mean PDC=0.80, 66.7% with PDC≥0.8). After controlling for baseline demographics and characteristics, fingolimod was associated with significantly higher likelihood of PDC≥0.8 or MPR≥0.8 than other DMTs.

CONCLUSIONS: Patients who initiated the oral DMT fingolimod had better adherence to treatment than patients who initiated other first-line DMTs, and the association was stronger in experienced users than in naïve users. Limitations to this study include application of claims data and lack of clinical measurements.

SPONSORSHIP: This research was conducted by Novartis Pharmaceuticals Corporation, East Hanover, NJ, without external funding.

TABLE Association of DMT Use with High Compliance[a]

		PDC≥0.8		MPR≥0.8	
DMT	# of Patients	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Fingolimod, experienced users	152	Referent		Referent	
Interferon beta-1b, experienced users	35	0.244	(0.112-0.534)	0.237	(0.091-0.622)
Intramuscular interferon beta-1a, experienced users	66	0.449	(0.241-0.834)	0.392	(0.170-0.904)
Subcutaneous interferon beta-1a, experienced users	98	0.364	(0.209-0.632)	0.265	(0.128-0.548)
Glatiramer acetate, experienced users	115	0.606	(0.356-1.034)	0.614	(0.283-1.328)
Fingolimod, naïve users	96	0.739	(0.419-1.304)	0.736	(0.323-1.675)
Interferon beta-1b, naïve users	167	0.308	(0.189-0.501)	0.291	(0.150-0.563)
Intramuscular interferon beta-1a, naïve users	313	0.423	(0.274-0.655)	0.408	(0.218-0.764)
Subcutaneous interferon beta-1a, naïve users	257	0.400	(0.255-0.627)	0.433	(0.227-0.826)
Glatiramer acetate, naïve users	592	0.459	(0.306-0.691)	0.462	(0.254-0.840)

[a]*Controlled for age, gender, region of residence, requirement of prior authorization, copayment, type of pharmacy dispensing the index prescription (specialty pharmacy vs. retailers), and whether index drug prescriptions have been filled via mail-in orders.*

DMT = disease-modifying therapies; MPR = medicaton possession ratio; PDC = proportion of days covered.

Comparison of Pharmacy Costs After Switching to Emtricitabine/Rilpivirine/Tenofovir DF Single-Tablet Regimen from a Ritonavir-Boosted Protease Inhibitor and 2 Nucleoside Reverse Transcriptase Inhibitors

Flamm J, Shamblaw D, Ruane P, Palella F, Ebrahimi R, Miner P, ***Olson JS****.* Gilead Sciences, 516 W. 47th St., Apt. s4g, New York, NY 10036; jeff.pharm@hotmail.com, 212.969.1888*

BACKGROUND: Antiretroviral (ARV) regimen simplification improves quality of life and long-term medication adherence and persistency while reducing risks for human immunodeficiency virus (HIV) virologic failure and decreasing financial costs. Emtricitabine/rilpivirine/tenofovir DF (FTC/RPV/TDF) is a well-tolerated, once-daily single-tablet regimen (STR) treatment option. This is the first study to evaluate the efficacy, safety, and costs of switching from ritonavir-boosted protease inhibitor (PI+RTV)-based highly active antiretroviral therapy (HAART) to a simplified regimen of FTC/RPV/TDF STR.

OBJECTIVE: To evaluate the efficacy, safety, and costs of switching from PI+RTV-based HAART to FTC/RPV/TDF.

METHODS: This was a randomized, open-label, multicenter, international, 48-week study to evaluate the safety and efficacy associated with switching from PI+RTV regimens to FTC/RPV/TDF in virologically suppressed (HIV RNA<50 copies/mL) HIV-1 infected persons. Eligible participants were randomized 2:1 to switch to FTC/RPV/TDF or maintain their current PI+RTV regimens. The primary endpoint was noninferiority (12% margin) of FTC/RPV/TDF compared with PI+RTV regimens in maintaining plasma HIV-1 RNA<50 copies/mL at Week 24 using the Snapshot analysis. Estimates of pharmacy costs assume all study participants remained on therapy for 24 weeks; wholesale acquisition cost (WAC) were based on Feburary 1, 2012, First Data Bank published rates.

RESULTS: A total of 476 participants were randomized and received at least 1 dose of the study drug (317 FTC/RPV/TDF; 159 PI+RTV).

TABLE Comparison of Pharmacy Costs After Switching

PI+RTV Regimens	Participants	WAC/Participant for 24 Weeks ($)	Total PI+RTV Cost ($)
LPV/RTV	58	4,078	236,524
ATV+RTV	54	6,896	372,384
DRV+RTV	33	7,201	237,633
fAMP+RTV	12	7,129	85,548
SQV+RTV	2	7,984	15,968
Totals	**159**		**948,057**

Mean PI+RTV WAC = $948,057/159 participants = $5,963.

NRTI Regimens	Participants	WAC/Participant for 24 Weeks ($)	Total NRTI Cost ($)
FTC/TDF	130	6,511	846,430
ABC/3TC	24	5,472	131,328
ZDV/3TC	5	5,062	25,310
Totals	**159**		**1,003,068**

Mean NRTI WAC = $1,003,068/159 participants = $6,309.

WAC for PI+RTV regimen/participant for 24 weeks = $5,963 + $6,309 = $12,272.

WAC for FTC/RPV/TDF/participant for 24 weeks = $10,275.

WAC difference between FTC/RPV/TDF and PI+RTV/participant for 24 weeks = $1,997.

FTC/RPV/TDF = emtricitabine/rilpivirine/tenofovir DF; NRTI = nucleoside reverse transcriptase inhibitors; PI+RTV = ritonavir-boosted protease inhibitor; WAC = wholesale acquisition cost.

Baseline characteristics were similar. Switching to FTC/RPV/TDF was noninferior to maintaining a PI+RTV regimen (93.4% vs. 89.9%) at Week 24 for HIV RNA<50 copies/mL (95% CI [-2.0%, 8.9%]). The costs for FTC/PRV/TDF and PI+RTV regimens were $10,275 and $12,272 for 24 weeks of therapy, respectively, representing a savings of $1,997 (16%) per FTC/RPV/TDF participant over the 24-week study period (table).

CONCLUSIONS: Switching to the FTC/RPV/TDF STR from a PI+RTV regimen in virologically suppressed HIV-1-infected participants maintained HIV suppression and saved $1,997 (16%) in medication costs per participant over 24 weeks per WAC evaluation.

SPONSORSHIP: This research was conducted by Gilead Sciences, Foster City, CA, without external funding.

Comparisons of Costs and Clinical Outcomes in Hypertensive Patients Treated with Chlorthalidone or Hydrochlorothiazide

***Sun SX**,* Leahy MJ, Dabbous O, Yu AP, Lu M, Chen KS, Wu E. Forest Research Institute, Harborside Financial Center, Plaza V, Ste. 1900, Jersey City, NJ 07311; shawn.sun@frx.com, 201.427.8316*

BACKGROUND: Hydrochlorothiazide (HCTZ) is a diuretic frequently prescribed to treat hypertension. However, clinical studies indicate that chlorthalidone (CLD) has a longer duration of action and is 1.5-2 times more potent than HCTZ.

OBJECTIVE: To compare clinical and economic outcomes between hypertensive patients treated with CLD versus HCTZ.

METHODS: The I3 claims database was used to identify adults with hypertension (ICD-9-CM codes 401-405) who had at least 2 prescriptions for CLD or HCTZ between January 2000 and June 2008. Patients had to be continuously enrolled for at least 6 months before and 24 months after their first prescription of either study drug. We matched the HCTZ and CLD cohorts in a 5:1 ratio using propensity scores. Using chi-square and Wilcoxon tests, we compared hypertension-related complications, resource utilization, and average health care costs between the cohorts over a 2-year follow-up period.

RESULTS: Our sample included 634 patients taking CLD and 3,170 taking HCTZ. Compared with the HCTZ group, the CLD group had significantly lower rates of hypertension-related complications (19.9% vs. 23.6%, $P=0.044$) and significantly lower total health care costs ($1,141 vs. $1,252 per month, $P=0.026$); this result was primarily driven by the lower medical costs for the CLD group ($921 vs. $1,017 per month, $P=0.046$). Hypertension-related medical costs were significantly lower for patients treated with CLD versus those treated with HCTZ ($179 vs. $227 per month, $P=0.045$). Moreover, the CLD group had fewer patients who had hospitalizations (22.1% vs. 23.3%, $P=0.502$) or emergency department visits (17.7% vs. 18.6%, $P=0.575$) than the HCTZ group although the differences were not significant.

CONCLUSIONS: Hypertensive patients treated with CLD had fewer hypertension-related complications and incurred lower medical and total health care costs than patients treated with HCTZ over 2 years. The clinical and economic benefits of CLD for the treatment of patients with hypertension should be further studied.

SPONSORSHIP: This research was funded by Takeda Pharmaceuticals U.S.A., Inc., Deerfield, IL.

Comparisons of Costs and Clinical Outcomes in Patients Treated with Angiotensin Receptor Blockers Plus Chlorthalidone or Hydrochlorothiazide

***Leahy MJ**,* Sun SX, Yu AP, Chen KS, Wu E, Mattson M, Tang J. University of Illinois College of Medicine, 507 E. Armstrong Ave., Peoria, IL 61637; mjleahy@uicomp.edu, 321.447.2342*

BACKGROUND: Combination therapies for hypertension are recommended for patients whose blood pressure is >20/10 mm Hg above goal. When used in combination, angiotensin receptor blockers (ARBs) are more frequently paired with hydrochlorothiazide (HCTZ) than with chlorthalidone (CLD), although physicians often perceive HCTZ and CLD to be interchangeable.

OBJECTIVE: To compare costs and clinical outcomes between ARB+CLD and ARB+HCTZ.

METHODS: Patients with a diagnosis of essential hypertension (ICD-9 code 401) before they received an ARB+CLD or an ARB+HCTZ were retrospectively identified using 1999-2007 Integrated-Health-Care-Information-Services Database covering approximately 25 million lives in the United States. Other criteria were use of only CLD or HCTZ within 30 days of the ARB, at least 1 refill of study drug, and continuous enrollment in a health plan for 6 months before and 12 months after the start of therapy. We matched the ARB+HCTZ and ARB+CLD cohorts in a 5:1 ratio using propensity score matching (greedy method) based on baseline characteristics. We compared cumulative 1-year medical, pharmacy, and total costs, adjusted to 2007 dollars, between the groups using a Wilcoxon test. We compared hospitalization and urgent-care rates using a Kaplan-Meier survival method. Data were censored at the end of their availability or at 3 years.

RESULTS: A total of 836 patients received an ARB+CLD, and 4,180 received an ARB+HCTZ. At 1 year, compared with the ARB+HCTZ group, the ARB+CLD group had significantly lower medical ($5,374 vs. $5,507, $P=0.005$) and total ($7,927 vs. $8,063, $P=0.008$) costs, a significantly lower rate of urgent care use (19.6% vs. 23.5%, $P=0.002$), and fewer hospitalizations (10.9% vs. 11.5%, $P=0.313$), although the latter was not statistically significant.

CONCLUSIONS: Medical and total health care costs and urgent care rates were lower for patients receiving an ARB+CLD than for patients receiving an ARB+HCTZ. A study limitation was selection bias, which was minimized with matching.

SPONSORSHIP: This research was funded by Takeda Pharmaceuticals U.S.A., Inc., Deerfield, IL.

Cost-Effectiveness of Multiple Sclerosis Therapies: An Indirect Comparison

***Agashivala N**,* Kim E. Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936; neetu.agashivala@novartis.com, 862.778.0019*

BACKGROUND: Cost-effectiveness (CE) models are developed to determine the most efficient treatment option based on best available data. A major challenge to CE models in multiple sclerosis (MS) is heterogeneity in randomized clinical trials (RCTs).

OBJECTIVE: To adapt an existing CE model comparing fingolimod with other first-line disease-modifying treatments (DMTs) using results of a mixed treatment comparison (MTC).

METHODS: The original model compared the cost per relapse avoided for first-line DMTs based on relative relapse reduction (RRR) from RCTs. Mixed treatment comparison (MTC) meta-analyses were performed on the annualized relapse rate (ARR) endpoint to produce relative effect estimates between all the first-line treatments for relapsing remitting multiple sclerosis (RRMS) that adjusted for differences in trial populations and endpoint definitions. The original model was adapted to include the MTC results as efficacy inputs in place of the RRR from the clinical trials and using prices as of July 2012. Results of the adapted model were compared with the original model. Sensitivity analyses were also performed using confidence intervals from the MTC.

RESULTS: Adjusted RRR in the MTC compared with placebo were 57% for fingolimod, 35% for subcutaneous (SC) interferon (IFN) beta (β)-1b (Extavia/Betaseron), 38% for glatiramer acetate, 33% for SC IFN β-1a, and 17% for intramuscular (IM) IFN β-1a. In the original model (using August 2011 prices), the cost per relapse avoided were $74,843 for fingolimod, $94,423 for SC IFN β-1b (Extavia), $102,530 for SC IFN β-1b (Betaseron), $124,512 for glatiramer acetate, $108,940 for SC IFN β-1a, and $197,073 IM IFN β-1a. In the re-analysis using the MTC inputs, the costs per relapse avoided were $83,853 for fingolimod, $104,376 for SC IFN β-1b (Extavia), $113,049 for SC IFN β-1b (Betaseron), $108,081 for glatiramer acetate, $121,424 for SC IFN β-1a, and $237,872 IM IFN β-1a. Sensitivity analyses showed that these results were robust and the rank-order of the results remained unaffected by any changes in the efficacy input.

CONCLUSIONS: Fingolimod remained the lowest cost per relapse avoided among all first-line DMTs after adjusting for MTC of efficacy results and using July 2012 pricing.

SPONSORSHIP: This research was conducted by Novartis Pharmaceuticals Corporation, East Hanover, NJ, without external funding.

Direct and Indirect Costs Associated with Relapse of Multiple Sclerosis

*Parisé H, **Laliberté F**,* Lefebvre P, Duh M, Abouzaid S, Kim E, Weinstock-Guttman B. Groupe d'analyse, Ltèe, 1000 De la Gauchetière West, Ste. 1200, Montréal, QC H3B 4W5; flaliberte@analysisgroup.com, 514.394.4488*

BACKGROUND: Multiple sclerosis (MS) has been generally characterized by steady progression, with unpredictable relapses that often involve complex pharmaceutical and rehabilitative interventions. Early onset and frequency of MS relapses have been associated with a greater risk of more rapid progression to a severe level of disability.

OBJECTIVE: To assess the direct and indirect cost burden associated with MS relapses of different severities.

METHODS: Medical and pharmacy claims (1999-2011) from 60 self-insured U.S. companies were analyzed. Adult patients with ≥2 diagnosis claims of MS (ICD-9-CM: 340.x) were selected. A ≥6 months baseline period of eligibility preceding the first MS diagnosis (index date) was required. Recorded relapses and costs were assessed during a follow-up of 12 months after the index date. MS patients with relapse(s) were categorized according to the most severe definition of relapse occurring during the follow-up. The low/moderate severity relapse cohort was defined as patients with ≥1 MS-related outpatient or emergency room visit followed by ≥1 IV or oral corticosteroid claim within 7 days. The high severity relapse cohort was defined as patients with ≥1 MS-related hospitalization with MS as the primary diagnosis. All-cause and MS-related direct and indirect costs of the nonrelapse cohort were compared with the low/moderate and high severity relapse cohorts. MS-related costs were defined as the subset of claims with a diagnosis of MS. Indirect costs included disability and medically related absenteeism costs.

TABLE Direct and Indirect Costs for Nonrelapse and Relapse MS Patients

Annual Health Care Costs (U.S. $2,011)	Nonrelapse MS	Relapse MS	
		Low/Moderate Severity	High Severity
Direct costs			
Number of patients, n	7,686	1,220	515
All-cause, mean ($)	17,545	28,348[a]	41,969[b]
MS-related, mean ($)	8,803	18,981[a]	29,355[b]
Ratio MS-related/all-cause (%)	50.2	67.0	69.9
Indirect costs			
Number of patients, n	1,687	322	84
All-cause, mean ($)	4,146	5,610[a]	9,226[b]
MS-related, mean ($)	1,613	3,238[a]	6,939[b]
Ratio MS-related/all-cause (%)	38.9	57.7	75.2

[a]*Denotes statistically significant comparison (P<0.01) of Nonrelapse MS versus Low/Moderate Severity Relapse MS.*

[b]*Denotes statistically significant comparison (P<0.01) of Nonrelapse MS versus High Severity Relapse MS.*

RESULTS: A total of 9,421 MS patients (nonrelapse: n=7,686; low/moderate severity relapse: n=1,220; high severity relapse: n=515) were identified. Mean (SD) age for the nonrelapse, low/moderate, and high severity cohorts were 50.3 (13.8), 45.1 (11.4), and 50.7 (15.9) years, respectively; 72.0%, 75.2%, and 72.8% were female. Compared with the nonrelapse cohort, the low/moderate severity relapse and the high severity relapse cohorts incurred significantly higher annual all-cause direct costs ($28,348 vs. $17,545 cost difference=$10,803, $P<0.01$; $41,969 vs. $17,545 cost difference=$24,424, $P<0.01$) and MS-related direct costs ($18,981 vs. $8,803 cost difference=$10,178, $P<0.01$; $29,355 vs. $8,803 cost difference=$20,552, $P<0.01$). Low/moderate and high severity MS relapses were also associated with significantly higher indirect costs relative to nonrelapse MS patients (table). Of note, MS-related costs represented an important proportion (40%-75%) of all-cause direct and indirect costs and increased with MS relapse severity (table).

CONCLUSIONS: MS relapses are associated with a significant direct and indirect cost burden for patient and society. Providing therapeutic interventions that can decrease the number and severity of MS relapses will translate into a positive cost-benefit approach.

SPONSORSHIP: This research was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Discontinuation Rates Among Atypical Antipsychotics for Schizophrenia: An Indirect Treatment Comparison

*Rajagopalan K, O'Day K, **Meyer K**,* Pikalov A, Loebel A. Xcenda, 4114 Woodlands Pkwy., Ste. 500, Palm Harbor, FL 34685; kellie.meyer@xcenda.com, 617.650.3267*

BACKGROUND: Formulary decision makers seek comparative effectiveness data from various sources, including prospective comparative effectiveness trials, retrospective studies, indirect treatment comparisons, and network meta-analyses. The Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study is a head-to-head trial of atypical antipsychotics (AAPs) comparing the older AAPs: olanzapine, risperidone, quetiapine, and ziprasidone. However, AAPs such as aripiprazole or lurasidone were not included in the CATIE study.

