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REFERENCE

Alan King was born in the town of Greenwich, England, located in southeast London, in February 1952. His interest in art began in childhood—he first started to draw at John Evelyn Primary School in Deptford (also in southeast London). King often drew in his textbooks, which did not please his teachers! In 1963, he enrolled at Eltham Green School in Greenwich where he studied for his A-level art certification under art instructors Richard Box and Jim Riddock. There King was introduced to the artists of the Surrealist movement and was fascinated by the work of Yves Tanguy, Giorgio de Chirico, and of course, Salvador Dali. Later, he studied the optical-illusion art of M. C. Escher and Oscar Reutersvärd, plus the architecture and interior design of Frank Lloyd Wright. Science fiction writers Isaac Asimov, Arthur C. Clarke, and Ray Bradbury also fueled King’s imagination and influenced his work. He now listens to many of their audio books while creating his art.

King received his A-level art degree in 1968 and began his professional artistic journey by working as a commercial artist in London’s highly competitive advertising industry. He produced his own fine art on the side. After 2 years, King left the commercial art industry for sales and marketing, but he continued to pursue his personal creative ambitions. By the early 1970s, he was exhibiting and selling his art throughout London. In 1977, King moved from London to Milton Keynes, England. He spent 28 years there—living and showing his art—but decided to move once again in 2005 to the Dorset village of Bloxworth in southwest England.

During the late 1990s, King started to experiment with a combination of digital and traditional art methods, and the result was “Massurrealist” works of art. Massurrealism is the name given to an art movement that was founded in 1992 by American artist James Seehafer, who credits the Internet with a major role in promoting the genre. It is characterized by the convergence of mass media and Surrealism, and often includes elements of Pop Art. King is considered to be one of the first Massurrealists in the United Kingdom. Over the years, he has developed his own unique and recognizable style by cleverly combining his masterful computer skills and expert drawing ability. King is able to express the images seen in his mind’s eye by using the computer, and utilizes traditional art materials such as oils, acrylics, watercolors, and calligraphy ink for completing his digital paintings. His vibrant artwork is said to “bridge the gap between Surrealist imagery and new-media techniques.” In 2004, Seehafer invited King to become an official member of the Massurrealists.

It comes as no surprise that King has a wonderful Web site: kingart.co.uk. The site showcases his Massurrealist art with several gallery pages, provides information about his art exhibitions, and has a page that lists some critiques. One particular critique succinctly describes his work: “Alan’s art is defined by his creation of intoxicating landscape compositions executed in a style that he refers to as ‘Artytechture.’ Alan’s distinct works evoke the landscapes of prominent Surrealist painters, but have a definite contemporary edge to them.”

Another interesting page on King’s Web site is called “The Process” which outlines the process he uses to create his art. “I am often asked how I produce my digital artwork,” he says. “All my work starts out as a rough design sketch. Once finished, some [digital] prints are hand colored.” He has posted actual photographs of several works in progress, from the initial sketch to the finished piece. One such example found on this page is King’s fabulous painting titled The Gate. Reminiscent of an Escher composition, it seems to present the impossible, such as a straight bar that appears to cross both in front of and behind a twisted bar. The Gate is very 3-dimensional—the foreground object appears to float in mid-air above a background that resembles a photograph of the earth taken from outer space.

King has exhibited his art in England, Hungary, Germany, Portugal, and Argentina. He has participated in both solo and group shows with England’s Poole & East Dorset Art Society and at the Peacock Gallery in Poole. Other English galleries that have shown the artist’s work include the Red Gate Gallery in London, the Jurassic Coast Gallery in Weymouth, and the White Stones Café Gallery in Portland. He is also a member of Artists in the World, a Web site “for artists who devote their lives to art, and who believe in freedom, equality, and peace.”