OBJECTIVE: To conduct an indirect treatment comparison to assess the estimated rates of (a) all-cause discontinuations and (b) discontinuations due to lack of efficacy for aripiprazole, lurasidone, olanzapine, quetiapine, risperidone, and ziprasidone for subsequent cost-effectiveness modeling of AAPs in patients with schizophrenia using a Markov cohort decision analytic model.

METHODS: An indirect comparison of treatments from 3 separate parallel-group comparison studies was conducted to estimate rates of (a) all-cause discontinuations and (b) discontinuations due to lack of efficacy. Discontinuation rates among olanzapine, quetiapine, risperidone, and ziprasidone patients at 18 months from CATIE were converted into annualized discontinuation rates assuming a continuous

TABLE Discontinuation Rates Among Atypical Antipsychotics for Schizophrenia

	Aripiprazole	Lurasidone	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Total discontinuation (%)	66.2	53.4	49.1	67.8	58.8	64.9
Discontinuation due to lack of efficacy (%)	18.3	14.3	9.9	19.6	19.2	16.8

exponential function. Data for lurasidone were obtained from a multiregional, 12-month, double-blind, parallel-group comparison study versus quetiapine (Loebel et al., 2010). The hazard ratio for lurasidone versus quetiapine was used to estimate the annual discontinuation rates of lurasidone versus other CATIE AAPs. Data for aripiprazole were obtained from a published 52-week open-label comparison with olanzapine in patients with chronic schizophrenia (Chrzanowski et al., 2006). All-cause discontinuations and discontinuations due to lack of efficacy were used to estimate the annual discontinuation rates of aripiprazole versus other CATIE AAPs.

RESULTS: Indirect comparison of the AAPs indicated that olanzapine and lurasidone had the lowest all-cause discontinuation rate: 49.1% and 53.4%, respectively, and the lowest discontinuation rate due to lack of efficacy: 9.9% and 14.3%, respectively (table). All-cause discontinuation rates were found to be highest among quetiapine (67.8%) and aripiprazole (66.2%) patients.

CONCLUSIONS: This indirect treatment comparison indicated that the estimated all-cause discontinuation rates and discontinuations due to lack of efficacy were lowest for lurasidone and olanzapine compared with aripiprazole, quetiapine, and ziprasidone. Results from this analysis are important, given that treatment discontinuations are believed to reflect AAP effectiveness in clinical practice.

SPONSORSHIP: This research was funded by Sunovion Pharmaceuticals, Inc., Marlborough, MA.

Economic Burden of Warfarin Underutilization in Adults with Nonvalvular Atrial Fibrillation

Casciano JP, Dotiwala Z, Szamreta EA, Martin BC, Kwong WJ. eMAX Health Systems, LLC, 445 Hamilton Ave., Ste. 1102, White Plains, NY 10601; juliancasciano@emaxhealth.net, 914.302.6809*

BACKGROUND: Despite warfarin's well-established efficacy in stroke prevention in atrial fibrillation (AF), previous studies consistently show that oral anticoagulation (OAC) is often underutilized in this population.

OBJECTIVE: To estimate the economic burden associated with suboptimal warfarin exposure in a commercially insured AF population with moderate to high stroke risk.

METHODS: We conducted a retrospective cohort analysis of the MarketScan database (2003-2007), including Medicare beneficiaries with secondary commercial insurance, to estimate costs and consequences of warfarin underuse in adults newly diagnosed with AF. Subjects with valvular or transient AF, $CHADS_2 < 2$, prior warfarin use, high bleeding risk per published bleeding risk schemes, or contraindications to OAC were excluded. Prescription claims, days of supply, and timing of prothrombin time/international normalized ratio (PT/INR) claims were used to calculate the proportion of days covered (PDC) by warfarin after AF diagnosis. Warfarin exposure was categorized as none (PDC=0), low (PDC≤0.80), or high (PDC>0.80). Descriptive statistics were used to examine stroke and bleeding rates in patients receiving (PDC>0) and not receiving (PDC=0) warfarin. The effects of PDC on health care resource use and costs during 18 months after AF index diagnosis were assessed using multivariate negative binomial regression and generalized linear models with gamma distribution, respectively.

RESULTS: Only 53% of 13,289 patients included in the analysis received warfarin. Patients who received warfarin had significantly lower rates of ischemic stroke (1.77 vs. 4.41, $P<0.001$) and transient ischemic attack (0.61 vs. 1.77, $P<0.001$) and higher rates of major gastrointestinal bleed (1.87 vs. 1.41, $P=0.003$) but similar intracranial (0.61 vs. 0.54, $P=0.30$) and other bleeds (0.28 vs. 0.22, $P=0.24$) per 100 person-years, compared with patients who did not receive warfarin. Patients with low PDC had similar likelihood of inpatient and emergency department (ED) service utilization compared with patients who did not receive warfarin but were 21% more likely ($P<0.001$) to incur an outpatient visit during follow-up, which was presumably related to increased PT/INR monitoring. Patients with high PDC were 28% less likely ($P<0.001$) to incur hospitalization and 16% less likely ($P=0.019$) to incur ED visits, but 32% more likely ($P<0.001$) to incur outpatient visits than patients who did not receive warfarin. Low PDC was associated with 10% lower inpatient cost ($P<0.001$) and similar ED and outpatient costs compared with patients who did not receive warfarin. High PDC was associated with 12% lower inpatient cost ($P<0.001$), similar ED cost, and 27% lower outpatient cost ($P<0.001$) compared with patients who did not receive warfarin. Overall, total costs were 13% lower for patients with high PDC ($P<0.001$) but similar for patients with low PDC as compared with patients who did not receive warfarin.

CONCLUSIONS: OAC is underutilized in patients with AF. In those with intermediate or high risk of stroke and low or moderate risk of bleeding, OAC provided a stroke benefit without a significant increase in the frequency of intracranial bleeds. High warfarin PDC resulted in cost reduction compared with no warfarin exposure, which supports guideline recommendations for thromboprophylaxis and efforts to ensure adherence in this specific group of patients.

SPONSORSHIP: This research was funded by Daiichi Sankyo, Inc., Parsippany, NJ.

Exacerbation Rates and Costs in Treated Chronic Bronchitis Patients with a History of Exacerbation: A Managed Care Perspective

*AbuDagga A, **Sun SX**,* Tan H, Kavati A, Solem CT. Forest Research Institute, Harborside Financial Center, Plaza V, Ste. 1900, Jersey City, NJ 07311; Shawn.Sun@frx.com, 201.427.8316*

BACKGROUND: Little research is available on chronic obstructive pulmonary disease (COPD) exacerbation rates and costs among managed care patients treated with COPD maintenance medications for chronic bronchitis (CB) using real-world data.

OBJECTIVE: To estimate COPD exacerbation rates and costs among managed care treated CB patients who have a history of exacerbations.

METHODS: A retrospective analysis was conducted using administrative claims data from 13 geographically dispersed commercial health plans, representing 45 million U.S. lives. Inclusion criteria were as follows: age ≥40 years, ≥2 years of continuous health plan enrollment, ≥1 hospitalization or emergency department (ED) visit or ≥2 outpatient visits with CB diagnosis (ICD-9-CM 491.xx) from January 1, 2004, to May

31, 2011, ≥2 pharmacy fills for COPD medications during the follow-up year (first fill served as index date), and a history of exacerbation (≥1 moderate or severe exacerbation during 1 year pre-index). COPD exacerbations were categorized as severe (hospitalization with COPD as primary diagnosis) or moderate (ED visit with a primary COPD diagnosis or an oral corticosteroid filled within 7 days of a COPD-related office visit). When multiple exacerbations occurred within a 14-day window, only 1 was counted. Subgroup analysis was performed on patients with a history of ≥2 exacerbations.

RESULTS: 4,349 treated CB patients (52.7% female, mean age 68.3 ± 10.8 years) met study inclusion criteria. During the follow-up year, mean number of COPD maintenance medication fills was 8.9 ± 6.9 per patient. 57.4% experienced moderate or severe exacerbations (33.9% experienced severe exacerbations). Mean number of exacerbations was 1.6 ± 1.0. Mean exacerbation-related health care costs were $7,374 ± $19,904 per any exacerbation and $17,164 ± $28,726 per severe exacerbation. Among patients with ≥2 exacerbations during the pre-index year, 69.5% experienced moderate or severe exacerbations (44.0% experienced severe exacerbations) during follow-up. Mean number of exacerbations was 2.6 ± 1.1. Mean exacerbation-related costs were $7,372 ± $15,401 per any exacerbation and $17,195 ± $24,948 per severe exacerbation. Among overall population, pre-index exacerbation rate was the most significant predictor of follow-up exacerbation rates (β = 0.2098, $P < 0.0001$) and exacerbation costs (β = 0.1632, $P < 0.0001$).

CONCLUSIONS: Despite treatment with COPD maintenance medications, patients with prior exacerbations continued to have exacerbations during follow-up. Patients with prior exacerbation history have unmet needs and may require additional treatment strategies to reduce exacerbations and associated costs.

SPONSORSHIP: This research was conducted by Forest Research Institute, Jersey City, NJ, without external funding.

First-Line Chemotherapy Treatment Patterns, Treatment Outcomes, and Cost Among Elderly Advanced Non-Small Cell Lung Cancer Patients

Lang K, Sussman M, Federico V,* ***Finnern H****, Foley D, Neugut A, Menzin J. Boston Health Economics, Inc., 20 Fox Rd., Waltham, MA 02451; klang@bhei.com, 781.290.0808*

BACKGROUND: Data on treatment patterns and costs of first-line chemotherapies among patients 66 years or older with advanced non-small cell lung cancer (NSCLC) in a real-world setting are limited.

OBJECTIVE: To describe first-line chemotherapy treatment patterns and costs among elderly advanced NSCLC patients.

METHODS: Using the most currently available data in 2011 from the Surveillance and Epidemiology End Results-Medicare (SEER-Medicare) database, we identified patients newly diagnosed with stage IIIB/IV NSCLC from January 2002 through December 2007 who received intravenously administered (IV) chemotherapy. Patients were required to be aged 66+ years with no prior history of any cancer and to have continuous Part A and B Medicare coverage for the entire study period. Patients were followed from 1 year before the date of their first chemotherapy claim through death or December 31, 2009. First-line regimens were identified using claims-based algorithms (using HCPCS J-codes) developed in collaboration with clinical experts. Treatment patterns (30+ day gap in therapy, regimen modification [dropping 1 treatment from a doublet/triplet], therapy discontinuation, switch to a second-line IV chemotherapy regimen), adverse events (AEs), disease-related symptoms (DRS), and all-cause health care costs (2010 dollars) were assessed. A generalized linear model was estimated to predict per-patient per-month (PPPM) all-cause costs during first-line therapy; covariates included selected AEs/DRSs, age, sex, race, region, Charlson score, stage at diagnosis, type of first-line regimen (i.e., monotherapy, doublet, or triplet therapy), and mortality during first-line therapy.

RESULTS: 8,368 patients met the inclusion criteria (mean age 74 + 5 years, 55% male) with average follow-up of 14 + 15 months. Platinum + taxane (53%), platinum + gemcitabine (16%), and taxane therapy (5%) were the most frequently prescribed IV chemotherapies. Average duration of first-line therapy was 4.2 + 2.8 months. During first-line therapy, 19% of patients had a gap in therapy, 11% had a regimen modification, and 36% switched to second-line IV therapy. 64% of patients discontinued first-line therapy, of whom 92% died during therapy or within 2.8 months (median) of discontinuation. Common AEs included dehydration (40%), infusion reaction (39%), and anemia (39%). Serious AEs included bacterial/fungal infections (18%), hemorrhage (13%), and thromboembolic events (17%). DRSs included dyspnea (41%), chest pain (27%), and cough (13%). Mean monthly all-cause costs during first-line therapy were $6,461 ± $5,922, 40% of which were inpatient costs. Claims noting AEs/DRS accounted for 48% of costs. In multivariate analysis, presence of selected AEs/DRS (e.g., chest pain, deep vein thrombosis, dehydration, hemorrhage, infection, thromboembolic events, and respiratory failure), triplet therapy, and death were associated with significantly ($P < 0.05$) higher costs.

CONCLUSIONS: Platinum-based therapies were found to be administered most frequently in this elderly advanced NSCLC population. Treatment discontinuation and AEs were found to be common. Selected AEs and triplet therapy were associated with higher costs.

SPONSORSHIP: This research was funded by Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT.

Health Care Resource Utilization Associated with Uncontrolled Serum Uric Acid in Patients with Gout

Krishnan E, ***Akhras KS****,* Tawk R, Sharma H, Marynchenko M, Wu E, Shi L. Takeda Pharmaceuticals U.S.A., Inc., One Takeda Pkwy., Deerfield, IL 60015; kasem.akhras@takeda.com, 224.554.6037*

BACKGROUND: The impact of high serum uric acid (sUA) on the health care resource utilization in patients with gout has not been well documented in the literature.

OBJECTIVE: To evaluate the impact of uncontrolled sUA on resource utilization among patients with gout using data from the U.S. Veterans Affairs Network.

METHODS: Adult male patients (age > 18 years) with at least 2 gout diagnoses (ICD-9 CM: 274.xx) and 2 sUA measurements between January 1, 2002, and January 1, 2011, were selected from the Veterans Integrated Services Network (VISN) 16 database. The study period from index date until the end of eligibility was divided into 6-month cycles to allow for a longitudinal design. Any cycle with sUA level > 7 mg/dL was considered uncontrolled while sUA ≤ 7 was considered to be controlled. A sensitivity analysis was subsequently performed using 6 mg/dL as threshold (sUA ≤ 6 as controlled). Logistic regression was used to obtain the odds ratio (OR) and Poisson regression model was used to obtain the incident rate ratio (IRR) for all-cause and gout-related hospital and outpatient visits. All regression models used sUA levels and gout-related medications as time-varying covariates and adjusted for repeated measures within subjects while also controlling for demographic information, baseline comorbidities, and resource use at baseline.

RESULTS: A majority of the 2,553 patients selected for the study were white (52%); average age was 63.5 years; mean body mass index (BMI) was 31.1 kg/m2; and average follow-up time was approximately 6 years. Hypertension (94%), hyperlipidemia (69%), cardiovascular diseases

(33%), diabetes (23%), renal disease (12%), and smoking (8%) were the most common comorbidities at baseline. Uncontrolled sUA (using >7 cut-off) was associated with an increased risk of all-cause hospitalization (OR: 1.25; 95% CI, 1.10 to 1.43), all-cause outpatient visits (OR: 1.32; 95% CI, 1.15 to -1.51), and increased number of all-cause hospitalizations (IRR: 1.23; 95% CI, 1.07 to 1.42). Similarly, the risk for gout-related hospitalization (OR: 1.49; 95% CI, 1.23 to 1.81), risk for gout-related outpatient visits (OR: 1.09; 95% CI, 1.02 to 1.18), the number of gout-related hospitalizations (IRR: 1.47; 95% CI, 1.22 to 1.78), and the number of gout-related outpatient visits (IRR: 1.12; 95% CI, 1.06 to 1.18) were also significantly higher for patients with uncontrolled sUA. All-cause outpatient visits associated with uncontrolled sUA were not statistically different from those with controlled sUA (IRR: 1.00; 95% CI, 0.95 to 1.05). Using 6 mg/dL as a cut-off point for controlled versus uncontrolled sUA levels exhibited similar trends in utilization.

CONCLUSIONS: In this retrospective study, gout patients with uncontrolled sUA utilized more hospital and outpatient care services than those with well-controlled sUA, imposing a greater burden on the health care system. A study limitation was that all enrollees were in the Veterans Affairs network, with a majority of male patients, which may reduce the representativeness of the study sample.

SPONSORSHIP: This research was funded by Takeda Pharmaceuticals U.S.A., Inc., Deerfield, IL, and Analysis Group, Inc., Chicago, IL.

Impact of a Self-Administration Training and Support Program on Site of Care in Patients with Hereditary Angioedema Receiving Nanofiltered C1 Esterase Inhibitor for Routine Prophylaxis

Gregory C, Landmesser LM, Mariano D. Specialty Pharmacy Nursing Network, Inc., 1800 2nd St., Ste. 720, Sarasota, FL 34236; cgregory@spnninc.com, 877.330.7766 ext. 103*

BACKGROUND: In 2009, a plasma-derived nanofiltered C1 esterase inhibitor (C1 INH-nf) was FDA-approved for self-administration for the routine prophylaxis of swelling attacks in adolescents and adults with hereditary angioedema (HAE). Since HAE is a chronic genetic disease that may require twice weekly therapy, self-administration is an important option for these patients. An analysis of a patient database (n = 516) to assess the site of care (SOC) was conducted in June 2010. Six months later, a self-administration training and support program led by skilled infusion nurses was implemented to educate eligible patients on self-administration of C1 INH-nf.

OBJECTIVE: To determine the impact of the self-administration training and support program of the SOC for patients receiving routine prophylactic C1 INH therapy.

METHODS: In early 2012, patient-reported demographic data from a dynamic C1 INH-nf database of HAE patients were examined. These results were compared with the 2010 analysis and reflect distributions of SOC for similar lengths of time before and after the initiation of the training and support program. Data were categorized and sorted; the results were based on descriptive statistics.

RESULTS: The SOC for patients receiving C1 INH-nf (n = 789) was 75.8%, 16.1%, 8.1% at home, infusion center, and physician's office, respectively, compared with 47.1%, 23.3%, and 27.5% from the 2010 analysis. Of the 75.8% patients who infused at home, 57.9% self-administered; 26.6% were infused by a home health agency nurse; 14.7% were infused by a family member; and 0.8% were infused by other. Overall, self-administration was reported in 43.7% of patients compared with 20.0% from the 2010 analysis. Patients aged 30-64 years reported the highest percentage of home (60.8%) and self-administration (71.0%) overall. Per the previous analysis, no patients aged 12 years or younger or 65 years or older self-administered. However, in the current analysis, 10 patients aged 65 years or older learned to self-administer. Of the 234 patients enrolled in the program, 55% were successfully trained, and 13% were in the process of learning self-administration. Patients required an average of 5 visits to be successfully trained. Discontinuation rates of trained patients (5%) compared with untrained patients (10%) suggest that nonprogram patients were twice as likely to discontinue therapy.

CONCLUSIONS: These data suggest that a self-administration training and support program for HAE patients receiving routine prophylactic C1 INH therapy positively impacts the SOC in favor of home/self-administration as well as adherence to routine preventive therapy.

SPONSORSHIP: This research was conducted by ViroPharma Incorporated, Exton, PA, and Specialty Pharmacy Nursing Network, Inc., Sarasota, FL, without external funding.

Impact of a Step-Therapy Policy Restriction for Pregabalin on Health Care Utilization and Expenditures in a Commercial Population

Louder AM, Udall M, Suehs BT, Cappelleri JC, **Joshi AV**, Patel NC. Pfizer Inc., 235 E. 42nd St., MS 235/9/1, New York, NY 10017; margarita.udall@pfizer.com, 212.733.0234*

BACKGROUND: Prior research has examined the impact of prior authorization policies for pregabalin on health care resource utilization (HCRU) and associated expenditures in members from Medicaid and commercial health plans. Step therapy (ST) is a related formulary policy; however, the impact associated with implementation of a ST policy for pregabalin has not been examined.

OBJECTIVE: To compare year-over-year changes in HCRU and costs among commercial members with diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), or fibromyalgia (FM) in a health plan implementing a pregabalin ST policy to similar members in health plans without pregabalin formulary restrictions.

METHODS: A retrospective, parallel-group, pre- /post-study design was used to examine outcomes associated with implementation of a ST policy on the use of pregabalin. Pharmacy and medical claims data from Humana ("restricted" cohort; ST implemented January 1, 2009) and Thomson Reuters MarketScan ("unrestricted" cohort) were used to conduct the analyses. Members aged 18-65 with ≥1 medical claim with an ICD-9-CM code for DPN, PHN, or FM during calendar years 2008 (baseline) or 2009 (follow-up), and a claim for a pain medication or pain intervention procedure were identified. The study cohorts were matched 1:1 on diagnosis and geographic region of residence. A difference-in-differences (DID) approach was used to examine year-over-year changes in disease-related and all-cause utilization and costs. The baseline to follow-up change in HCRU and costs was determined within each cohort, and the between-cohort DID was calculated as follows: DID = (Restricted cohort2009 - Restricted cohort2008) - (Unrestricted cohort2009 - Unrestricted cohort2008).

RESULTS: A total of 3,876 members was identified in the restricted cohort and matched to 3,876 members from the unrestricted cohort. The majority of members identified were diagnosed with FM (84.7%, n = 3,284 in each cohort). Members in the unrestricted cohort were slightly older (mean ± SD: 49.0 years ± 10.4 vs. 47.6 years ± 10.5, $P < 0.001$) and had a higher pharmacy-based comorbidity score (RxRisk-V score: 5.4 ± 3.2 vs. 4.4 ± 2.9, $P < 0.001$) than members in the restricted cohort. The restricted cohort demonstrated a greater year-over-year decrease in the utilization of pregabalin compared with the unrestricted cohort (-2.6%, $P = 0.008$). DID results were not significant for utilization of

gabapentin, opioids, nonopioid analgesics, antidepressants, muscle relaxants, or topical anesthetics. Compared with the unrestricted cohort, the restricted cohort experienced a greater increase in physical therapy use and disease-related outpatient utilization (3.7%, $P=0.010$, and 3.6%, $P=0.022$, respectively). DID calculations for all-cause total health care costs ($-140, $P=0.832$), medical costs ($-101, $P=0.867$), and pharmacy costs ($-39, $P=0.806$) were not significant. Similarly, DID results were not significant for disease-related health care costs ($86, $P=0.580$), medical costs ($65, $P=0.598$), or pharmacy costs ($21, $P=0.818$).

CONCLUSIONS: Consistent with prior research around pregabalin prior authorization policies in commercial health plans, this study found that implementation of a ST restriction resulted in lower pregabalin utilization, but the restriction was not associated with reductions in medical or pharmacy costs.

SPONSORSHIP: This research was funded by Pfizer Inc., New York, NY, and Humana, Inc., Louisville, KY.

Impact of an Extensive Pharmacist-Delivered Counseling Program on Patient Adherence to Target and Nontarget Chronic Medications

Taitel MS, Chen C, Fensterheim LE, Farley MA, Rough TB, Sanchez RJ, Mardekian J. Walgreen Co., 1415 Lake Cook Rd., MS L444, Deerfield, IL 60015; michael.taitel@walgreens.com, 847.964.8102*

BACKGROUND: Community pharmacists are well positioned to proactively counsel patients on the importance of medication adherence. Previous studies have shown that face-to-face interventions delivered by pharmacists can effectively increase medication adherence. Notably, the act of counseling patients on a specific target medication has been shown to improve patient adherence to that medication; it may also have the added benefit of increasing their adherence to other chronic medications.

OBJECTIVE: To determine the impact of an extensive pharmacist-delivered counseling program on patient adherence to target and nontarget chronic medications.

METHODS: This was a *post hoc* analysis of a retail pharmacy pilot study that randomly enrolled patients filling atorvastatin, pregabalin, and tolterodine between October 2008 and March 2009 to an intervention group or a usual care control group. Patients in the intervention group received enhanced pharmacist counseling that included adherence education, coaching, and reminder aids. Those who were new-to-therapy (NTT) received a NTT counseling session and were eligible for a first refill counseling session, and continuing therapy patients received 1 counseling session. A 6-month pre-index period was used to determine if patients were NTT or continuing on the target medications and to evaluate baseline group differences. One-year adherence rates for the 3 target medications as well as all nontarget chronic medications were assessed based on proportion of days covered (PDC). A general linear model was used to adjust PDC to control for age, gender, pre-index pill count, and number of chronic medications.

RESULTS: There were 3,329 intervention and 2,313 control patients included in the analysis. The average age of the intervention and control patients was 55.7 years (SD±13.8) and 54.1 years (SD±14.6), respectively. For target medications, the PDC at 1 year was 0.40 for the intervention group and 0.30 for the control group ($P<0.001$). For nontarget chronic medications, the PDC was 0.42 for the intervention group versus 0.37 for the control group ($P<0.001$). For NTT patients, PDC in the intervention group was 0.30 versus 0.22 for the control group ($P<0.001$) for target medications, and 0.38 versus 0.35 ($P=0.002$) for nontarget medications. For continuing patients, PDC in the intervention group was 0.51 versus 0.39 for the control group ($P<0.001$) for target medications, and 0.46 versus 0.40 ($P<0.001$) for nontarget chronic medications. These results show that patients receiving counseling had 32.7% greater adherence to target medications than patients in the control group; they also exhibited 12.2% greater adherence to nontarget chronic medications. Compared with patients in the control group, patients receiving the intervention who were NTT had 36.8% and 8.7% greater adherence to target medications and nontarget medications, respectively, and continuing patients had 30.5% and 15.2% greater adherence to target medications and nontarget medications, respectively.

CONCLUSIONS: Patients participating in an extensive pharmacist-delivered counseling program demonstrated improved adherence to target medications. Furthermore, patients generalized their improved adherence behavior, to a lesser extent, to nontarget chronic medications that were not directly addressed by the intervention.

SPONSORSHIP: This research was funded by Walgreen Co., Deerfield, IL, and Pfizer Inc., New York, NY.

Impact of the Patient Protection and Affordable Care Act Provision on Contraception as a Preventive Benefit: Contraception Costs for Commercial Health Plans

Pocoski J, Law AW, Dieguez G, Fitch K, Pyenson B. Bayer HealthCare Pharmaceuticals Inc., 6 W. Belt, Wayne, NJ 07470; Amy.Law@bayer.com, 973.487.5855*

BACKGROUND: Provisions of the Patient Protection and Affordable Care Act (PPACA) require health plans to cover contraceptive methods and counseling as a preventive service without cost sharing. Comments by the U.S. Department of Health and Human Services suggested that the cost of PPACA's required contraceptive coverage would be outweighed by the savings associated with reducing the number of unintended pregnancies. The literature does not contain information on how PPACA will impact costs of covering contraceptives from a health plan perspective. As the rules are currently not finalized at the time of writing, it is unclear whether all or just some of the currently approved and available contraceptive methods will be considered preventive.

OBJECTIVE: To quantify the per member per month (PMPM) cost of eliminating member cost sharing on contraception under 3 benefit design scenarios and to explore the elasticity between cost sharing and utilization for contraceptive methods.

METHODS: Data from the Thompson Reuters MarketScan Commercial Claims Database for 2009, trended to 2012, on female enrollees were used in the analysis. Per-member and per-patient costs and utilization for 6 contraception methods—oral contraceptives (OC), vaginal rings, implantable rods, injectables, intrauterine devices (IUD), and sterilization—were identified through National Drug Code (NDC) or procedure codes. We modeled the impact of the preventive contraception coverage rule under 3 benefit design scenarios: zero cost sharing for (a) generic products only, (b) generic products and products without a generic alternative, and (c) all generic and branded products. We also analyzed the elasticity between cost sharing and utilization for these methods. Linear regression was used to estimate elasticity curves from the data. Elasticity factors were applied to contraception utilization in the 3 scenarios to project change in net PMPM costs.

RESULTS: Our analysis estimated that the national average cost increase to payers of contraception coverage due to the inclusion of contraception as a preventive service without cost sharing will range from $0.43 (scenario 1) to $1.02 (scenario 3) PMPM. Four of the 6 contraception methods showed price elasticity: OC, vaginal rings, injectables, and IUD. Evidence for elasticity for implantable rods and female

TABLE PMPM Impact of Preventive Contraception Services Provision

	Scenario 1 ($)	Scenario 2 ($)	Scenario 3 ($)
Net cost pre-reform	2.39	2.39	2.39
Net cost post-reform	2.82	3.00	3.41
Net impact	0.43	0.61	1.02

PMPM = per member per month.

sterilization was not conclusive. The number of IUD users per 1,000 women of childbearing age increased as member cost sharing decreased. For OC, vaginal rings, and injectables, there was an increase in utilization with decreased cost sharing through improved compliance of existing users rather than an increase in the number of users. The cost-sharing gap between the branded and generic OC may also affect the use of OCs.

CONCLUSIONS: Providing contraception methods as preventive health services with no cost sharing results in a modest increase in contraception costs to payers, which will vary depending on the final rule's details.

SPONSORSHIP: This research was conducted by Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ, without external funding.

Is History of Patient Adherence to Asthma Controller Medication Associated with Initial Choice of Prescription for Inhaled Corticosteroid and Long-Acting β2-Adrenergic Agonist Combination Therapy?

Williams S, Trudo F, Suchower L, Tunceli O, Kern D, Pethick N, Elhefni H,* ***Bullano M****. AstraZeneca LP, 1800 Corcord Pike, Wilmington, DE 19850; setareh.williams@astrazeneca.com,302.885.1239*

BACKGROUND: Patient history of past adherence to prescribed asthma controller regimen may be a marker of future adherence. Physicians may consider previous patient compliance in their choice of treatments, especially if they perceive ease of use with type of inhaler associated with adherence.

OBJECTIVE: To evaluate the association between patients' adherence to prior asthma controller medication and choice of therapy initiation with budesonide/formoterol combination (BFC) or fluticasone/salmeterol combination (FSC).

METHODS: In a retrospective analysis of HealthCore Integrated Research Database, asthma patients aged 12-64 years with ≥1 pharmacy claim for inhaled corticosteroid/long-acting β2-adrenergic agonist (ICS/LABA) between June 1, 2007, and August 31, 2011, with ≥12 months' continuous enrollment before therapy initiation (index date) were identified. Patients with chronic obstructive pulmonary disease and other respiratory diseases or prescription fills for >1 type of ICS/LABA therapy were excluded. Adherence was measured using medication possession ratio (MPR) for patients with ≥1 pre-index controller prescription. MPR was assessed for monotherapies (ICS, LABA, leukotriene receptor antagonist [LTRA], theophylline, omalizumab) and treatments prescribed together (ICS+LABA, ICS+LTRA, and LABA+LTRA). Composite-weighted MPR measure, ranging from 0-1, was created based on percentage of time each medication was used. Patients were considered adherent if MPR >0.80.

RESULTS: 9,706 BFC and 27,975 FSC patients were identified. Mean age was 40 years for BFC patients and 38 years for FSC patients. Overall, 19% and 14% of BFC and FSC patients, respectively, had ≥1 prescription fill for LTRA and ICS, while <5% of patients filled prescriptions for all other asthma controller medications. ICS and LTRA monotherapies were prescribed together for 6% of patients. Composite-weighted MPRs were comparable between BFC and FSC patients (n, mean±SD, median: 4537, 0.81±0.23, 0.91 vs. 10,163, 0.82±0.24, 0.95). Mean difference (−0.005) was not statistically significant between cohorts (95% CI, −0.013 to 0.0031; $P=0.221$). 64% of BFC and 65% of FSC patients were adherent (MPR>0.80) to their controller therapies (OR=0.92; 95% CI, 0.85-0.99, $P=0.023$).

CONCLUSIONS: Adherence to prior controller therapy in asthma patients was similar between BFC and FCS cohorts and does not appear to have an impact on physician choice of type of combination therapy initiated. Other factors, including patient preferences and formulary access, may affect the physician's choice of prescribing these agents for asthma management.

SPONSORSHIP: This research was conducted by AstraZeneca, LP, Wilmington, DE, without external funding.

Medication Therapy Management: Methods to Increase Comprehensive Medication Review Participation, Phase 2

Harrell T,** Hettich Barnhart L. The University of Arizona College of Pharmacy, Medication Management Center, 1295 N. Martin Ave., Tucson, AZ 85721; harrell@pharmacy.arizona.edu, 317.733.8718*

BACKGROUND: Current Centers for Medicare and Medicaid Services' (CMS) guidelines require Part D sponsors to offer a Comprehensive Medication Review (CMR) to each beneficiary participating in a Medication Therapy Management Program (MTMP). A CMR is a review of a beneficiary's medications that is intended to aid in assessing medication therapy and optimizing patient outcomes. CMS has recently adopted the Pharmacy Quality Alliance (PQA) MTM Completion Rate as a performance metric by which program sponsors will be evaluated. Beginning with calendar year 2013, health plans' MTM CMR Completion Rate will be displayed on the CMS website using 2011 data. In 2014, the MTM CMR Completion Rate will be a STAR metric using 2012 data. Sponsors of MTMPs and/or their MTMP providers are responsible for creating innovative processes to increase CMR completion rates in order to improve health outcomes and maximize quality bonus payments associated with this measure.

OBJECTIVE: To evaluate process improvements implemented by an MTMP call center that were designed to increase the rate of MTMP beneficiaries participating in a CMR.

METHODS: The industry average of CMR completion rates in 2010 have been reported to be just over 8% (9.6% for Medicare Advantage Prescription Drug [MAPD] plans and 6.6% for Medicare Prescription Drug Plans [PDP]). Assumptions of reasonable performance have been hypothesized to be between 10% and 15%. Process improvements were implemented by an MTMP call center to minimize barriers to completing CMRs, increase the completion rates, and ultimately maximize future quality bonus payments associated with this metric. Changes include utilization of prior year's claims data to increase the pool of MTMP beneficiaries qualifying in the first quarter of the year; eliminating any wait period after members qualify for the MTMP prior to providing services; offering a CMR upon every Targeted Medication Review (TMR) member outreach; increased number of clinical interventions that trigger TMRs; and ongoing monitoring of CMR completion rates throughout the year.

RESULTS: In calendar year 2011, prior to implementing additional process changes, a total of 153,560 beneficiaries participated in the MTM program, with 10,636 members completing a CMR, for a total participation rate of 6.93%. Through the first quarter of the 2012 program

year, 247,478 members have qualified for the MTMP. Of those members, 6,982 members have completed a CMR. Based on first-quarter experience, the process changes are expected to result in a CMR participation rate greater than 10%. Updated results will be provided through the third quarter of 2012.

CONCLUSIONS: This program is associated with a projected 44% increase in the participation rate of CMRs.

SPONSORSHIP: This research was conducted by The University of Arizona College of Pharmacy, Medication Management Center, Tucson, AZ, without external funding.

Methods for Improving Outcomes and Increasing Fill Rates for Antiplatelet Therapy After Stent Implantation

McConnell DM, Mikhail P, Mazonkey L, Lenker SE, Berger PB, Jones JR, Jones JB. Geisinger Health Plan, 100 N. Academy Ave., MC3245, Danville, PA 17822; pmmikhail@thehealthplan.com, 570.214.1737*

BACKGROUND: Antiplatelet therapy following bare metal or drug eluting stent implantation is crucial in preventing further cardiovascular events. Following hospital discharge, a patient who delays filling antiplatelet therapy, is nonadherent to therapy, or discontinues therapy early may be at risk for an adverse cardiovascular outcome.

OBJECTIVE: To decrease the time to first fill of antiplatelet medication, prevent early discontinuation of therapy, decrease vessel restenting and new stents, decrease cardiac related hospitalizations, and emergency department visits.

METHODS: From January 1, 2009, through December 31, 2009, 248 members insured by Geisinger Health Plan were identified as having a stent implantation requiring antiplatelet therapy. Members as part of the pre-intervention group were followed 1 year post-stent implantation to evaluate outcomes through electronic health record documentation and pharmacy and medical claims. The intervention group patients (n = 429) were identified through discharge summaries from hospitals included inside and outside of the Geisinger Health System clinical enterprise. Patients were discharged alive following stent placement in ≥ 1 coronary artery from February 2011 to February 2012. The pre-intervention group was used as a comparator for the year prior to intervention group. Antiplatelet medications included were clopidogrel, prasugrel, and ticagrelor. The offer to counsel and provide the medication prior to discharge was made by inpatient pharmacists. Upon discharge, a Geisinger Health Plan pharmacist, an adherence pharmacy technician, or a case manager offered additional counseling and addressed adherence barriers for 1 year post-stent placement or until discontinuation of therapy as recommended by physician. Satisfaction surveys were sent to members upon completion of therapy for program evaluation and process improvement feedback.

RESULTS: Significant differences among members receiving medication prior to or upon discharge were observed comparing the pre-intervention group (n = 248) with the intervention group (n = 429), 52% versus 93%, respectively. No claims submitted for medication decreased from 21% in the pre-intervention group to < 1% in the intervention group. One member receiving medication following drug-eluting stent has discontinued, while rate of discontinuation for bare metal stent is approximately 19%. Among the bare metal stent population, there were varying prescribing habits for length of therapy and reasons of discontinuation. Length of therapy ranged from 2 weeks and beyond, and observed reasons for discontinuation were initiation of anticoagulation therapy, surgery, therapy completed per physician, and financial barriers. At day 30 post-stent, the intervention group cardiac-related hospitalization and emergency department visits were decreased by approximately 50%, while revascularization and new stents were decreased by approximately 23% when compared with the pre-intervention group. Feedback from member surveys showed overwhelming satisfaction with the program and gratefulness on behalf of members for the health plan's dedication to their overall health.

TABLE Rates Per 1,000 Patients

	Days Post-Stent	Pre-Intervention (# of Patients)	Post-Intervention (# of Patients)
Restenting/ revascularization	7	24	5
	30	28	26
Emergency department/ hospitalizations	7	149	55
	30	69	52

CONCLUSIONS: This study shows that pre-discharge counseling and offering to fill medication, as well as consistent post-discharge contact improves patient outcomes. Potential limitations of this study were that claims data and electronic health record notes were highly utilized and all of the intervention patients have not reached 1-year post-discharge.

SPONSORSHIP: This research was conducted by Geisinger Health Plan, Danville, PA, without external funding.