King’s visual illusions, such as those seen in The Gate, both stimulate and challenge the onlooker. A compilation of his extraordinary artwork has been published in a new book titled A Room of Illusions: The Massurreal & Illusionary Art of Alan King, available on Amazon.com. The book cover features King’s haunting painting, The Mask.
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- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Brief Communications
- Commentary/Editorials
- Letters

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ABSTRACT

BACKGROUND: Medication therapy management (MTM) was officially recognized by the federal government in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, which requires Medicare Part D plans that offer prescription drug coverage to establish MTM programs (MTMPs) for eligible beneficiaries. Even though the term “MTM” was first used in 2003, pharmacists have provided similar services since the term “pharmaceutical care” was introduced in 1990. Fairview Health Services, a large integrated health care system, implemented a standardized pharmaceutical care service system in 1998, naming it a pharmaceutical care-based MTM practice in 2006.

OBJECTIVE: To present the clinical, economic, and humanistic outcomes of 10 years of delivering MTM services to patients in a health care delivery system.

METHODS: Data from MTM services provided to 9,068 patients and documented in electronic therapeutic records were retrospectively analyzed over the 10-year period from September 1998 to September 2008 in 1 health system with 48 primary care clinics. Patients eligible for MTM services were aged 21 years or older and either paid for MTM out of pocket or met their health care payer’s criteria for MTM reimbursement; the criteria varied for Medicaid, Medicare, and commercially insured enrollees. All MTM was delivered face to face. Health data extracted from the electronic therapeutic record by the present study’s investigators included patient demographics, medication list, medical conditions, drug therapy problems identified and addressed, change in clinical status, and pharmacist-estimated cost savings. The clinical status assessment was a comparison of the first and most recent MTM visit to measure whether the patient achieved the goals of therapy for each medical condition (e.g., the blood pressure of a patient with diabetes and hypertension will be less than 130/80 millimeters mercury [mmHg] in 1 month; the patient with allergic rhinitis will be relieved of his complaints of nasal congestion, runny nose, and eye itching within 5 days). Goals were set according to evidence-based literature and patient-specific targets determined cooperatively by pharmacists, patients, and physicians. Cost-savings calculations represented MTM pharmacists’ estimates of medical services (e.g., office visits, laboratory services, urgent care visits, emergency room visits) and lost work time avoided by the intervention. All short-term (3-month) estimated health care savings that resulted from addressing drug therapy problems were analyzed. The expenses of these avoided services were calculated using the health system’s contracted rates for services provided in the last quarter of 2006. The return on investment (ROI) was calculated by dividing the pharmacist-estimated savings by the cost of MTM services in 2008 (number of MTM encounters times the average cost of an MTM visit). The humanistic impact of MTM services was assessed using the results from the second patient satisfaction survey administered in 2008 (new patients seen from January through December 2008) for the health system’s MTM program.

RESULTS: A total of 9,068 patient records were in the documentation system as of September 30, 2008. During the 10-year period, there were 33,706 documented encounters (mean 3.7 encounters per patient). Of 38,631 drug therapy problems identified and addressed by MTM pharmacists, the most frequent were a need for additional drug therapy (n = 10,870, 28.1%) and subtherapeutic dosage (n = 10,100, 26.1%). In the clinical status assessment of the 12,851 medical conditions in 4,849 patients who were not at goal when they enrolled in the program, 7,068 conditions (55.0%) improved, 2,956 (23.0%) were unchanged, and 2,827 (22.0%) worsened during the course of MTM services. Pharmacist-estimated cost savings to the health system over the 10-year period were $2,913,850 ($86 per encounter) and the total cost of MTM was $2,258,302 ($67 per encounter), for an estimated ROI of $1.29 per $1 in MTM administrative costs. In the patient satisfaction survey, 95.3% of respondents agreed or strongly agreed that their overall health and well-being had improved because of MTM.

CONCLUSION: Pharmacist estimates of the impact of an MTM program in a large integrated health care system suggest that the program was associated with improved clinical outcomes and cost savings. Patient satisfaction with the program was high.