Multiple Sclerosis Specialty Drug Utilizers Cost of Care Trends 2008 to 2010: An Integrated Medical and Pharmacy Claims Analysis

Starner CI, Shah N, Alexander C, Gunderson B, Ritter S, ***Gleason PP.***** Prime Therapeutics, LLC, 1305 Corporate Center Dr., Eagan, MN 55121; pgleason@primetherapeutics.com, 612.777.5190*

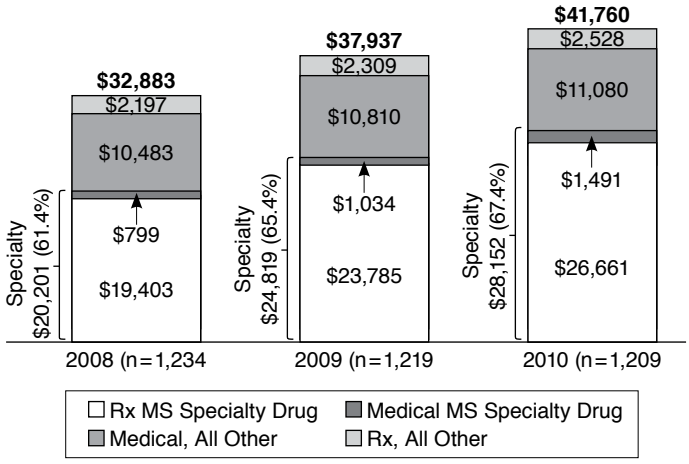
BACKGROUND: In 2011, multiple sclerosis (MS) drugs accounted for 3.6% of all pharmacy benefit (Rx) costs and the average per prescription cost was $3,135, an increase of 15.2% from 2010, among a 9-million member commercially insured cohort. It is unknown if the increases in MS drug costs are associated with decreases in medical costs.

OBJECTIVE: To describe the cost of care trends among commercially insured individuals utilizing an MS specialty drug stratified by specialty and nonspecialty costs within the medical and Rx benefits.

METHODS: Integrated Rx and medical claims data from 1.2 million commercially insured members were queried. Members were required to be age 0 to 64 and continuously enrolled for a full year during 2008, 2009, or 2010. To define a member as having an MS diagnosis, the following criteria were used: (a) 2 or more medical claims with an MS ICD-9 diagnosis code, (b) 1 medical claim with MS and 1 MS drug claim, or (c) 2 or more MS drug claims. All MS drugs were considered specialty drugs and included the following: glatiramer, interferon beta-1a and 1b, natalizumab, dalfampridine, and fingolimod. Each year, the prevalence of members with an MS diagnosis and MS drug treatment was identified. Among members using MS drugs, the annual average member total cost of care was calculated (PMPY). Total cost of care was also separated into 4 categories: medical MS drug, medical all other, Rx MS drug, and Rx all other. Costs were the total paid amount, which includes both the individual out-of-pocket and insurer payments. Descriptive statistics were used to describe the annual total cost of care and spending in each of the 4 categories. The compound annual growth rate (CAGR) was used to describe cost trends.

RESULTS: MS diagnosis prevalence was 17 per 10,000 continuously enrolled members in 2008 (1,742 of 1,038,638) and did not change through 2010. MS drug utilization among members with a diagnosis was consistent over the 3 years at a rate of 1,234 (70.8%) of 1,742

FIGURE Annual Average Cost of Care for Multiple Sclerosis Patients Treated with Specialty Drugs[a]



[a]*Commerially insured members continuously enrolling during analysis year. MS = multiple sclerosis; Rx = pharmacy benefit.*

members in 2008 and 1,209 (71.8%) of 1,685 members in 2010. Although MS drug utilization remained constant, the total cost of care CAGR was 12.7% from 2008 to 2010 (figure). All other medical costs were $10,483 in 2008 and increased to $11,080 in 2010, CAGR 2.8%. Combined MS medical and Rx specialty drug costs accounted for $20,201 (61.4%) of $32,883 total cost of care in 2008 and increased to 67.4% in 2010 ($28,152 of $41,760), CAGR 18.1%. The medical and Rx specialty drug CAGRs over the 3-year period were 36.6% and 17.2%, respectively. MS drug costs were 95% from the Rx benefit.

CONCLUSIONS: In 2010, MS medical and Rx specialty drug costs were more than two-thirds of the total cost of care. The fastest growing category within the total cost of care was specialty drugs to treat MS, at 6.5 times the rate of all other medical costs (CAGR 18.1% vs. 2.8%). As drug utilization remained relatively unchanged and more than 95% of MS drug expenditures were from the Rx benefit, most of the increase in spending was due to manufacturer price increases. The increasing MS drug costs do not appear to be associated with decreasing medical costs. Health plans and insurers need to have a full understanding of where dollars are being spent in conditions such as MS and how to best manage the increasing burden of specialty drug costs. More research in other specialty conditions is necessary to broaden the knowledge base among specialty care.

SPONSORSHIP: This research was conducted by Prime Therapeutics, LLC, Eagan, MN, without external funding.

Nonadherence with Oral 5-ASA Therapy and Disease Burden with Ulcerative Colitis

***Yen L**,* Wu J, Nichol MB. Shire Development LLC, 725 Chesterbrook Blvd., Wayne, PA 19087; lyen@shire.com, 484.358.6220*

BACKGROUND: Ulcerative colitis (UC) is 1 of the 2 major types of inflammatory bowel disease (IBD). First-line treatment with 5-aminosalicylic acid (5-ASA) is recommended for mild-to-moderate disease. Systematic literature review has shown that UC is a costly disease, with hospitalizations contributing significantly to direct medical costs. There is little published literature assessing medication adherence and its association with emergency room visits and inpatient hospitalization using medical claim data.

OBJECTIVE: To evaluate the prevalence of nonadherence with oral 5-ASA therapy and its association with UC-related and all-cause disease burden in UC patients.

METHODS: IMS LifeLink Health Plan claims data (January 2007 to June 2011) were analyzed. Adult patients (18 years or older) were selected if they met the following criteria: (a) initiated at least 1 oral 5-ASA prescription fill (index date) during July 2007 to July 2010; (b) presence of at least 1 diagnosis of UC (ICD-9-CM code = 556.x [ulcerative colitis]) in the 6 months prior to or the 12 months post-index date; (c) continuous enrollment in both health and pharmacy plans for at least 6 months prior to and the 12 months post-index; (d) no prescription fill for 5-ASAs, corticosteroids, and immunosuppressive/biologic agents 6 months prior to index date. Patients with a diagnosis of Crohn's disease (ICD-9-CM: 555.x [regional enteritis]) or irritable bowel syndrome (ICD-9-CM: 564.1 [irritable bowel syndrome, irritable colon, spastic colon]) in the 6 months prior to and the 12 months post-index date were excluded. Nonadherence was determined by a proportion of days covered (PDC) < 0.8 for any 5-ASA. Disease burden was defined as emergency department or inpatient visits. Multiple logistic regression models were used to assess nonadherence with oral 5-ASA and other risk factors associated with UC-related and all-cause disease burden.

RESULTS: We identified 5,964 UC patients. Mean age was 48 years; 53% were female. Overall, 79% of patients were nonadherent with oral 5-ASA treatment; 10% had UC-related disease burden; and 28% had all-cause disease burden. When compared with patients who adhered with 5-ASA treatment, nonadherers were more likely to have UC-related burden (OR = 1.41, 95% CI = 1.12-1.77) or all-cause disease burden (OR = 1.35, CI = 1.16-1.57). Other factors significantly associated with UC-related/all-cause disease burden included noncommercial payer type ([OR = 1.25, CI = 1.02-1.54]/[OR = 1.25, CI = 1.08-1.45]); comorbidities (≥ 2 comorbidities: [OR = 2.00, CI = 1.62-2.47]/[OR = 2.75, CI = 2.38-3.18]; 1 comorbidity: [OR = 1.36, CI = 1.09-1.70]/[OR = 1.57, CI = 1.36-1.82]); more severe UC as measured by corticosteroid use ([OR = 3.39, CI = 2.82-4.09]/[OR = 2.18, CI = 1.92-2.46]); or immunosuppressive/biologic agents use ([OR = 2.11, CI = 1.61-2.76]/[OR = 1.48, CI = 1.18-1.85]) in post-index date. Additionally, age older than 65 years (OR = 1.28, CI = 1.07-1.54); female gender (OR = 1.24, CI = 1.10-1.39); patients from different regions (Midwest: OR = 1.29, CI = 1.06-1.56; West: OR = 1.47, CI = 1.17-1.86 as compared with Northeast); and specialist care use (OR = 1.18, CI = 1.04-1.34) were significantly associated with all-cause disease burden.

CONCLUSIONS: Prevalence of nonadherence with oral 5-ASA treatment was high as reflected in these administrative claims of UC patients. Nonadherence with 5-ASA treatment was significantly associated with UC-related or all-cause disease burden. These associations reinforce the importance of improving medication adherence as a strategy to avoid potential emergency department or inpatient hospitalization events.

SPONSORSHIP: This research was conducted by Shire Development LLC, Wayne, PA, without external funding.

Pain Characteristics, Related Treatment Patterns, and Health-Related Quality of Life Among Patients with Painful Diabetic Peripheral Neuropathy

Patel A, Annunziata K, Chow W, **Pesa J**. Janssen Scientific Affairs, LLC, 1000 US-202, Rm. 3263, Raritan, NJ 08869; wchow3@its.jnj.com, 908.927.5102*

BACKGROUND: Pain is a debilitating symptom of diabetic peripheral neuropathy affecting 10%-20% of diabetics annually. Opioids are

reserved for combination therapy or second-line use when treatment with other therapies, such as antidepressants or anticonvulsants, provides insufficient pain relief. Research efforts have focused on disease burden of painful diabetic peripheral neuropathy (pDPN), yet little has been done to understand pain characteristics, related treatment, and health-related quality of life (HRQoL) in this population.

OBJECTIVE: To evaluate pain characteristics, treatment patterns, and HRQoL in patients with pDPN.

METHODS: A nationally represented U.S. sample of adults (N = 75,000) who completed the 2011 National Health and Wellness Survey (NHWS) online and reported both a diagnosis of "neuropathic pain as a result of diabetes," and pain in the past month were included. Patients were excluded if they were receiving pain medication primarily for cancer, migraine, dental, or menstrual pain. Pain characteristics (3-level severity, frequency, and intensity in the past week), related treatments, and HRQoL collected using the Short Form Health Survey (SF-12 v2; i.e., Mental Component Summary [MCS] and Physical Component Summary [PCS] scores) were reported descriptively.

RESULTS: Of the 1,625 pDPN patients (mean/median age = 60/62 years; 64.4% males; 79.3% whites) included in the analysis, 68.6% were diagnosed by their primary care physicians, with an average pain duration of 6.17 years. Sleep difficulties (43.5%), depression (36.9%), and anxiety (21.7%) were frequently reported comorbidities, while many patients reported diagnoses of arthritis (46.1%), back (36.4%), and joint (30.2%) pain. When asked about the cause of pain in the past month, 70.2% reported neuropathic pain followed by arthritis (51.9%), joint (50.3%), and back (48.7%) pain. Overall, patients reported an average pain intensity of 5.88, and the majority (65.3%) experienced pain daily. Nearly 75% rated their neuropathic pain as moderate to severe, and only 56.4% were currently treating with a prescription analgesic. Among prescription users, more than half used monotherapy, most commonly opioids (32.3%), anticonvulsants (14%), or nonsteroidal anti-inflammatory drugs (NSAIDs; 8.5%), while about two-fifths used combination therapy. Most common combinations included anticonvulsants/opioids (16.4%), opioids/NSAIDs (16.6%), or opioids/other drugs (12.1%). Opioid users, which comprised the majority of prescription users, were primarily using such treatment for back (47.9%), neuropathic (29.1%), or arthritis (21.7%) pain. As for the HRQoL measure, pDPN patients reported high activity impairment (69.2%) and had lower MCS and PCS scores (45.17 and 33.28, respectively), relative to the general population (mean score = 50).

CONCLUSIONS: Patients with painful diabetic peripheral neuropathy commonly have other pain conditions and use opioids either alone or in combination for their neuropathic and nociceptive pain. Despite having moderate-to-severe neuropathic pain, only about half of the studied population is treated with prescription pain medications, which may have contributed to lower HRQoL. Further analyses of these data will assess the impact of treatment on other patient-reported outcomes.

SPONSORSHIP: This research was conducted by Janssen Scientific Affairs, LLC, Raritan, NJ, without external funding.

Prescription of Inhaled Corticosteroids and GOLD Severity Stage Among Patients with Chronic Obstructive Pulmonary Disease

*Tian H, **Zhang J**,* Gorsh B, Lin J, Goodman M. Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936; jie.zhang@novartis.com, 862.778.3303*

BACKGROUND: Chronic obstructive pulmonary disease (COPD) treatment guidelines recommend that maintenance inhaled corticosteroid (ICS) therapy be reserved for patients at high risk, that is, severe or very severe airflow limitation (Global Intiative for Obstructive Lung Disease [GOLD] III or IV) and repeated exacerbations. Reports in different populations indicate that ICS may be overutilized in patients with less severe disease. This is of concern, given the potential adverse effects of ICS use in patients with COPD.

OBJECTIVE: To describe the pattern of ICS prescriptions according to COPD severity based on GOLD 2010 stages using the General Electric Centricity electronic medical record (GE EMR) database.

METHODS: A retrospective cohort study was conducted using data from the GE EMR database (2005-2009) that contains around 21 million patients from 45 states and 30,000 clinicians (85% are primary care). Patients with at least 1 forced expiratory volume in 1 second (FEV1) result test between January 1, 2005, and December 31, 2009, were included with the date of first spirometry testing as the index date. Additional inclusion criteria included the following: age ≥ 40, diagnosis of COPD (ICD-9: 491.xx, 492.xx, 496.xx) prior to the index date, 1 year of GE system history post-index, and no diagnosis of asthma (ICD-9: 493.xx) in the study period. Patients were staged using FEV1% predicted values based on the GOLD 2010 guidelines. Prescription use of ICS was summarized by GOLD 2010 COPD stage.

RESULTS: 6,478 COPD patients were identified for inclusion into this study (59% >65 years, 48% female, mean FEV1% predicted: 63%). Among them, 24% were classified as mild COPD; 42% were classified as moderate COPD; 25% were classified as severe COPD; and 9% were classified as very severe. ICS therapy was prescribed for 35% (n = 554) of mild patients and 39% (n = 1,073) of moderate patients.

CONCLUSIONS: A high percentage of patients in mild-to-moderate COPD were prescribed ICS therapy by their physicians in the GE database. Use of ICS therapy in these stages of COPD is inconsistent with the GOLD 2010 guidelines recommendations.

SPONSORSHIP: This research was conducted by Novartis Pharmaceutical Corporation, East Hanover, NJ, without external funding.

Prevalence of Opioid Abuse and Related Costs in a Commercial Managed Care Population

***Pasquale MK**, Joshi AV,* Dufour R, Schaaf D, Mardekian J, Andrews GA, Patel NC, Harnett J. Pfizer Inc., 235 E. 42nd St., MS 235/9/1, New York, NY 10017; ashish.joshi@pfizer.com, 212.733.3747*

BACKGROUND: While treatment with opioids is an important component of pain management, increased use of these medications has been accompanied by a dramatic increase in the rate of opioid drug abuse. Although the prevalence of diagnosed opioid abuse in managed care claims is relatively small, opioid abuse-related costs are significant and have not been documented extensively.

OBJECTIVE: To measure the prevalence and resource use/cost burden of diagnosed opioid abuse in Humana commercial members.

METHODS: This study was a retrospective analysis of claims data for Humana commercial members (January 1, 2007, to June 30, 2011). Overall prevalence of opioid abuse was assessed using ICD-9 codes indicating opioid abuse/dependence (304.0X, 304.7X, 305.5X, 965.0X). To assess incremental resource use and costs related to diagnosed opioid abuse among members with opioid use, those with an ICD-9 claim for abuse (cases) between January 1, 2008, and June 30, 2010, were matched 1:2 with members with opioid use but no abuse (controls). Matching was based on line of business, region, enrollment period, age, and gender. The date of diagnosed opioid abuse is defined as the index date, and resource use, comorbidities, and costs were examined 12 months pre- and post-index date. Exclusion criteria were ASO members, pregnancy, an opioid abuse diagnosis in the pre-index period, and members not

continuously enrolled during the entire study period. Multivariate analyses were conducted using generalized linear modeling (GLM) with log-transformed abuse-related costs as the dependent variable.

RESULTS: The 6-month prevalence (per 1,000) of diagnosed opioid abuse increased from 0.84 in 1st half of 2008 to 1.15 in 1st half of 2010, while the prevalence of opioid use decreased from 118 to 115 per 1,000 during the same time period. Opioid abusers (cases) were similar to nonabusers (controls) in terms of age (63.0 vs. 63.1), gender distribution (56% female), and region (78% South). Compared with nonabuse controls, opioid abuse cases had a significantly higher mean RxRisk score (5.2 vs. 3.2, $P<0.001$), number of opioid prescriptions (14.1 vs. 2.4, $P<0.001$), and total number of pain medication prescriptions during the pre-index period (25.8 vs. 5.5, $P<0.001$). Opioid abuse cases also reported significantly higher substance abuse (53 vs. 8%, $P<0.001$), psychiatric diagnoses (73 vs. 17%, $P<0.001$), and hepatitis (3.1 vs. 0.3%, $P<0.001$) in the pre-index period than nonabuser controls. In the pre-index period, total abuse-related costs were $3,185 higher in abusers ($P<0.001$), whereas all-cause direct costs were $17,068 higher ($P<0.001$). In the post-index period, total abuse-related costs were $2,236 higher in abusers ($P<0.001$), whereas all-cause direct costs were $16,258 higher ($P<0.001$). In the multivariate model, adjusted costs were 270% higher for opioid abusers than nonabuser controls, 172% higher for members living in the West region (compared with the South), and were 124% higher for females ($P<0.001$). Costs were also more likely to be higher for members with pain-related conditions (126%, $P<0.001$) and higher RxRisk scores (124%, $P<0.001$).

CONCLUSIONS: Members with diagnosed opioid abuse in the Humana commercial population experienced significantly higher health care-related costs than nonabusers. To our knowledge, this study provides the first published estimates of diagnosed opioid abuse and its cost burden in the Humana commercial membership.

SPONSORSHIP: This research was funded by Humana, Inc., Louisville, KY, and Pfizer Inc., New York, NY.

Quality Care Improvement Through Engaged Provider Response to Medication Therapy Management Recommendations

***Olmon MA**,* Robertson DW, Graalum DC, Noonan-Harnsberger H. Providence Health Plans, 3601 S.W. Murray Blvd., Beaverton, OR 97005; Margaret.Olmon@providence.org, 503.574.6457*

BACKGROUND: A variety of Medication Therapy Management (MTM) programs have evolved over the past 6 years. Programs are challenged to engage providers by identifying important patient issues with variable access to clinical data.