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What is already known about this subject

• The pharmacy profession has been moving from a product-focused to a patient-focused practice. The recognition of medication therapy management (MTM) by the federal government in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 provides pharmacists with the opportunity to expand and to be reimbursed for direct patient care services.
• Types of MTM programs vary from drug utilization reviews to comprehensive face-to-face pharmaceutical care services.
• Studies have demonstrated the effectiveness of MTM programs in improving the control of several disease states such as hypertension. In one randomized controlled trial (RCT) of community pharmacy-based MTM in patients with diabetes and hypertension, the percentage of patients at goal blood pressure increased from 16.0% to 48.0% in patients who received MTM and decreased from 20.0% to 6.67% in the control group. In another RCT of physician/pharmacist collaboration in patients with hypertension, mean blood pressure decreased from baseline to 6-month follow-up by 6.8/4.5 millimeters mercury (mmHg) in the control group and by 20.7/9.7 mmHg in the group that received collaborative care.

What this study adds

• In an MTM program implemented in a large integrated health care system, pharmacists found that 85% of patients had at least 1 drug therapy problem, and 29% of patients had 5 or more drug therapy problems.
• The results suggest that the major drug therapy problem in this population is the underutilization of effective medications. Of 38,631 drug therapy problems identified and addressed by MTM pharmacists, the most frequent were a need for additional drug therapy (n=10,870, 28.1%) and subtherapeutic dosage (n=10,100, 26.1%).
• Pharmacist-estimated cost savings to the health system over the 10-year period were $2,913,850 ($86 per encounter), and the total cost of MTM was $2,258,302 ($67 per encounter), for an estimated return on investment of $1.29 per $1 in MTM costs.
Medication therapy management (MTM) was officially recognized by the federal government in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA 2003). The Centers for Medicare and Medicaid Services (CMS), through the MMA 2003, requires each Medicare Part D plan to establish MTM programs (MTMPs) for eligible beneficiaries as part of their benefits. MTMPs must be designed to “optimize therapeutic outcomes through improved medication use” and “reduce the risk of adverse events, including adverse drug reactions.” Pharmacists were the only health care provider specifically mentioned as potential MTM providers; however, “other qualified providers” can also deliver these services. Additionally, the MMA 2003 did not include a specific list of services that should be provided to Medicare beneficiaries.

The draft Medicare Prescription Drug Benefit Manual released by CMS in December 2006 stated that “CMS believes that existing standards and performance measures are insufficient to support further specification for MTM services and service level requirements, and therefore plans need the discretion to decide on which methods and which providers are best for providing MTM services available under their specific MTMP.”

Even though the term “MTM” was introduced with the MMA 2003, pharmacists have previously developed and implemented similar programs called “pharmaceutical care.” Whereas MTM in the MMA 2003 is specific to Part D enrollees, pharmaceutical care can be provided to anyone. Pharmaceutical care is a practice in which the pharmacist works directly with a patient and other health care providers using interventions designed to enhance the results obtained from medication therapies. MTM provided to Part D patients is a logical extension of the provision of pharmaceutical care services to diverse groups of patients, which has been performed by pharmacists for many years. Programs of this kind represent the pharmacy profession’s shift from a product-focused to patient-centered practice.

Several studies have shown the effectiveness of pharmaceutical care in patients with diabetes, in patients with heart failure, and in high-risk Medicare beneficiaries. Other studies also demonstrate the positive effect of various pharmacist interventions on patients’ outcomes. Planas et al. (2009) found in a randomized controlled trial (RCT) that a community pharmacy-based MTM program was effective in improving blood pressure control of managed care enrollees with diabetes and hypertension; the percentage of patients at blood pressure goal increased from 16.0% to 48.0% in patients who received MTM and decreased from 20.0% to 6.67% in the control group. In another RCT, Doucette et al. (2009) evaluated the effect of a diabetes care service provided by community pharmacists on primary clinical outcomes and on patients’ reported self-care activities. These authors found that compared with the control group, patients who received pharmacists’ interventions significantly increased the number of days per week that they engaged in a set of diet and diabetes self-care activities, although changes in hemoglobin A1c, low-density lipoprotein cholesterol (LDL-C), and blood pressure were not significantly different between the 2 study groups.