OBJECTIVE: To (a) evaluate the impact of pharmacist clinical recommendations on the quality of vulnerable elder care, (b) measure provider response to recommendations, and (c) determine the impact of adding the number of MTM recommendation responses as a component of an existing provider quality bonus program.

METHODS: MTM at Providence Health Plans is provided by in-house clinical pharmacists. These pharmacists complete a Comprehensive Medication Review (CMR) or Individual Targeted Medication Review (I-TMR) for 100% of the almost 4,000 members enrolled. For both types of reviews, the pharmacist examines prescription and medical claims and, when accessible, provider electronic medical records. For a CMR, the pharmacist contacts the member by phone, discussing medical history, medication-related questions, and issues related to health status. If the member declines a conversation, the completed evaluation is called an I-TMR. Following both types of reviews, recommendations are sent to providers focusing on up to 3 key concerns. For this analysis, the impact on patient quality was measured for members who were continuously enrolled in MTM and could act as their own control. In 2011, an addition to the existing quality bonus was offered to providers who returned any response to at least 80% of MTM recommendations sent to them. In this review, the percentage of provider responses received in 2010 and 2011 were compared to measure increased provider engagement and evaluate medication changes expected based on provider responses received.

RESULTS: The 1,631 members continuously enrolled from 2009 through 2011 were included for analysis. In 2010, 1,443 identified issues led to recommendations. In 2011, 2,698 provider recommendations were made. In a chronically ill population that had grown a year older, a number of clinical measures improved or remained stable from 2010 to 2011. The number of individuals with documented hemoglobin A1c (A1c) values remained stable (507 vs. 504), the percentage of members with A1c <8% increasing 1.9% (86.0% to 87.9%). The rates of use of at least 1 high-risk medication (HRM; 36.4% vs. 34.5%) and the use of 2 or more HRMs (9.7% vs. 8.9%) both decreased. The percentage of members diagnosed with rheumatoid arthritis who also were dispensed a disease-modifying antirheumatic drug grew from 69.0% to 73.1%. Members also remained persistent on chronic medications: angiotensin-converting enzyme inhibitors (96.7% to 95.9%), digoxin (96.4% to 98.7%), diuretics (95.9% to 94.8%), and anticoagulants (70.1% to 70.1%). Comparing data from 2010 to 2011, there was a 7% increase in both the percentage of providers responding to recommendations (63% to 70%) and in provider agreement to consider a change in treatment (50% to 57%).

CONCLUSIONS: A pharmacist with member-specific care plan recommendations that result from medical as well as pharmacy data can lead to stronger provider engagement and improvements in quality measures while meeting Medicare MTM requirements.

SPONSORSHIP: This research was conducted by Providence Health Plans, Beaverton, OR, without external funding.

Resource Utilization and Costs of Multiple Sclerosis Patients with High Relapse Rate Using a Claims Database

***Raimundo K**,* Tian H, Zhang X, Zhou H, Kahler K, Agashivala N, Kim E. Novartis Pharmaceuticals Corporation/University of Utah, One Health Plaza, East Hanover, NJ 07936; karina.raimundo@novartis.com, 862.778.3707*

BACKGROUND: Multiple sclerosis (MS) is a chronic disease that affects adults. Multiple relapses can indicate high disease activity (HDA) and can restrict the individual's life, resulting in a major financial burden and high health care resource utilization. There are very few studies evaluating the impact of HDA on outcomes using real-world claims data.

OBJECTIVE: To identify HDA MS patients and compare the differences in resource utilization and costs between HDA and non-HDA patients, controlling for baseline demographics and comorbidities

METHODS: A retrospective longitudinal study was conducted using MarketScan commercial claim and Medicare database. Patients included had at least 1 ICD-9 for MS (340.XX) in 2009 and 1 in the prior year, were 18 years or older in 2009, and had continuous enrollment in the year of 2009 and 2010. HDA was defined in 2009 as having 2 relapses in the year, and relapse was defined according to Chastek 2010 algorithm. Multivariate analyses were conducted to compare all-cause and MS-specific emergency room (ER) and hospitalizations (logistic regression) and all-cause costs (Gamma regression with log link) in 2010 between HDA and non-HDA patients, controlling for age, gender, geographic region, health plan type, employment status, Charlson

comorbidity index (CCI), MS symptoms, and disease-modifying treatment (DMT) use in 2009.

RESULTS: 19,219 patients met the study criteria. 94.71% (n = 18,202) had less than 2 relapses and 5.29% (n = 1,017) had more than 2 relapses in 2009. HDA patients were younger (50 vs. 52 years) and less likely to be employed (50.15% vs. 56.47%). Mean CCI was 0.82 for HDA (vs. 0.56). HDA patients had more MS symptoms (82.1% vs. 68.8%) and were more likely to use DMT in 2009 (67.7% vs. 63.6%, $P = 0.008$). Unadjusted results in 2010 showed that HDA patients had more all-cause and MS-specific hospitalizations (23.21% vs. 11.43% and 7.37% vs. 1.63%) and ER visits (32.84% vs. 22.70% and 15.24% vs. 7.6%) compared with non-HDA patients. After adjusting for patient demographics, CCI, MS symptoms, and DMT use, HDA patients were more likely to be hospitalized (OR all-cause: 2.2 95% CI: 1.8, 2.5; OR MS specific: 3.9, 95% CI: 2.9; 5.1) and have ER visits (OR all-cause: 1.5, 95% CI: 1.3; 1.7; OR MS specific: 1.9, 95% CI: 1.6; 2.3) than non-HDA patients. Mean unadjusted total all-cause cost (excluding DMT drug costs) for the HDA group was US$30,286 compared with US$14,568 for the non-HDA group. Adjusted cost difference between HDA and non-HDA was $12,648 ($27,700 vs. $15,052; 95% CI: $10,568; 15,035; $P < 0.0001$) for all.

CONCLUSIONS: Patients with 2 or more relapses annually have high resource utilization and are more costly. After adjusting for differences in patient characteristics, the results were robust. Two or more relapses annually seems to be indicative of HDA; however, a more robust algorithm needs to be developed to also incorporate clinical aspects of the HDA definition.

SPONSORSHIP: This research was conducted by Novartis Pharmaceuticals Corporation, East Hanover, NJ without external funding.

Retrospective Analysis of Drug Therapy Continuation Following Implementation of a Limited Pharmacy Network

Roman B,* *Pazirandeh M, Voloudakis M. CVS Caremark, 620 Epsilon Dr., Pittsburgh, PA 15238; brian.roman@caremark.com, 412.967.8235*

BACKGROUND: Restricted pharmacy networks, where 1 or more retail pharmacy chains are excluded from coverage, are growing in popularity with pharmacy benefit programs. These networks are attractive to payers due to the cost savings achieved with low member disruption; however, there is little research showing how limiting member access to retail pharmacies affects clinical outcomes.

OBJECTIVE: To measure drug therapy continuation rates for prescription drug utilizers within a payer client that implemented a restricted pharmacy network.

METHODS: A large employer client implemented a restricted pharmacy network where 1 national retail pharmacy chain was excluded from coverage. Affected members received a letter identifying 3 pharmacy alternatives near their homes with instructions on transferring their prescriptions. A pre-/post-analysis was conducted on continuously enrolled members who filled 2 or more prescriptions for maintenance medications and where at least 1 prescription was filled at the pharmacy chain to be excluded upon implementation of the restricted network. Members were tracked for 6 months prior to and 6 months after the implementation of the restricted pharmacy network. Members who filled at least 1 prescription for a drug in the same therapeutic class during the post-period were identified as having continued their drug therapy. Members with no fill for a drug in the same therapeutic class during the post-period were identified as discontinuing drug therapy. The percentage of members continuing drug therapy was calculated both overall and at the therapeutic class level with further analysis of continuation by age, sex, and distance to the nearest alternative pharmacy.

TABLE Therapy Continuation Rates: Top 10 Therapeutic Classes by Number of Utilizers in the Pre-Period

Therapeutic Class	% Utilizers Continued Therapy	% Utilizers Discontinued Therapy
HMG-CoA reductase inhibitors	94.5	5.5
Beta blockers cardio-selective	95.5	4.5
Antihypertensive combinations	94.9	5.1
Proton pump inhibitors	93.3	6.7
Ace inhibitors	94.4	5.6
Nonsteroidal anti-inflammatory agents	93.1	6.9
Calcium channel blockers	93.6	6.4
Thyroid hormones	96.3	3.7
Biguanides	95.9	4.1
Selective serotonin reuptake inhibitors	93.7	6.3

RESULTS: A total of 12,713 members met the inclusion criteria for the pre-period. Of these members, 11,843 (93.2%) continued, and 870 (6.8%) did not continue their drug therapy during the post-period. Therapy continuation rates ranged from 93.1% to 96.3% of utilizers within the top 10 therapeutic classes. Therapeutic classes with the lowest continuation rates included valproic acid (82.5%), combination contraceptives-oral (86.9%), antihististamines-nonsedating (87.6%), steroid inhalants (89.5%), and antineoplastic-hormonal and related (89.9%). All other therapeutic classes had continuation rates of 90.0% or higher. Although members who continued therapy were significantly older ($t = 12.7$, $P = 0.004$; 59.8 vs. 53.3 years), distance to a network pharmacy ($t = 1.2$, $P = 0.218$; 1.3 vs. 1.4 miles) and member sex ($\chi 2 = .02$, $P = 0.883$) had no impact on likelihood of therapy continuation.

CONCLUSIONS: Most members who used a soon-to-be noncovered retail pharmacy successfully transitioned to a pharmacy alternative post-implementation of a restricted pharmacy network. Additional outreach targeted to specific age groups and within certain therapeutic classes may lead to higher continuation rates for plans considering this strategy.

SPONSORSHIP: This research was conducted by CVS Caremark, Woonsocket, RI, without external funding.

Retrospective Analysis of Generic Dispensing Rates, Gross Cost, and Drug Therapy Continuation Rates Following Implementation of a Value Formulary

Goldberg L,* *Sun J, Roman B, Voloudakis M. CVS Caremark, 620 Epsilon Dr., Pittsburgh, PA 15238; lauren.goldberg@caremark.com, 412.967.8234*

BACKGROUND: With many factors contributing to overall increasing health care costs, payer clients are seeking ways to save on their prescription benefits. The implementation of a Value Formulary, a closed but therapeutically comprehensive formulary focusing on generic coverage with brand coverage where clinically necessary, can drive significant savings for payer clients. The Value Formulary complies with health care reform on preventative therapy and applies utilization management tools including prior authorization, step therapy, and quantity limits where appropriate. The Value Formulary is a clinically sound tool that may be used to drive generic utilization and overall cost savings; however, there is little research on the impact of therapy continuation rates with implementation of such formularies.

OBJECTIVE: To measure pre- and post-generic dispensing rates (GDR), gross costs, and drug therapy continuation rates for prescription drug

TABLE Therapy Continuation Rates

Condition	CAD	DM	HF	HTN	Asthma	CHO
2010-2011 therapy continuation rates (%)	70.0	89.0	92.0	87.0	64.0	86.0
2011-2012 therapy continuation rates (%)	79.0	86.0	75.0	87.0	50.0	83.0
P value	0.282	0.231	0.010	0.975	0.034	0.171

Members may overlap in more than 1 disease state. The year 2010 includes paid claims from September 15, 2010, through December 31, 2010. The year 2011 includes paid claims from January 1, 2011, through March 31, 2011.

CAD = coronary artery disease; DM = diabetes; HF = heart failure; HTN = hypertension; CHO = hyperlipidemia.

utilizers within an employer payer client who implemented a Value Formulary.

METHODS: A pre- and post-analysis was conducted from 2011 through the first quarter of 2012. GDR and gross cost per member per month (PMPM) were calculated. To assess therapy continuation, members that were continuously eligible were evaluated, and claims history for maintenance medications were compared 3 months prior to and 3 months after the implementation. Members who filled at least 1 maintenance prescription in the same therapeutic class during the post-period were identified as having continued their drug therapy. Members with no fill for a maintenance prescription in the same therapeutic class were identified as having discontinued their drug therapy. The percent of members continuing drug therapy was calculated for 6 common chronic conditions and compared with previous therapy continuation rates.

RESULTS: Based on utilization, GDR increased from 73.0% in 2011 to 87.0% in 2012 (t = 51.2, *P* = 0.001). In addition, gross cost PMPM was significantly reduced from $75 PMPM to $56 PMPM (t = 9.4, *P* = 0.003). Therapy continuation rates ranged from 50.0% to 87.0% within the 6 common chronic conditions (table). Therapy continuation rates from 2010 to 2011 were similar when compared with therapy continuation rates from 2011 to 2012 with the exception of heart failure and asthma.

CONCLUSIONS: Implementation of the Value Formulary showed a statistically significant increase in GDR and decrease in gross cost PMPM compared with a traditional formulary. Most members continued their maintenance drug therapy in the 6 common chronic conditions analyzed. Additional outreach targeted within certain therapeutic classes, as well as improved point of sale messaging, may lead to higher continuation rates for plans considering this strategy.

SPONSORSHIP: This research was conducted by CVS Caremark, Pittsburgh, PA, without external funding.

Single-Pill Versus Loose-Dose Combination Triple Therapy for Hypertensive Patients: Managed Care Formulary Impact

***Ogden K**,* Panjabi S, Neil N. Oxford Outcomes, an ICON plc Company, 188 The Embarcadero, Ste. 200, San Francisco, CA 94105; kristine.ogden@iconplc.com, 425.742.9804*

BACKGROUND: Hypertension is a pervasive chronic illness in the United States that requires sustained treatment in order to avoid morbidity and mortality. Most patients with hypertension require 2 or more agents to achieve adequate blood pressure (BP) control; many require 3 or more agents. BP control is strongly associated with reduced cardiovascular disease risk and, in turn, lower medical care costs. However, a major obstacle to BP goal attainment is poor regimen adherence and persistence, which are exacerbated by regimen complexity.

OBJECTIVE: To estimate the managed care budget impact of regimen simplification via greater use of triple-agent single-pill combination (SPC) regimens (valsartan/amlodipine/hydrochlorothiazide or olmesartan/amlodipine/hydrochlorothiazide) within a formulary of comparable 2- and 3-pill loose-dose combination (LDC) regimens (angiotensin II receptor blockers [ARB] + amlodipine + hydrochlorothiazide) for hypertensive patients not controlled on dual therapy.

METHODS: We used a budget-impact model to consider the impact of increasing the use of triple-therapy SPC regimens for hypertensive patients not controlled on dual therapy. Our analysis assumes that 10,568 patients in a hypothetical plan size of 5 million would be eligible for triple antihypertensive therapy as a 1-, 2-, or 3-pill daily regimen of ARB + amlodipine/hydrochlorothiazide. Price, market share, and tier/copay for each aforementioned antihypertensive agent was obtained from published sources, as were percent of patients with 30- versus 90-day refill schedules. Adherence and persistence with therapy vary by regimen type, which, in turn, influence pharmacy costs, cardiovascular outcomes, and medical care costs.

RESULTS: Among hypertensive patients not controlled on dual therapy, our model estimated that a doubling of SPC triple-therapy use (to 31% from 16%) within a formulary of 1-, 2-, and 3-pill alternative regimens would result in higher pharmacy costs ($7.0 million vs. $6.2 million), fewer cardiovascular events (311 vs. 313), and lower medical care costs ($67.1 million vs. $67.5 million) over the course of 1 year. Taken together, the model projects a net-neutral economic impact from the health plan perspective ($0.005 lower per-member-per-month costs with 31% use of SPC therapy).

CONCLUSIONS: Improved patient adherence/persistence with SPC triple antihypertension therapy is associated with better cardiovascular outcomes and reduced medical care costs, which offset incremental drug acquisition costs.

SPONSORSHIP: This research was funded by Daiichi Sankyo, Inc., Parsippany, NJ.

Statin Medication Adherence Association with Hospitalizations or Emergency Room Visits and Total Cost of Care over 2 Years

***Gleason PP**,* Qiu Y, Starner CI, Ritter S. Prime Therapeutics, LLC, 1305 Corporate Center Dr., Eagan, MN 55121; pgleason@primetherapeutics.com, 612.777.5190*

BACKGROUND: Poor medication adherence has been reported to be associated with worse medical outcomes and increased medical costs. However, minimal data are available quantifying outcome and cost differences in members adherent and nonadherent to statin medications among commercially insured individuals followed for more than 1 year.

OBJECTIVE: To examine the association between medication adherence, hospitalization or emergency room (ER) visits, medical costs, and pharmacy costs among individuals adherent and nonadherent to their statin medications.

METHODS: Retrospective pharmacy and medical claims data from a 1.2 million member commercial plan were queried to identify members continuously enrolled from 2007 through 2010. Members were required to have either 2 separate hypercholesterolemia office visit claims or a hypercholesterolemia-related hospitalization claim in 2008. The members' first 2008 medical encounter was defined as the index date. Members were required to have a statin supply on index date or a high risk condition diagnosis in the year prior to index date. High-risk conditions were defined as diabetes mellitus (DM), coronary artery disease (CAD), embolic stroke, or peripheral vascular disease (PVD). All

TABLE Multiple Sclerosis Specialty Drug

2-Year Outcomes Assessment	Adherent (PDC ≥80%) n=21,693	Nonadherent (PDC <80%) n=24,176	*P* Value[a]
Unadjusted all cause hospitalization/ER visit	26.5%	29.1%	<0.0001
All medical costs[b], $ (SD)	12,487 (7,490)	13,254 (9,016)	<0.0001
All pharmacy costs, $ (SD)	5,585 (3,409)	3,979 (2,595)	<0.0001
Total cost of care (medical and pharmacy), $ (SD)	18,034 (10,481)	17,225 (11,172)	<0.0001

[a]*Hospitalization/ER visit rate compared by log-rank test and costs compared by GLM.*

[b]*All medical costs are allowed amounts (plan and member paid) from all facility and professional claims including office visits, hospitalizations, procedures, laboratory testing, and ancillary.*

ER = emergency room; GLM = generalized linear model; PDC = proportion of days covered; SD = standard deviation.

members were followed for 2 years after their 2008 index dates. All statin drug claims were assessed to identify members as adherent (proportion of days covered [PDC] ≥80%) or nonadherent (PDC<80%). All medical and pharmacy claim total allowed amounts (plan and member) were summed to determine total cost of care. The Kaplan-Meier method was used for observed hospitalization- and ER-rate calculation and association with adherence was analyzed using a Cox proportional hazard regression model with adjustment for age; gender; zip-code derived income and education; Charlson Comorbidity score; existence of baseline depression or bipolar disorder; DM, CAD, PVD, or embolic stroke; and high-deductible health plan enrollment. Cost analyses were performed using the generalized linear model (GLM) with Gamma log link and adjusted for the same covariates.

RESULTS: Of the 45,869 members meeting all inclusion criteria, 21,693 (47.3%) were adherent and 24,176 (52.7%) nonadherent during the 2-year follow-up. The adherent group was associated with a significantly lower hospitalization/ER visit rate (HR of 0.91, 95% CI, 0.87 to 0.94), significantly lower medical costs ($767), but higher pharmacy costs $1,606, and higher total cost of care $809.

CONCLUSIONS: In this 2-year total cost of care analysis, individuals adherent to statin medication had an associated unadjusted 2.6 percentage point lower hospitalization/ER visit rate, which remained significantly lower risk in the multivariate Cox model. Although medical costs were significantly lower, higher pharmacy costs resulted in higher total costs of care. Future analyses are required to determine if longer follow-up will identify lower total cost of care among members adherent to their statin medications.

SPONSORSHIP: This research was conducted by Prime Therapeutics, LLC, Eagan, MN, without external funding.

The Identification and Exclusion of Non-FDA Approved Drugs in a Commercial 3-Tier Open Formulary

***Cotter ND**.* Blue Cross and Blue Shield of Florida, 4800 Deerwood Campus Pkwy., Bldg. 900, Jacksonville, FL 32246; Nancy.Cotter@bcbsfl.com, 904.905.5037*

BACKGROUND: The FDA estimates that there are several thousand illegal, unapproved drugs that are on the market today. This estimate is composed of drugs that contain several hundred different active ingredients in various strengths, combinations, and dosage forms. The FDA estimates that unapproved drugs represent approximately 2% of all prescriptions dispensed in the United States.

TABLE Pharmacy Claims & Unique Members

Total Claims-Unapproved Drugs	Unique Utilizing Members	Plan-Paid Savings
83,006	35,938	Approximately $3.0 million

OBJECTIVE: The FDA has described the widespread utilization of unapproved drugs as a significant public health issue and has increased resources and activities to remove these products from the market. The majority of Blue Cross and Blue Shield of Florida's (BCBSF) commercial pharmacy members have a 3-tier open formulary for their pharmacy benefits. BCBSF completed a retrospective analysis of 2009 commercial pharmacy claims to identify pharmacy claims for selected unapproved drugs and unique utilizing members.The results of this analysis were that BCBSF paid for more than 50,000 claims in 2009 for these unapproved drugs for approximately 28,000 members. To help ensure the health and safety of our members, BCBSF in conjunction with our pharmacy benefit management company (PBM), Prime Therapeutics, determined that the development of a repeatable process to identify and exclude unapproved prescription drugs from our 3-tier open formulary on an ongoing basis was needed

METHODS: The FDA does not maintain a list of unapproved drugs. Development of an unapproved drug list requires a manual case by case review of specific drugs. However, the FDA databases do allow for verification of the approval status of a drug by utilizing the National Drug Code Directory. After the initial unapproved list was compiled by BCBSF, a retrospective pharmacy claims analysis was completed to validate the exclusion list. This analysis included all paid commercial pharmacy claims in 2009 and identified almost 36,000 members that had a claim for at least 1 of the unapproved drugs on the exclusion list. The table lists the total unapproved drug claim counts and unique utilizing members from this analysis as well as estimated plan-paid savings. The plan-paid savings is based on the annualized spend for these drugs in 2009.

RESULTS: The non-FDA approved exclusions were implemented for all BCBSF pharmacy plans on January 1, 2010. Prior to implementation of the drug exclusions, BCBSF completed extensive communications to our members and providers. Our network pharmacies also received detailed communications with all drugs listed that would no longer be covered in addition to point-of-sale messaging.

CONCLUSIONS: Since the initial identification and exclusion of unapproved drugs was implemented on January 1, 2010, BCBSF has expanded the exclusion list 4 times. Additional unapproved drugs were added to the exclusion list in April and October 2010 as well as in April and October 2011. Through the case-by-case review process, BCBSF identified and implemented the exclusion or removal of approximately 800 drugs and topical products from BCBSF's open formulary in 2010. BCBSF's goal is to continue this ongoing process supported by our PBM, Prime Therapeutics, to identify additional illegally marketed drugs and topical products for removal from our open formulary. Health plans working in conjunction with the FDA have a vital role in reducing the utilization of unapproved drugs and ultimately improving medication safety for consumers in the United States.

SPONSORSHIP: This research was conducted by Blue Cross and Blue Shield of Florida, Jacksonville, FL, without external funding.

The Role of Community Pharmacy Disease Management Programs in a Value-Based Insurance Design: Results from Kroger Pharmacy Coaching Programs

Kirby J, Frede S, Berry E, Heaton PC. The Kroger Co., 150 Tri-County Pkwy., Cincinnati, OH 45246; james.kirby@kroger.com, 513.782.3366*

BACKGROUND: Pharmacist-provided care improves patient outcomes, resulting in fewer emergency room visits, fewer inpatient hospitalizations, better guideline concordant care, and lower health care costs. By lowering out-of-pocket expenses to plan participants, value-based insurance design improves medication adherence and outcomes.

OBJECTIVE: To determine if a combined approach of medication copay waiver/reduction and disease management improves clinical outcomes for active employees and retirees of self-insured employers in Cincinnati, Ohio.

METHODS: From 2008-2010, specially trained Kroger pharmacists enrolled eligible employees from the City of Cincinnati and The Kroger Company into either (a) a Diabetes Coaching Program (DCP) or (b) a Heart Healthy Coaching Program (HHCP). Participants were seen every 1 to 3 months for medication therapy management and health-related counseling. Blood pressure and body mass index (BMI) were assessed every visit, while hemoglobin A1c (A1c) and a total lipid panel were analyzed every 3 to 6 months. Patients received waived/reduced copays on all disease-related medications for active participation in the program.

RESULTS: There were 478 and 468 patients enrolled in the DCP and HHCP from 2008-2010, respectively. Average A1c values for patients enrolled in the DCP dropped from 7.60 at the time of program enrollment to 6.93 1 year after enrollment. The proportion of patients in the DCP with an A1c less than 7 rose from 46.5% at the time of enrollment to 62.3% 1 year after enrollment. DCP patients' average low-density lipoprotein (LDL) levels and systolic blood pressure dropped from 92.28 to 82.24 and 135.05 to 130.11 during the same time period, respectively. For patients enrolled in the HHCP, average LDL levels and systolic blood pressure dropped from 103.75 to 98.50 and 134.05 to 127.03 from the time of program enrollment to 1 year after enrollment, respectively.

CONCLUSIONS: Community pharmacy disease management programs in conjunction with a value-based insurance design can lead to improved patient outcomes.

SPONSORSHIP: This research was conducted by University of Cincinnati, Cincinnati, OH, without external funding.

Understanding Reasons for Nonadherence to Atypical Antipsychotic Medications in Claims Data: Results from a Pilot Study

***Cutts S**,* Gorsh B, Kostarides S, Makanji S, Makanji H, Lord T. CDMI Health, 360 Thames St., Ste. 4B, Newport, RI 02840; Scutts@cdmihealth.com, 401.619.5212*

BACKGROUND: Atypical antipsychotics are indicated for the treatment numerous conditions, including schizophrenia and bipolar disorder. Adherence in both patient populations remains a challenge, with numerous studies reporting high percentages of non- or partially adherent patients. Lower adherence to antipsychotic medications is linked to a greater risk for hospitalizations and emergency room (ER) visits. By identifying specific patient-reported barriers, health plans can design targeted interventions aimed at improving adherence in this patient population.

OBJECTIVE: To identify patient-reported barriers and reasons for atypical antipsychotic medication nonadherence in claims data.

METHODS: Using a large health plan pharmacy database (approximately 1.2 million lives), health plan members with at least 3 prescriptions for the same oral atypical antipsychotic (AA) prescriptions in Q3 and Q4 of 2011 were identified. From this patient population, nonadherent patients were identified (medication possession ratio [MPR] <0.80) during the measurement year. Additional exclusion criteria included <18 years of age, long-acting injectable drugs, and oral solutions of AAs. A group of nurses and pharmacists implemented a telephonic intervention program in order to capture specific barriers reported in this patient population, with the ultimate goal of improving adherence. Upon initial outreach, 40 randomly chosen patients were identified for this analysis. Baseline characteristics were measured for the pilot patients between 2011-2012.

RESULTS: The mean age of this population was 44.0 years, and 47.5% were female. Baseline mean MPR was reported as 0.55. Patients had an average of 5.75 AA drug dispensings throughout the study period. 67.5% of patients had a gap in therapy of >45 days with an average of a 68.5-day maximum gap in therapy. Mean out-of-pocket costs for AAs were shown to be $38.07 (standard deviation: 67.08) for the baseline period. Of the 40 patients surveyed, 77.5% did not feel that there were any issues with taking the medications as prescribed. Additionally, 20.0% of patients cited out-of-pocket cost as a barrier, followed by side effects (17.5%) and a doctor change in therapy (17.5%) for reasons for low adherence. 12.5% of patients did not perceive the drug to be effective, and 5.0% cited forgetfulness and supply issues (out of stock) as a barrier.

CONCLUSIONS: The majority of surveyed patients did not feel that there were any issues with nonadherence to their AA medications. These results are inconsistent with the claims data and are a potential educational opportunity for future outreach to these patients.

SPONSORSHIP: This research was conducted by CDMI Health, Newport, RI, without external funding.

Utilization of Augmentation Agents for the Treatment of Depression: Analysis of a Psychiatric Electronic Medical Record Dataset

*Gersing K, Sheehan J, Burchett B, Zhu L, Forbes A, **Kalsekar I**.* Bristol-Myers Squibb, 777 Scudders Mill Rd., MS P23-31, Plainsboro, NJ 08536; iftekhar.kalsekar@bms.com, 609.897.5693*

BACKGROUND: The American Psychiatric Association (APA) recommends consideration of treatment augmentation for patients with depression after 4-8 weeks of inadequate response to initial antidepressant treatment. However, limited real-world data exist on implementation of augmentation strategies in this population.

OBJECTIVE: To examine the real-world utilization of augmentation agents in depression and assess demographic and clinical characteristics of patients receiving these agents.

METHODS: A cross-sectional design was used. Patients without psychosis/psychotic features initiating augmentation therapy for treatment of depression between January 2001 and June 2011 were identified from a psychiatric electronic medical record (EMR) dataset (MindLinc). Augmentation was defined as the prescription of a combination of antidepressants or an antidepressant in conjunction with an agent that is not conventionally used as first-line monotherapy (i.e., atypical antipsychotics, mood stabilizers/anticonvulsants, or stimulants). Patient demographics and clinical profile, psychiatric drug utilization patterns, and site characteristics were obtained from EMR data. Clinical severity of patients at the time of augmentation was documented using the Clinical Global Impressions-Severity (CGI-S) scale. Logistic regression models were used to assess the clinical and demographic predictors of type of augmentation agent (in a multivariate framework). Augmentation with an atypical antipsychotic was used as the reference category for the analyses, since it constitutes the only FDA-approved augmentation option.

RESULTS: A total of 3,209 patients initiated augmentation therapy for depression with most receiving treatment in an academic center (54.1%) or community mental health center (32.7%). Patients were 70.7% white and 69.8% female, with a mean age of 43.8 years. Most patients augmented with a combination of antidepressants (75%), followed by atypical antipsychotics (11.1%), mood stabilizers/anticonvulsants (8.3%), and stimulants (5.2%). Within combination antidepressants, patients most commonly received an SSRI (selective serotonin reuptake inhibitor) in combination with bupropion (23.1%) followed by SSRI+serotonin modulator or norepinephrine-serotonin modulator (15.9%). Patients receiving atypical antipsychotic augmentation most commonly received quetiapine (39.6%) or aripiprazole (31.2%). Gabapentin (39.1%) and lamotrigine (21.4%) were the most common mood stabilizers/anticonvulsants; methamphetamine (55.7%) and dextroamphetamine (35.3%) were the most common stimulants. Logistic regression demonstrated that baseline clinical severity of patients was the strongest and most consistent predictor of the augmentation strategy adopted. Compared with patients with mild symptoms (CGI-S: 2-3), patients with severe clinical symptoms (CGI-S: 5-7) were 2.75 times more likely to receive an atypical antipsychotic versus combination of antidepressant (95% CI=1.87-4.04). These severe patients were also more likely to receive atypical antipsychotics compared with mood stabilizers (OR=3.35, 95% CI=1.90-5.91) or stimulants (OR=4.05, 95% CI=1.78-9.21). Regression results also indicated that male patients, nonwhites, those with concomitant psychiatric diagnoses, and users of benzodiazepines were significantly more likely to receive augmentation with an atypical antipsychotic.

CONCLUSIONS: Clinicians primarily prescribe a combination of antidepressants for augmentation of initial antidepresant treatment and appear to disproportionately use atypical antipsychotics, the only approved augmentation option, for patients with severe depression.

SPONSORSHIP: This research was funded by Bristol-Myers Squibb, Princeton, NJ, and Otsuka Pharmaceutical Co., Ltd, Tokyo, Japan.

Utilization Patterns of Biologics Before and After Implementation of a Managed Care Step-Therapy Policy

Ingham M, Kozma C, Paris A, Schmeichel-Mueller C. Janssen Scientific Affairs, LLC, 850 Ridgeview Dr., Horsham, PA 19044; MIngham2@its.jnj.com, 267.221.0524*

BACKGROUND: Significant increases in the use of step-edit policies affecting intravenously (IV) delivered biologics in the rheumatology, gastroenterology, and dermatology therapeutic areas are being implemented in an attempt to reduce utilization and costs in new patients initiating biologics. Published evidence on the effect of these policies on overall utilization of services is limited.

OBJECTIVE: To assess utilization patterns of abatacept (ABT), adalimumab (ADA), certolizumab (CTZ), etanercept (ETA) and infliximab (IFX) before and after the implementation of a step-therapy policy.

METHODS: The Wolters Kluwer Source Rx and Medical databases from January 1, 2006, through April 30, 2011, were used to conduct a longitudinal descriptive analysis of the number of patients with biologic claims within 365 days before and after step-edit implementation. Available data included payer, prescription (Rx), diagnosis (Dx) and procedure (Px) information with unique anonymized patient identifiers associated with each claim. To be included in the analysis, patients were required to have at least 1 National Drug Code (NDC) or Healthcare Common Procedure Coding System (HCPCS) billed claim for ABT, ADA, CTZ, ETA or IFX, regardless of indication, at any time during the study period (365 days pre- and post-index). To establish a proxy for eligibility, patients were required to have at least 1 prescription claim (any type) and medical claim (all cause) more than 1 year before and after the policy change date (index). The number and percentage of patients receiving a biologic was described in quarterly increments for the 365 days before and after implementation of the policy change. The analysis was stratified by product. Quarters 1-4 constituted the 365-day pre-index period and quarters 5-8 constituted the 365-day post-index period.

RESULTS: A total of 252 patients who were members of 4 different plans that implemented a policy change and who met the analysis criteria were included. The majority of patients (71.4%) had a claim for a biologic during the first quarter (i.e., constituted an existing patient population not likely to be impacted by a new step-therapy policy change focused on new patients). 87.3% of the patients in the pre-index and 75.4% in the post-index periods received only 1 biologic. Less than 10% of patients initiated therapy in any of quarters 2-8, with the percentages of patients initiating therapy declining each quarter. The percentage of patients by product in the pre- /post-index periods were 3.2%/4.4% (ABT); 37.6%/37.6% (ADA); 0.8%/2.0% (CTZ); 44.8%/38.4% (ETA); 9.6%/11.6% (IFX); and 92.0%/84.8% (Overall). Percentage changes were +37.5% (ABT); 0.0% (ADA); +150.0% (CTZ); -14.3% (ETA); +20.8% (IFX); and -7.8% (Overall). Eligibility had to be established based on plan information in the pharmacy claims data. This may lead to an under-representation of patients with low utilization rates. These data contained relatively few patients who initiated therapy after the policy change, who would be the typical patients impacted by the change to a new step-therapy policy.

CONCLUSIONS: Policies designed to reduce overall patient proportions using infusion biologics did not appear to have the desired effect in this population.

SPONSORSHIP: This research was conducted by Janssen Scientific Affairs, LLC, Horsham, PA, without external funding.

Managed Care and Other Pharmacy Residencies and Fellowships

This list of residencies and fellowships is published to coincide with the Academy of Managed Care Pharmacy's annual Educational Conference. These programs are described briefly below; more complete and continuously updated information is available online on the AMCP website (http://www.amcp.org/Residencies/), including start dates, minimum requirements, fringe benefits, and program features. "Candidate" in the "Accreditation Status" field indicates that the program has submitted an application for accreditation but has not yet undergone an on-site survey. The 4 categories of programs include accredited managed care pharmacy residency programs, other accredited pharmacy residency programs, nonaccredited pharmacy residency programs, and fellowships.

ACCREDITED MANAGED CARE PHARMACY RESIDENCY PROGRAMS

American Health Care

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: For APPE purposes: California Northstate College of Pharmacy, Touro University, University of the Pacific, Western University
Application Deadline: January 15
Estimated Stipend: $50,000
Contact Information:
Christine Lee, PharmD, BCPS, CLS, Chief Clinical Officer
American Health Care
2217 Plaza Drive, Rocklin, CA 95765;
Tel.: 916.773.7227; E-mail: residency@americanhealthcare.com

Blue Cross Blue Shield of California

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 15
Estimated Stipend: $50,000
Contact Information:
Diem Huynh, PharmD, Director, Residency Program,
Clinical Pharmacy Programs Coordinator
Blue Shield of California
50 Beale Street, 21-C0347, San Francisco, CA 94105;
Tel.: 415.229.5994; E-mail: Diem.Huynh@Blue Shieldca.com
https://www.Blue Shieldca.com/bsc/pharmacy/pharmacy_residencies.jhtml

Blue Cross Blue Shield of Michigan

PGY1 Managed Care Pharmacy
Accreditation Status: candidate
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of Michigan
Application Deadline: January 6
Estimated Stipend: $43,000
Contact Information:
Laurie Wesolowicz, PharmD, Director of Pharmacy
Blue Cross Blue Shield of Michigan
600 E. Lafayette Boulevard, Detroit, MI 48226-2998;
Tel.: 313.448.5956; E-mail: lwesolowicz@bcbsm.com

Coventry Health Care of Kansas, Inc.