Welch et al. (2009) assessed the impact of an MTMP on mortality, health care utilization, and prescription medication costs. They found that Medicare Part D beneficiaries who opted into the MTM were less likely to die compared with beneficiaries who opted out (adjusted odds ratio [OR] = 0.5, 95% confidence interval [CI] = 0.3-0.9) but were more likely to be hospitalized (OR = 1.4, 95% CI = 1.1-2.0) and to have increased medication costs (OR = 1.4, 95% CI = 1.1-1.9) during follow-up. Moreover, Carter et al. (2009) found in an RCT that patients treated with collaborative intervention between pharmacist and physician achieved significantly better mean blood pressure and overall blood pressure control rates compared with a control group, with mean blood pressure declining from baseline to 6-month follow-up by 20.7/9.7 millimeters mercury (mmHg) in the intervention group and by 6.8/4.5 mmHg in the control group. However, in another RCT, Nietert et al. (2009) found no significant differences between time to refill of prescriptions for common chronic conditions, comparing patients contacted by pharmacists via telephone or fax with patients in usual care.

The pharmacy profession has developed and reached consensus on an MTM definition. Although this definition has not been officially recognized by CMS or most other nonpharmacy entities, in 2005 the American Medical Association established Current Procedural Terminology (CPT) codes for reimbursement of MTM services provided by a pharmacist.

In 2005, the Minnesota state legislature authorized coverage of MTM services provided by pharmacists to medical assistance and general assistance medical care recipients. Medical assistance is the largest of Minnesota’s 3 publicly funded health care programs, providing coverage for low-income senior citizens, children and families, and people with disabilities. MTM is defined in Minnesota statute as the provision of pharmaceutical care services by a licensed pharmacist to “optimize the therapeutic outcomes of the patient’s medications.” Coverage of MTM services is provided for medical assistance recipients “taking four or more prescriptions to treat or prevent two or more chronic medical conditions, or when prior authorized by the commissioner for a recipient with a drug therapy problem that is identified and has resulted, or is likely to result, in significant nondrug program costs.” The Minnesota statute promulgated requirements for the types of services encompassed by MTM (Figure 1). This legislation also specified the requirements for pharmacists’ enrollment as providers and the space and privacy requirements for the consultation area where the patient receives MTM services. In 2007, the results of a nonpeer-reviewed report evaluating the effectiveness of the first year of the Minnesota MTM care program showed significant improvement in patients’ clinical outcomes but no significant differences in health care expenditures in a preliminary analysis. A significant body of evidence has been produced in Minnesota related to MTM from the time that pharmaceutical care theory was put into practice until more recently when investigations of MTM outcomes began.
Description of the Fairview MTM Program

The MTM program assessed in the present study is a service of Fairview Pharmacy Services, a subsidiary of Fairview Health Services, a Minnesota nonprofit corporation and one of the largest health care provider organizations in the state. Fairview Health Services, in partnership with the University of Minnesota, is a network of 7 hospitals, 48 primary care clinics, 55 specialty clinics, and 28 retail pharmacies that serves Minneapolis-St. Paul, as well as communities throughout greater Minnesota and the Upper Midwest. More than 2.7 million patients are seen in 1.1 million Fairview clinic visits annually. From 1997-1998, Fairview Pharmacy Services established pharmaceutical care practices, initially in Fairview retail pharmacies and then in primary care clinics, where pharmacists were not associated with dispensing activities and could more easily become part of the health care team. All MTM pharmacists within the system use the same standardized patient care process and are overseen by the MTM management team to promote consistency.

Fairview Pharmacy Services provides MTM to the following groups: (a) Medicaid beneficiaries taking 4 or more prescriptions to treat or prevent 2 or more chronic medical conditions; (b) patients enrolled with contracted Medicare Part D plan sponsors; (c) beneficiaries of contracted self-funded employers; (d) all Fairview employees regardless of the number of diseases or medications; and (e) private-pay patients. The eligibility criteria for MTM services vary among Medicare Part D plan sponsors and contracted employers. Some employers target participants based on the number of chronic medications used, whereas others target specific disease states.