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of Missouri, Kansas City (UMKC)
Application Deadline: January 11
Estimated Stipend: $43,000
Contact Information:
Diana Toe, PharmD, Residency Program Director,
Regional Clinical Pharmacist
Coventry Health Care of Kansas, Inc.
8320 Ward Parkway, Kansas City, MO 64114;
Tel.: 866.795.3995; E-mail: dctoe@cvty.com
http://www.cvty.com

CVS Caremark

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2 positions in Texas
Affiliation: none
Application Deadline: January 11
Estimated Stipend: competitive
Contact Information:
Melissa Jay, PharmD, Clinical and Client Operations Manager
CVS Caremark
750 West John Carpenter Freeway, Irving, TX 75039;
Tel.: 469.524.5832; E-mail: melissa.jay@caremark.com
http://info.cvscaremark.com/careers/intern-resident-programs#97

CVS Caremark

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1 (Pittsburgh, PA)
Affiliation: University of Pittsburgh School of Pharmacy
Application Deadline: January 11
Estimated Stipend: competitive
Contact Information:
Mike Safranyos, PharmD, Clinical Pharmacist
CVS Caremark
105 Mall Boulevard, Monroeville, PA 15146;
Tel.: 800.238.7828, ext. 56149; E-mail: michael.safranyos@caremark.com

Department of Defense Pharmacoeconomic Center

PGY1 Managed Care Pharmacy
Accreditation Status: pre-candidate
Length of Program: 12 months
Number of Positions: 1-2
Affiliation: none
Application Deadline: January 11
Estimated Stipend: $50,000+ or commensurate with rank for active duty
Contact Information:
Amy Lugo, PharmD, BCPS, BC-ADM, Residency Program Director
Department of Defense Pharmacoeconomic Center
4130 Stanley Road, Suite 208, Fort Sam Houston, TX 78234-6102;
Tel.: 210.295.1271; E-mail: amy.m.lugo@amedd.army.mil

Express Scripts (formerly Medco Health Solutions, Inc.)

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: not recruiting for 2013
Estimated Stipend: $42,000
Contact Information:
Doris Fishman, MS, RPh, Vice President, Clinical Practices & Therapeutics
Express Scripts, Department of Clinical Practices and Therapeutics
100 Parsons Pond Drive, Mail Stop: B3-MS2, Franklin Lakes, NJ 07417;
Tel.: 201.269.6270; E-mail: ExpressScriptsRProg@express-scripts.com

Geisinger Health Plan

PGY1 Managed Care Pharmacy
Accreditation Status: candidate
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 18
Estimated Stipend: $39,998.40
Contact Information:
Daniel McConnell, PharmD, Residency Program Coordinator
Geisinger Health Plan
100 N. Academy Avenue, MC 32-45, Danville, PA 17822;
Tel.: 570.214.1737; E-mail: dmmcconnell@thehealthplan.com

Group Health Cooperative

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 11
Estimated Stipend: $54,800
Contact Information:
Jim Carlson, PharmD, Director, Pharmacy Health Plan Services
Group Health Cooperative
12400 E. Marginal Way S., Seattle, WA 98168;
Tel.: 206.901.4425; E-mail: carlson.j@ghc.org
http://www.ghc.org/about_gh/employ/rxresidency.jhtml

HCA Management Services/ University of Tennessee College of Pharmacy

PGY1 Managed Care Pharmacy
Accreditation Status: candidate
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of Tennessee
Application Deadline: January 14
Estimated Stipend: $41,000
Contact Information:
Alicia Perry, PharmD, Residency Program Director
HCA Management Services
One Park Plaza, Clinical Services Group Building 2-4 West, Nashville, TN 37203; Tel.: 615.344.2993; E-mail: alicia.perry@hcahealthcare.com

Health Net Pharmaceutical Services

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of the Pacific, University of California San Francisco, University of California San Diego, California Northstate, Shenandoah University, Tuoro University
Application Deadline: January 15
Estimated Stipend: $50,000
Contact Information:
Cathrine Misquitta, PharmD, BPCS, FCSHP, Director,
Clinical Pharmacy Services
Health Net Pharmaceutical Services
10540 White Rock Road, Suite 280, Rancho Cordova, CA 95670;
Tel.: 916.463.9602; E-mail: cathrine.v.misquitta@healthnet.com

Health Plan of San Joaquin

PGY1 Managed Care Pharmacy
Accreditation Status: ASHP/AMCP
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of the Pacific, San Joaquin General Hospital
Application Deadline: January 15
Estimated Stipend: $45,000
Contact Information:
Allen Shek, PharmD, Residency Program Director, Professor and Vice Chair
Health Plan of San Joaquin, University of the Pacific
7751 South Manthey Road, French Camp, CA 95231;
Tel.: 209.461.2209; E-mail: ashek@hpsj.com
http://www.hpsj.com/english/careers/pharmacy-intern.aspx

HealthPartners

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 13
Estimated Stipend: competitive
Contact Information:
Daniel Rehrauer, PharmD, Clinical Pharmacy Program Manager
HealthPartners
8170 33rd Avenue South, Mail Stop 21111B, Bloomington, MN 55425;
Tel.: 952.967.5133; E-mail: Daniel.J.Rehrauer@HealthPartners.com

HealthSpring, Inc.

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 3
Estimated Stipend: $45,000
Contact Information:
Annie Rakoczy, PharmD, Director of Clinical Pharmacy
HealthSpring, Inc.
500 Great Circle Road, Nashville, TN 37228;
Tel.: 615.565.8110 ext. 508796; E-mail: annie.rakoczy@healthspring.com
http://www.healthspring.com

Highmark Blue Cross Blue Shield

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 15
Estimated Stipend: $43,000
Contact Information:
Michelle Holbrook, PharmD, MS, MBA, Manager,
Clinical Pharmacy Services
Highmark Blue Cross Blue Shield
120 5th Avenue, Suite 1812, Pittsburgh, PA 15222;
Tel.: 412.544.6018; E-mail: michelle.holbrook@highmark.com

Hill Physicians Medical Group

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 11
Estimated Stipend: $50,000
Contact Information:
Katherine Ramos, PharmD, Clinical Support Manager
Hill Physicians Medical Group
2409 Camino Ramon, San Ramon, CA 94583;
Tel.: 925.327.6799; E-mail: katherine.ramos@hpmg.com

Humana Inc.

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: December 21
Estimated Stipend: $43,000
Contact Information:
Debbie Meyer, RPh, Residency Program Director
Humana Inc.
325 W. Main Street, Louisville, KY 40202;
Tel.: 502.580.3045; E-mail: dmeyer@humana.com

Kaiser Permanente Medical Care Program—Central Valley Area

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: Kaiser Permanente
Application Deadline: January 1
Estimated Stipend: $23.38 per hour
Contact Information:
Laura Morodomi, PharmD, Clinical Operations Manager
Kaiser Permanente Medical Care Program—Central Valley Area
Attention: Susan Coburn 3rd floor pharmacy
7373 West Lane, Stockton, CA 95210;
Tel.: 209.476.3474; E-mail: laura.morodomi@kp.org
http://kaiserpharmacyresidency.org/programs/mcCentralValley/

Kaiser Permanente Medical Center Program—North Sacramento Valley Area

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: Kaiser Permanente
Application Deadline: January 4
Estimated Stipend: competitive
Contact Information:
Cecily Amato, PharmD, Clinical Operations Manager,
Residency Program Coordinator, Director
Kaiser Permanente Medical Center, Arden Annex-Pharmacy Operations
3240 Arden Way, Sacramento, CA 95825;
Tel.: 916.486.5174; E-mail: cecily.m.amato@kp.org
http://www.kaiserpharmacyresidency.org

Kaiser Permanente of Georgia

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 10
Estimated Stipend: $39,500
Contact Information:
Diane Erdman, PharmD, BCPS, CDE, Residency Program Director
Kaiser Permanente
750 Townpark Lane, Kennesaw, GA 30144;
Tel.: 770.514.5451; E-mail: Diane.Erdman@kp.org

Kelsey-Seybold Clinic

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: determined annually
Affiliation: none
Application Deadline: January 11
Estimated Stipend: $41,000
Contact Information:
Kirti Gandhi, PharmD, Interim Residency Coordinator
Kelsey-Seybold Clinic - Business Office
c/o Health Plan Pharmacy Services Attn: Residency Program
8900 Lakes at 610 Drive, Houston, TX 77054;
Tel.: 713.442.5592; E-mail: MCResidency@Kelsey-Seybold.com
http://www.kelsey-seybold.com/MS_RxResidency/index.cfm

Maxor Correctional Pharmacy

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 1
Estimated Stipend: $40,000
Contact Information:
Chrystal Holmes, PharmD, Utilization Management Pharmacist
Maxor Correctional Pharmacy
416 Mary Lindsay Polk Drive, Suite 515, Franklin, TN 37067;
Tel.: 615.771.1436; E-mail: chrystal.holmes@maxorcps.com

OptumRx (formerly Prescription Solutions)

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: OptumRx/UnitedHealth Group
Application Deadline: January 4
Estimated Stipend: $50,000
Contact Information:
Ann Nakahira, PharmD, Clinical Pharmacist, Clinical Programs,
Residency Program Coordinator
Prescription Solutions
2300 Main Street, Mail Stop CA134-0404, Irvine, CA 92614;
Tel.: 949.252.4308; E-mail: ann.nakahira@optum.com
http://www.prescriptionsolutions.com/residency

PerformRx

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 16
Estimated Stipend: $40,000

Contact Information:
Jamila Jorden, PharmD, Clinical Services, Formulary-DUR Specialist
PerformRx
200 Stevens Drive, Philadelphia, PA 19113;
Tel.: 215.863.6422; E-mail: jamila.jorden@performrx.com

Prime Therapeutics

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 11
Estimated Stipend: $45,000
Contact Information:
Kellie Rademacher, PharmD, Senior Clinical Pharmacist,
Prime Therapeutics
1305 Corporate Center Drive, Eagan, MN 55121;
Tel.: 612.777.5050; E-mail: krademacher@primetherapeutics.com

Providence Health Plan

PGY1 Managed Care Pharmacy
Accreditation Status: candidate
Length of Program: 12 months
Number of Positions: 1
Affiliation: Providence Health & Services
Application Deadline: January 10
Estimated Stipend: $45,000
Contact Information:
Deanna Moretz, PharmD, Clinical Pharmacy Specialist
Providence Health Plan
3601 S.W. Murray Boulevard, Suite 10, Beaverton, OR 97005;
Tel.: 503.574.7349; E-mail: deanna.moretz@providence.org
http://www.providence.org/healthplans

RegenceRx

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: Regence Blue Cross Blue Shield
Application Deadline: January 7
Estimated Stipend: $47,000
Contact Information:
Carly Fuhrman, PharmD
RegenceRx
P.O. Box 1071, M/S 2P, Portland, OR 97207-1071;
Tel.: 503.412.5613; E-mail: carly.fuhrman@regence.com
http://www.regencerx.com/meet/managedCare/index.html

SelectHealth (a service of Intermountain Healthcare)

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 10
Estimated Stipend: $47,000
Contact Information:
Jeffrey Dunn, PharmD, Formulary and Contract Manager
SelectHealth (formerly known as IHC Health Plans)
5381 Green Street, Murray, UT 84123;
Tel.: 801.442.7984; E-mail: jeffrey.dunn@selecthealth.org
http://www.selecthealth.org

Tennessee Department of Mental Health/ University of Tennessee

PGY1 Managed Care Pharmacy
Accreditation Status: candidate
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of Tennessee
Application Deadline: January 25
Estimated Stipend: $42,500
Contact Information:
Jason Carter, PharmD, Chief Pharmacy Officer
Tennessee Department of Mental Health and Substance Abuse Services
710 James Robertson Parkway, 11th Floor, Nashville, TN 37243;
Tel.: 615.532.6736; E-mail: jason.carter@tn.gov
http://www.tn.gov/mental

The Ohio State University Health Plan, Inc.

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: The Ohio State University
Application Deadline: January 7
Estimated Stipend: $40,000
Contact Information:
Amanda Bain, PharmD, Residency Program Director
The Ohio State University Health Plan, Inc.
700 Ackerman Road, Suite 440, Columbus, OH 43202;
Tel.: 614.247.1660; E-mail: amanda.bain@osumc.edu
http://www.osuhealthplan.com, http://www.rxoc.org

UMass Medical School Clinical Pharmacy Services

PGY1 Managed Care Pharmacy
Accreditation Status: ASHP/AMCP
Length of Program: 12 months
Number of Positions: 2-3
Affiliation: University of Massachusetts Medical School
Application Deadline: January 12
Estimated Stipend: $42,000
Contact Information:
Karen Lee, PharmD, BCPS, Director for Professional
Development
Commonwealth Medicine
UMass Medical School Clinical Pharmacy Services
333 South Street, Shrewsbury, MA 01545;
Tel.: 774.455.3445; E-mail: Karen.Lee@umassmed.edu
http://cps.umassmed.edu/

University of Southern California School of Pharmacy

PGY1 Managed Care Pharmacy
Accreditation Status: candidate
Length of Program: 12 months
Number of Positions: 1
Affiliation: CareMore Health Plan
Application Deadline: January 2
Estimated Stipend: $50,000
Contact Information:
William C. Gong, PharmD, Director, Residency and Fellowship Training,
Associate Professor of Clinical Pharmacy
University of Southern California School of Pharmacy
1985 Zonal Avenue, Los Angeles, CA 90089-9121;
Tel.: 323.442.2625; E-mail: wgong@usc.edu
http://pharmacyschool.usc.edu/programs/residency/

UPMC Health Plan

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: UPMC Health System, University of Pittsburgh School of Pharmacy
Application Deadline: January 5
Estimated Stipend: $40,000
Contact Information:
Jessica Daw, PharmD, MBA, Director, Clinical Pharmacy
UPMC Health Plan
US Steel Tower, 12th Floor, 600 Grant Street, Pittsburgh, PA 15219;
Tel.: 412.454.7822; E-mail: dawjr@upmc.edu

VA San Diego Healthcare System

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of California, San Diego, School of Medicine
Application Deadline: January 5
Estimated Stipend: $40,525
Contact Information:
Rashid Kazerooni, PharmD, BCPS, Pharmacoeconomics Clinical Specialist
Veterans Affairs San Diego Healthcare System
3350 La Jolla Village Drive (119), San Diego, CA 92161;
Tel.: 858.552.8585 ext. 5925; E-mail: rashid.kazerooni@va.gov
http://www.sandiego.va.gov/

VA Sierra Pacific Network (VISN 21)

PGY2 Managed Care Pharmacy Systems
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: University of Nevada, Idaho State University
Application Deadline: January 15
Estimated Stipend: $45,000
Contact Information:
Jannet Carmichael, PharmD, BCPS, FCCP, FAPhA,
VISN 21 Pharmacy Executive
VA Sierra Pacific Network (VISN 21)
Pharmacy Benefits Management Group
975 Kirman Avenue (10N21R), Reno, NV 59502;
Tel.: 775.326.5724; E-mail: jan.carmichael@va.gov

VRx Pharmacy Services

PGY1 Managed Care Pharmacy
Accreditation Status: pre-candidate
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 13
Estimated Stipend: $48,000
Contact Information:
Alisa Thomas, PharmD, BCPS, Residency Program Director
VRx Pharmacy Services
4190 S. Highland Drive #250, Salt Lake City, UT 84124;
Tel.: 801.365.0298; E-mail: athomas@veridicusrx.com
http://www.myvrx.com/

WellCare Health Plans, Inc.

PGY1 Managed Care Pharmacy
Accreditation Status: AMCP/ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 10
Estimated Stipend: $50,000
Contact Information:
David Mostellar, PharmD, Manager, Pharmacy Quality
WellCare Health Plans, Inc.
4110 George Road, Suite 300, Tampa, FL 33634;
Tel.: 813.206.1860; E-mail: David.Mostellar@Wellcare.com

ACCREDITED PHARMACY RESIDENCY PROGRAMS

Harvard Vanguard Medical Associates

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: Massachusetts College of Pharmacy and Health Sciences
Application Deadline: January 15
Estimated Stipend: $36,000
Contact Information:
Kathy Zaiken, PharmD
Massachusetts College of Pharmacy and Health Sciences
179 Longwood Avenue, Boston, MA 02115;
Tel.: 617.732.2740; E-mail: kathy.zaiken@mcphs.edu
http://www.mcphs.edu

HealthSpring, Texas Market

PGY1 Pharmacy—Emphasis on Managed Care
Accreditation Status: candidate
Length of Program: 12 months
Number of Positions: 2
Affiliation: University of Houston
Application Deadline: second Monday in January - January 14
Estimated Stipend: $45,000
Contact Information:
Omar Serna, PharmD, Clinical Pharmacy Manager
Texas HealthSpring
2900 North Loop West, Suite 1300, Houston, TX 77092;
Tel.: 713.936.6000; E-mail: omar.serna@healthspring.com
http://www.healthspring.com

Kaiser Permanente—California

PGY2 Medical Care/Drug Information
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 3
Affiliation: none
Application Deadline: January 6
Estimated Stipend: $70,000
Contact Information:
Mirta Millares, PharmD, FCSHP, FASHP
Kaiser Permanente
12254 Bellflower Boulevard, Suite 106, Downey, CA 90242;
Tel.: 562.658.3587; E-mail: mirta.millares@kp.org
http://www.kaiserpharmacyresidency.org

Kaiser Permanente Colorado

PGY2 Ambulatory Care Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 6
Affiliation: none
Application Deadline: January 4
Estimated Stipend: $57,500

Contact Information:
Rachana Patel, PharmD, Clinical Pharmacy Specialist in Primary Care and Residency Supervisor
Kaiser Permanente Colorado
1375 East 20th Avenue, Denver, CO 80205;
Tel.: 303.764.4479; E-mail: rachana.j.patel@kp.org

Kaiser Permanente Fontana Area

PGY2 Pharmacy Practice in Oncology
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 7
Estimated Stipend: $71,000
Contact Information:
Elizabeth Fong, PharmD, Ambulatory Care Supervisor, PGY2 Oncology Residency Director
Kaiser Permanente Fontana Area
17284 Slover Avenue, Suite 204, Fontana, CA 92337;
Tel.: 909.609.3340; E-mail: elizabeth.e.fong@kp.org
http://www.kaiserpharmacyresidency.org

Kaiser Permanente Medical Care Program—Fontana/Ontario

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 4
Estimated Stipend: $43,700
Contact Information:
Logan Saito, PharmD, BCPS, Clinical Operations Manager, Residency Program Director
Kaiser Permanente Fontana Area
17284 Slover Avenue, Suite 204, Fontana, CA 92337;
Tel.: 909.609.3338; E-mail: logan.h.saito@kp.org
http://www.kaiserpharmacyresidency.org

Kaiser Permanente Medical Care Program—Los Angeles Medical Center

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 7
Estimated Stipend: $48,630
Contact Information:
Helen Chun, PharmD, Ambulatory Care Pharmacy Supervisor, PGY1 Residency Coordinator
Kaiser Permanente Pharmacy Operations Services
1515 N. Vermont Avenue, Suite 237, Los Angeles, CA 90027;
Tel: 323.783.8306; E-mail: Helen.K.Chun@kp.org, Marlene.T.Morcos@kp.org, Joseph.D.Pai@kp.org, Lindsay.L.Gordon@kp.org
http://www.kaiserpharmacyresidency.org