The MTM program enrollment process is “opt-in.” Eligible patients are recruited directly by the program using mailed letters. In order to participate, patients must complete and return an enrollment form. The patient is then contacted to set up an appointment with the MTM pharmacist. To stay enrolled in the program, the patient must come to all appointments with the pharmacist, as agreed upon by the patient and the pharmacist at the first visit. Sponsors pay per visit to the pharmacist for patients enrolled in the program. The cost of the MTM visit depends upon the complexity of each patient’s case as determined by the patient’s number of current medications, number of medical conditions, and number of drug therapy problems identified by the pharmacist.

MTM is provided to patients through face-to-face consultations. Initial appointments are scheduled for 60 minutes, and follow-up visits are scheduled for 30 minutes. MTM is provided in a private space, usually a consultation/exam room at a clinic. As required by Minnesota law, the space is private and entirely devoted to patient care.

MTM pharmacists follow the philosophy and the patient care process of pharmaceutical care. Each MTM encounter follows a systematic review process designed to identify and resolve drug therapy problems and promote optimal patient outcomes (Figure 2). MTM pharmacists’ responsibilities include the following: (a) focus on the “whole” patient (i.e., the pharmacist assesses all of the patient’s diseases and medications); (b) identification of a patient’s drug-related needs; (c) promotion of appropriate indications, safety, and compliance for all drug therapies by identification, resolution, and prevention of drug-related problems; (d) achievement and documentation of therapy outcomes; and (e) collaboration with all members of a patient’s care team.

MTM pharmacists document therapeutic outcomes at every patient encounter using a pharmaceutical care software documentation program. Therapeutic goals are established for each of a patient’s medical conditions during the initial stage of care plan development. The patient, prescriber, and pharmacist communicate to discuss patient expectations and goals of therapy. For some medical conditions, such as diabetes, there are collaborative practice agreements in place under which the MTM pharmacist can initiate, modify, or discontinue drug therapy as well as order laboratory tests related to diabetes, hypertension, and hyperlipidemia, according to the terms of the collaborative agreements.

Ten pharmacists (6.1 full-time equivalents [FTEs]) provide MTM services in 17 of the 48 clinics in the Fairview system. All MTM pharmacists have been certified in the practice of

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**FIGURE 1** Minnesota Legislative Requirements for Pharmacists’ Provision of Medication Therapy Management Services for Medical Assistance and General Assistance Medical Care Recipients

Medication therapy management means the provision of the following services:

1. Performing or obtaining necessary assessments of the patient’s health status
2. Formulating a medication treatment plan
3. Monitoring and evaluating the patient’s response to therapy, including safety and effectiveness
4. Performing a comprehensive medication review to identify, resolve, and prevent medication-related problems, including adverse drug events
5. Documenting the care delivered and communicating essential information to the patient’s other primary care providers
6. Providing verbal education and training designed to enhance patient understanding and appropriate use of the patient’s medications
7. Providing information, support services, and resources designed to enhance patient adherence with the patient’s therapeutic regimens
8. Coordinating and integrating medication therapy management services within the broader health care management services being provided to the patient

*Minnesota legislative requirements are consistent with nationally accepted consensus statements on the content of an effective medication therapy management program.*

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25,30
FIGURE 2  Description of Drug Therapy Problem Categories and Assumed Medical Services Avoided

<table>
<thead>
<tr>
<th>Drug-Related Needs</th>
<th>Categories of Drug Therapy Problems</th>
<th>Examples</th>
<th>Assumed Medical Services Avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>1. The drug therapy is unnecessary because the patient does not have a clinical indication at this time.</td>
<td>Patient is taking 2 ACE inhibitors to treat hypertension. Patient is taking 2 different proton pump inhibitors to treat symptoms of reflux. Patient with diabetes requires low-dose aspirin to prevent heart attacks and/or strokes. Patient requires a second medication to control his or her blood pressure.</td>
<td>1 office visit 1 office visit 1 office visit 1 office visit</td>
</tr>
<tr>
<td></td>
<td>2. Additional drug therapy is required to treat or prevent a medical condition in the patient.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effectiveness</td>
<td>3. The drug product is not effective at producing the desired response in the patient.</td>
<td>Patient with otitis media is not responding to amoxicillin after 7 days of therapy. Patient is taking an antidepressant, which is not controlling his or her depression; a new medication is recommended. Patient is taking an antihypertensive medication and is not responding to the dose; an increase in dose is recommended. Patient is on a controller inhaler, which is not effectively controlling asthma; a dose increase is recommended.</td>
<td>1 urgent care visita 1 office visit 1 office visit</td>
</tr>
<tr>
<td></td>
<td>4. The dosage is too low to produce the desired response in the patient.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>5. The drug is causing an adverse drug reaction in the patient.</td>
<td>Patient has developed persistent cough caused by enalapril. Patient has increased anxiety while being treated for depression with bupropion. Patient developed bradycardia resulting from digoxin 0.5 mg per day. The dose was too high because of his age (72 years). Patient is having hypoglycemia because basal insulin dose is too high.</td>
<td>1 office visit 1 office visit 1 office visit 1 office visit</td>
</tr>
<tr>
<td></td>
<td>6. The dosage is too high, resulting in undesirable effects experienced by the patient.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance</td>
<td>7. The patient is not able or willing to take the drug therapy as intended.</td>
<td>Patient cannot afford the medication. Patient did not understand the instructions for a medication, resulting in incorrect administration.</td>
<td>None None</td>
</tr>
</tbody>
</table>

*a Represents pharmacists’ estimates of the reasonable and foreseeable cost savings resulting from the MTM intervention. MTM pharmacists assumed they saved office visits because: (a) Fairview MTM pharmacists work under collaborative practice agreements for medical conditions such as diabetes, and consequently they are able to initiate, modify, and interrupt medications used to treat hypertension, hypercholesterolemia, and diabetes; and (b) MTM pharmacists work at clinics with physicians, and as a result they are able to make recommendations to the provider at the time of an MTM visit, avoiding an additional office visit.

b The MTM pharmacist saved an urgent care visit because patients with otitis media nonresponsive to the first course of antibiotics likely have an urgent care visit.

c When the patient does not respond to an antidepressant, MTM pharmacists typically refer the patient back to the primary care physician for additional clinical assessment.

d The pharmacist saved an ER visit because patients with uncontrolled asthma normally have an ER visit.

ACE = angiotensin-converting enzyme; ER = emergency room; mg = milligrams; MTM = medication therapy management.

pharmaceutical care by the Peters Institute of Pharmaceutical Care at the University of Minnesota and credentialed by Fairview Pharmacy Services. A practice management team comprising a pharmacy director, a product manager, an operations manager, and a business specialist supports the MTM program. Moreover, MTM pharmacists are preceptors for pharmacy students during 10-week rotations in their last year of pharmacy school. The Fairview MTM program also offers a 1-year residency in pharmaceutical care. Practitioners and the management team of the MTM program are involved in education at the University of Minnesota, College of Pharmacy, by teaching pharmacy students and graduate students how the principles of MTM are put into practice. Quality assurance is a key component of the MTM program to promote consistency in the care provided to each patient. One important initiative is the biannual evaluation of practitioners’ documentation. A random sample of patients from all MTM practitioners is evaluated by the MTM operations manager for full documentation in accordance with the MTM program’s policies and procedures. Another quality improvement initiative is the monthly practitioners’ meeting, when MTM pharmacists present patients’ cases and discuss their practices.

The objective of the present study’s analysis was to describe the clinical, economic, and humanistic outcomes of services provided by the MTM program since September 1998.
A retrospective analysis of the 9,068 patients seen in the Fairview MTM program from September 1, 1998, through September 30, 2008, was conducted. All patients who were aged 21 years or older and who either met their healthcare payer’s reimbursement criteria for MTM or paid for MTM out of pocket were included. The described goals of therapy are general goals, which might change slightly according to the needs of a specific patient. 