Kaiser Permanente Medical Care Program—Riverside Area

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 6
Estimated Stipend: $43,700
Contact Information:
Patricia Gray, PharmD, FCHSP, Clinical Operations Manager, PGY1 Residency Coordinator
Kaiser Permanente Riverside Area, Pharmacy Administration
11080 Magnolia Avenue, Riverside, CA 92505;
Tel.: 951.602.4130; E-mail: patricia.l.gray@kp.org
http://www.kaiserpharmacyresidency.org

Kaiser Permanente Medical Care Program—Tri-Central Service Area

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 3
Affiliation: none
Application Deadline: January 7
Estimated Stipend: $48,600
Contact Information:
John Sie, PharmD, Pharmacy Residency Program Coordinator, Pharmacy Clinical Operation Manager
Kaiser Permanente Medical Care Program Tri-Central
Pharmacy Residency Program Pharmacy Administration
1011 Baldwin Park Boulevard, Baldwin Park, CA 91706;
Tel.: 626.851.5307; E-mail: john.l.sie@kp.org
http://www.kaiserpharmacyresidency.org/programs/ppTricentral/

Kaiser Permanente Northwest—Portland, Oregon

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 10
Estimated Stipend: $46,800
Contact Information:
Tanya Ramsey, PharmD, Residency Program Coordinator
Kaiser Permanente Northwest
5717 N.E. 138th Avenue, Portland, OR 97230;
Tel.: 503.261.7541; E-mail: Tanya.A.Ramsey@kp.org

Kaiser Permanente of the Mid-Atlantic States

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 4
Estimated Stipend: competitive
Contact Information:
Kristin Fink, PharmD, BCPS, CDE, Program Director
Kaiser Permanente of the Mid-Atlantic States
4920 Campbell Boulevard, Baltimore, MD 21236;
Tel.: 410.933.7621; E-mail: kristen.m.fink@kp.org

Marshfield Clinic

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 2
Affiliation: none
Application Deadline: January 15
Estimated Stipend: $48,000
Contact Information:
Sara Griesbach, PharmD, BCPS, BCACP, Pharmacy Residency Program Director
Marshfield Clinic
1000 North Oak Avenue, Marshfield, WI 54449;
Tel.: 800.541.2895; E-mail: griesbach.sara@marshfieldclinic.org
http://marshfieldclinic.org/residents

Providence Health and Services—Oregon

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: Providence Health & Services
Application Deadline: January 10
Estimated Stipend: $46,680
Contact Information:
Cathy Baker, PharmD, Residency Program Director
Providence Health & Services
4805 N.E. Glisan Street, Portland, OR 97213;
Tel.: 503.215.3950; E-mail: catherine.baker@providence.org
http://www.providenceiscalling.jobs/pharmacy/pdf/ResidencyProgram.pdf

Southern Arizona VA Health Care System

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 8
Affiliation: University of Arizona, Midwestern University—Glendale, University of Southern Nevada, Creighton University, Western University
Application Deadline: completed application materials must be submitted to Pharmacy Online Residency Centralized Application Service (PhORCAS) by December 31
Estimated Stipend: $41,098 plus benefits
Contact Information:
Joan Edwards, PharmD, Clinical Pharmacist
Southern Arizona Veterans Administration Health Care System
3601 South Sixth Avenue, Pharmacy Service 13-119, Tucson, AZ 85723;
Tel.: 520.792.1450 ext. 5156; E-mail: Joan.Edwards1@va.gov
http://www.tucson.va.gov/docs/PGY1_Pharmacy_Residency.doc

Sutter Health

PGY1 Pharmacy
Accreditation Status: candidate
Length of Program: 12 months
Number of Positions: 8
Affiliation: none
Application Deadline: January 15
Estimated Stipend: $50,000
Contact Information:
Joan Deady, PharmD, Residency Program Director
Sutter Health
2200 River Plaza Drive, Sacramento, CA 95833;
Tel.: 415.550.7198; E-mail: deadyj@sutterhealth.org

University of Texas Medical Branch Correctional Managed Care

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 1
Affiliation: UTMB
Application Deadline: February 15
Estimated Stipend: $45,000
Contact Information:
Stephanie Zepeda, PharmD, Director of Pharmacy
UTMB Correctional Managed Care
2400 Avenue I, Huntsville, TX 77340;
Tel.: 936.437.5363; E-mail: sdzepeda@utmb.edu
http://ehn.utmb.edu/correctionalmanagedcare/

Veterans Affairs Medical Center, Cincinnati

PGY1 Pharmacy
Accreditation Status: ASHP
Length of Program: 12 months
Number of Positions: 4
Affiliation: none
Application Deadline: January 13
Estimated Stipend: $42,678
Contact Information:
Jo-Ann Caudill, PharmD, Residency Program Director
Department of Veterans Affairs Medical Center
3200 Vine Street, Pharmacy 119, Cincinnati, OH 45220;
Tel.: 513.475.6322; E-mail: Jo-Ann.Caudill@va.gov
http://www.cincinnati.va.gov/services/RXResidency.asp

NONACCREDITED PHARMACY RESIDENCY PROGRAMS

B. Wellness Consulting, Inc.

Managed Care
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: March 15
Estimated Stipend: $36,200
Contact Information:
Shobhna Butler, PharmD, President
B. Wellness Consulting, Inc.
4458 Arbor Crest Place, Suwanee, GA 30024;
Tel.: 770.614.7120; E-mail: sdbutler@b-wellness.com

Blue Cross and Blue Shield of Nebraska

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of Nebraska Medical Center
Application Deadline: January 11
Estimated Stipend: $44,000
Contact Information:
Jeff Huether, PharmD, Manager, Clinical Pharmacy and Benefits
Blue Cross and Blue Shield of Nebraska
1919 Askarben Drive, Omaha, NE 68180;
Tel.: 402.982.6655; E-mail: jeff.huether@nebraskablue.com

Clinical Pharmacology Services, Inc.

Ambulatory Care/Drug Information/Clinical Research
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: February 1
Estimated Stipend: $45,000
Contact Information:
Daniel Buffington, PharmD, MBA, Director
Clinical Pharmacology Services
6285 E. Fowler Avenue, Tampa, FL 33617;
Tel.: 813.983.1500; E-mail: danbuffington@cpshealth.com
http://www.cpshealth.com

Covington Healthcare Associates, LLC

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 15

Estimated Stipend: $45,000
Contact Information:
Dane Higgins, PharmD, Chief Operating Officer
Covington Healthcare Associates, LLC
3800 Colonnade Parkway, Suite 110, Birmingham, AL 35243;
Tel.: 205.970.3939; E-mail: dahiggin@charx.com
http://www.charx.com

CVS Caremark

Managed Care Specialty—Analytics & Outcomes
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of Illinois at Chicago; Midwestern University-Chicago College of Pharmacy
Application Deadline: January 1
Estimated Stipend: $45,000
Contact Information:
Joy Nguyen, PharmD, Manager, Analytic Consulting Services, Residency Director
CVS Caremark
2211 Sanders Road, Northbrook, IL 60062;
Tel.: 847.559.5793; E-mail: joy.nguyen@caremark.com
http://info.cvscaremark.com/careers/intern-resident-programs#97

CVS Caremark

Managed Care—Specialty Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 7
Estimated Stipend: competitive
Contact Information:
Vanessa MacGregor, PharmD, Specialty Pharmacy Residency Director, Program Manager, Specialty Pharmacy Programs
CVS Caremark
2211 Sanders Road, Northbrook, IL 60062;
Tel.: 847.559.4848; E-mail: vanessa.macgregor@caremark.com
http://info.cvscaremark.com/careers/intern-resident-programs#97

Fidelis Care New York

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 16
Estimated Stipend: competitive
Contact Information:
Anish Patel, PharmD, BCPS
Fidelis Care New York
95-25 Queens Boulevard, Rego Park, NY 13374;
Tel.: 718.896.6500 ext. 11301; E-mail: apatel@fideliscare.org
http://fideliscare.org

Health Partners

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: April 2
Estimated Stipend: $52,000
Contact Information:
Julie Samuel, PharmD, Clinical Pharmacist
Health Partners of Philadelphia
901 Market Street, Philadelphia, PA 19107;
Tel.: 215.991.4097; E-mail: jsamuel@healthpart.com
http://www.healthpart.com/

Horizon NJ Health

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: Horizon BC
Application Deadline: January 15
Estimated Stipend: $35,000
Contact Information:
Jennifer Gauweiler, PharmD, BCPS; Kevin McCloy, PharmD, BCPS, Pharmacy Clinical Manager
Horizon NJ Health
210 Silvia Street, West Trenton, NJ 08628;
Tel.: 609.718.9001; E-mail: Jennifer_Gauweiler@horizonnjhealth.com, Kevin_McCloy@horizonnjhealth.com

OptumHealth

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 11
Estimated Stipend: $50,000 with benefits
Contact Information:
Ella Chung, RPh, Director, Pharmaceutical Solutions
OptumHealth
P.O. Box 9472, Minneapolis, MN 55440-9472;
Tel.: 610.277.2094; E-mail: ella.chung@optum.com

OptumInsight

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: UnitedHealth Group
Application Deadline: January 7
Estimated Stipend: $45,000
Contact Information:
Krista King, PharmD, MPH, BCOP, Director, Specialty Pharmacy Strategy & Analytics
OptumInsight
P.O. Box 9472K, Minneapolis, MN 55440-9472;
Tel: 724.625.7297; E-mail: krista.king@optum.com
http://www.optuminsight.com

Outcomes

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of Iowa
Application Deadline: December 31
Estimated Stipend: $46,500
Contact Information:
Tim Sullivan, PharmD, Director of Clinical Services
Outcomes
505 Market Street, Suite 200, West Des Moines, IA 50266-3861;
Tel.: 515.864.7949; E-mail: tsullivan@getoutcomes.com
http://www.getoutcomes.com

PharmMD

Medication Therapy Management
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1-2
Affiliation: none
Application Deadline: January 20
Starting Date: July 1
Contact Information:
Debi Armstrong, PharmD, Clinical Manager
PharmMD
5200 Maryland Way, Suite 200, Brentwood, TN 37027;
Tel.: 615.312.7041; E-mail: Debi.Armstrong@pharmmd.com
www.pharmmd.com/residency-program/

Rutgers University/Horizon Blue Cross Blue Shield of New Jersey

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 3
Affiliation: Ernest Mario School of Pharmacy, Rutgers State University of New Jersey/Horizon Blue Cross Blue Shield of New Jersey
Application Deadline: January 7
Estimated Stipend: $35,000
Contact Information:
Saira A. Jan, PharmD, Associate Professor, Rutgers University, Director, Pharmacy Management at Horizon BCBSNJ
Rutgers University/Horizon Blue Cross Blue Shield of NJ
Three Penn Plaza East, PP-13Q, Newark, NJ 07105;
Tel.: 973.466.4575; E-mail: saira_jan@horizon-bcbsnj.com
http://www.horizonblue.com

Tennessee Pharmacists Association

Health Policy & Outcomes Research
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: TN Pharmacists Research & Education Foundation
Application Deadline: March 15
Estimated Stipend: $40,000
Contact Information:
Micah Cost, PharmD, Director of Professional Practice
Tennessee Pharmacists Association
500 Church Street, Suite 650, Nashville, TN 37219;
Tel.: 615.256.3023; E-mail: tpa@tnpharm.org
http://www.tnpharm.org

Total Therapeutic Management, Inc. (TTM) and Mercer University College of Pharmacy and Health Sciences (COPHS)

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: TTM/Mercer University COPHS/Atlanta Medical Center
Application Deadline: January 18
Contact Information:
Ashish Advani, PharmD, Clinical Assistant Professor
Mercer University COPHS
3001 Mercer University Drive, Atlanta, GA 30341;
Tel.: 678.547.6223; E-mail: advani_aa@mercer.edu
http://cophs.mercer.edu/druginforesidency.htm

United Healthcare Pharmacy

Managed Care Pharmacy—Data Analytics & Strategic Development
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: none
Application Deadline: January 4
Estimated Stipend: $50,000 with benefits
Contact Information:
Lida Etemad, PharmD, MS; Nick Rogers, PharmD, Residency Co-Directors
United Healthcare Pharmacy
5901 Lincoln Drive, MN012-S234, Edina, MN 55436;
Tel.: 952.992.4288; E-mail: nicholas_rogers@uhc.com

University of Florida College of Pharmacy

Medication Therapy Management—Geriatrics
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of Florida College of Pharmacy
Application Deadline: January 31
Estimated Stipend: $40,000-$45,000
Contact Information:
Teresa Roane, PharmD, BCACP, Clinical Assistant Professor
University of Florida College of Pharmacy
2124 N.E. Waldo Road, Suite 2250, Gainesville, FL 32609;
Tel.: 352.273.9692; E-mail: troane@cop.ufl.edu
http://www.cop.ufl.edu/mtmcc

University of Maryland School of Pharmacy/CareFirst Blue Cross Blue Shield

Managed Care Pharmacy—Ambulatory Care
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: CareFirst Blue Cross Blue Shield of Maryland
Application Deadline: January 4
Estimated Stipend: $43,919
Contact Information:
Catherine Cooke, PharmD, Clinical Associate Professor
University of Maryland School of Pharmacy
5106 Bonnie Branch Road, Ellicott City, MD 21043;
Tel.: 410.480.5012; E-mail: Rxservices@hotmail.com
http://www.pharmacy.umaryland.edu/fellowsresidents/residencyprograms/managedcare.html

VIVA Health, Inc.

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 12 months
Number of Positions: 1
Affiliation: University of Alabama at Birmingham (UAB) Health System
Application Deadline: February 1
Estimated Stipend: $44,000
Contact Information:
Kimberly Ferguson, PharmD, Residency Director
VIVA Health, Inc.
1222 14th Avenue South, Birmingham, AL 35205;
Tel.: 205.558.7653; E-mail: kdferguson@uabmc.edu
http://www.vivahealth.com/

FELLOWSHIP PROGRAMS

Janssen Scientific Affairs, LLC

Fellowship
Accreditation Status: none
Length of Program: 24 months
Number of Positions: 1
Affiliation: Jefferson School of Population Health
Application Deadline: December 31
Estimated Stipend: competitive
Contact Information:
Zoe Clancy, PharmD, Fellow, Health Economics & Outcomes Research
Janssen Scientific Affairs, LLC
1125 Trenton-Harbourton Road, Titusville, NJ 08560;
Tel.: 609.730.3655; E-mail: zclancy@its.jnj.com
http://www.janssenpharmaceuticalsinc.com/innovation-and-research

Novartis Pharmaceuticals Corporation

Outcomes Research Fellowship
Accreditation Status: none
Length of Program: 24 months
Number of Positions: 1-5 (Rutgers program has incoming fellows beginning in July of even years only, University of Utah Analytics program has incoming fellows beginning in July of odd years only)
Affiliation: Scott & White Health Plan/University of Texas at Austin; Rutgers University; University of Utah; University of Maryland; Thomas Jefferson University
Application Deadline: December 31
Estimated Stipend: $45,000-$52,000
Contact Information:
Kristijan Kahler, RPh, PhD, Executive Director,
Outcomes Research Methods & Analytics
Novartis Pharmaceuticals Corporation
One Health Plaza, East Hanover, NJ 07936-1080;
Tel.: 862.778.6635; E-mail: Kristijan.Kahler@novartis.com

Rutgers, EMSOP

Pharmaceutical Industry Fellowship
Accreditation Status: none
Length of Program: 12-24 months
Number of Positions: 80
Affiliation: Ernest Mario School of Pharmacy
Application Deadline: January 1
Estimated Stipend: competitive
Contact Information:
Michael Toscani, PharmD, Fellowship Administrator
Rutgers, EMSOP
160 Frelinghuysen Road, Room 405, Piscataway, NJ 08854;
Tel.: 848.445.6810; E-mail: ifellows@pharmacy.rutgers.edu
http://pharmafellows.rutgers.edu

Scott & White Health Plan

Managed Care Pharmacy
Accreditation Status: none
Length of Program: 24 months
Number of Positions: 1
Affiliation: College of Pharmacy, The University of Texas at Austin
Application Deadline: February 1 (early January preferred)
Estimated Stipend: $37,921-$44,779
Contact Information:
Paul Godley, PharmD, Pharmacy Managed Care
Fellowship Program Director
Scott & White Health Plan Pharmacy
1206 West Campus, MS-A4-102, Temple, TX 76502;
Tel.: 254.298.6143; E-mail: pgodley@swmail.sw.org

UMass Medical School Clinical Pharmacy Services

Health Outcomes and Pharmacoeconomics Research
Accreditation Status: none
Length of Program: 24 months
Number of Positions: 1
Affiliation: University of Massachusetts Medical School
Application Deadline: January 12
Estimated Stipend: $42,000
Contact Information:
Karen Lee, PharmD, BCPS, Director for Professional Development
Commonwealth Medicine
UMass Medical School Clinical Pharmacy Services
333 South Street, Shrewsbury, MA 01545;
Tel.: 774.455.3445; E-mail: Karen.Lee@umassmed.edu
http://cps.umassmed.edu/

University of California, San Francisco, & Amgen, Inc.

Fellowship
Accreditation Status: none
Length of Program: 24 months
Number of Positions: 1
Affiliation: University of California, San Francisco, & Amgen, Inc.
Application Deadline: August 31
Estimated Stipend: $45,000-$55,000
Contact Information:
Leslie Wilson, PhD
University of California, San Francisco
3333 California Street, Suite 420, Box 0613, San Francisco, CA 94143;
Tel.: 415.990.1012; E-mail: wilsonl@pharmacy.ucsf.edu

Western University of Health Sciences

Outcomes Fellowship
Accreditation Status: ACCP Peer-reviewed
Length of Program: 24 months
Number of Positions: 1
Affiliation: Western University of Health Sciences
Application Deadline: March 31
Estimated Stipend: $45,000
Contact Information:
Anandi Law, PharmD, Associate Professor and Chair,
Department of Pharmacy Practice and Administration
Western University of Health Sciences
309 E. Second Street, Ponoma, CA 91766;
Tel.: 909.469.5645; E-mail: alaw@westernu.edu
http://www.westernu.edu

Xcenda

Health Outcomes Research Fellowship and Managed Markets
Accreditation Status: none
Length of Program: 24 months
Number of Positions: 1-2
Affiliation: University of Florida College of Pharmacy
Application Deadline: December 21
Contact Information:
Timothy S. Regan, BSPharm, RPh, CPh, Executive Director
Xcenda
4114 Woodlands Parkway, Suite 500, Palm Harbor, FL 34685;
Tel.: 727.771.4100; E-mail: tim.regan@xcenda.com
http://www.xcenda.com