Methods

A retrospective analysis of the 9,068 patients seen in the Fairview MTM program from September 1, 1998, through September 30, 2008, was conducted. All patients who were aged 21 years or older and who either met their healthcare payer’s reimbursement criteria for MTM or paid for MTM out of pocket were included in the analysis. Data were abstracted from the MTM documentation system (Assurance System) that stored all the documented data from all patients enrolled in the MTM program during the 10-year period. Data abstracted by the first author of this article included the following fields: patients’ demographics, number of MTM consultations, number of medications taken, number and types of medical conditions, types of drug therapy problems identified and addressed, types of interventions implemented to resolve drug therapy problems, change in patients’ clinical status, and pharmacist-estimated health care savings.

The number of medications taken by patients included all active over-the-counter (OTC) medications, supplements, herbal products, medications used to treat acute conditions or used for a limited time period (e.g., antibiotics, analgesics), and medications prescribed for chronic conditions (e.g., antihypertensive medications, antidepressant agents). The presence of medical conditions was determined using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes documented first in the patient’s electronic medical record and then in the Assurance System by the MTM pharmacist.

Drug Therapy Problems

Drug therapy problems were classified into 4 major categories—indication, effectiveness, safety, and compliance—and 7 subcategories (Figure 2). The classification of drug therapy problems was carried out using a systematic process of problem solving referred to as Pharmacotherapy Workup.6,36 The workup algorithm asks if the medication is appropriate for that specific patient; if the medication is the most effective and the right dose to help the patient achieve his or her clinical goals; if the medication is the safest for that patient; and if the patient is able and willing to adhere to the drug regimen. Nonadherence is defined in the pharmaceutical care practice model as the patient’s inability or unwillingness to take a drug regimen that the practitioner has clinically judged to be appropriately indicated, adequately efficacious, and able to produce the desired outcomes.5 In this decision-making process, before evaluating patients’ medication-taking behaviors (following or not following the instructions), practitioners attempt to certify that patients are taking all the medications and only the medications that they need and that all of the medications they are taking are effective and safe. The documentation of drug therapy problems also includes the medications involved, the medical conditions affected, the causes of the problem, and the interventions implemented to attempt resolution of the problem. For nonadherence, the MTM pharmacist documents the main reason the patient is nonadherent, which will determine the intervention used to address this drug therapy problem.

Clinical Status Assessment

For each patient, change in clinical status was evaluated and documented by the MTM pharmacist at each MTM consultation.6 A clinical outcome status was documented as “resolved,” “stable,” “improved,” or “partially improved” when the patient was considered to be achieving the goal of therapy for a specific medical condition, and the following terms were used when the patient was not achieving the goal of therapy:
“unimproved,” “worsened,” or “failure.”

The pharmacist, patient, and physician cooperatively determined goals of therapy that served as the agreed-upon targets for care plan actions and interventions. For each drug therapy indication, goals included clinical parameters described in the literature and patient-specific goals. Drug therapy goals were intended to be measurable, observable, realistic, and achievable within a specified time frame (Figure 3).

For the present study’s analysis, we evaluated the patients’ clinical status at the first and at the most recent MTM consultation. Specifically, for patients not at goal at the first MTM visit, the number of patients not at therapy goal (including clinical status unimproved, worsened, and failure) and the number with improved clinical status (resolved, stable, improved, or partially improved) in the last visit were documented. This approach was deemed reliable and valid based on the results of a quality assessment analysis conducted by Isetts et al. (2003), in which a 12-member panel of physicians and pharmacists reviewed clinical determinations made by Fairview MTM pharmacists from January 1999 through March 2002 for 300 randomly selected patient records. For each patient, 4 types of determinations were assessed, including identification of the drug therapy problem, actions taken to resolve the problem, assessment of clinical status including goal achievement, and estimate of cost avoided by the intervention. Panel members concurred with 94.2% of determinations, disagreed with 2.2%, and expressed neutrality on 3.6%. Intraclass correlation coefficients ranged from 0.73 to 0.85.

To assess clinical status outcomes in more detail, a subset of data for employees of a self-funded employer was analyzed. This analysis focused on the clinical outcomes of 110 patients with diabetes who were followed by MTM pharmacists from August 2007 to December 2008. Even though the MTM pharmacist assesses all of a patient’s conditions and medications, for the purposes of this analysis only the clinical outcomes associated with diabetes care were described. Five measures (“the D5”) that assess optimal diabetes care, as it is suggested by the State of Minnesota, were used to determine the clinical outcomes of this group of patients. The D5 is a set of 5 treatment goals that when achieved together represent the gold standard for managing diabetes. Reaching all 5 goals greatly reduces a patient’s risk for the cardiovascular problems associated with diabetes. The D5 goals include the following: (a) A1c less than 7%; (b) blood pressure less than 130/80 mmHg; (c) LDL-C less than 100 milligrams per deciliter (mg per dL); (d) daily aspirin use (for patients aged ≥1 to 75 years), and (e) documented tobacco-free status. The percentage of MTM patients reaching all 5 goals in December 2008 was compared with the percentage of patients reaching all goals in the first MTM visits that occurred in August 2007.

Economic Outcomes

To estimate the economic impact of MTM, all health care savings documented by MTM pharmacists in the Assurance System were reviewed. MTM pharmacists projected the short-term (3-month) cost savings resulting from their interventions to resolve drug therapy problems (Figure 2). Direct savings included medical services avoided as a result of the intervention, including office visits, emergency room (ER) visits, urgent care visits, long-term care stays, and hospitalizations. Avoidance of lost work time was also estimated. Only those savings considered reasonable and foreseeable by the MTM pharmacist and the MTM management team, based on clinical judgment, quality control procedures, and those changes allowed per the program’s collaborative agreements, were included in the documentation system. This process was standardized, meaning that a particular problem was almost always associated with the same avoided medical service. Additionally, the estimates included only short-term (3-month) savings that might be realized as a direct result of an MTM encounter, not any longer-term savings that might have occurred as a result of implementing preventive drug therapies, such as aspirin to prevent myocardial infarction and stroke, calcium supplementation to prevent osteoporosis and fractures, or immunizations to prevent influenza or pneumonia.

As a quality control procedure, the cost savings claims were adjudicated by an independent clinical pharmacist, external to the Fairview system, who could disallow or downgrade the cost-savings estimate if evidence documented by the practitioner was insufficient. Each time an MTM pharmacist determined that a hospital admission, ER visit, or nursing home admission was avoided as a result of MTM, additional documentation of agreement by the patient and the patient’s primary physician was required. This method of estimating health care cost savings was included in the Isetts et al. study that assessed the validity of determinations made by Fairview MTM pharmacists.

To estimate total cost avoidance, the expenses of the avoided health care services were linked to the average costs of services provided and charged by Fairview Health Services in the last quarter of 2008. Specifically, for each medical service, total avoided expense was calculated by multiplying the number of avoided services by the average cost per service. The value of avoiding lost work time was estimated by multiplying $30.00 (average hourly wage in Fairview) by 8 (daily working hours), then multiplying that result by the number of workdays gained by the intervention, as determined by the pharmacist. For a calculation of the return on investment (ROI) for the program, the cost of providing MTM services was determined by multiplying the average cost of an MTM visit in the last quarter of 2008 by the number of MTM consultations during the 10-year period. The ROI was calculated by dividing the pharmacist-estimated total health care savings by the cost of MTM visits in 2008.

Patient Satisfaction

Since 2001, patient satisfaction surveys have been administered biannually to all patients enrolled in the MTM program in that year. The survey consists of a 7-item questionnaire using a Likert-type scale with 5 options (i.e., agree, strongly agree, neither agree nor disagree, disagree, strongly disagree) that measures patients’ satisfaction with MTM services. Respondents are asked to evaluate the following statements: (1) The pharmacist provided me with education that will help me achieve my goals of therapy;
(2) The pharmacist helped me to understand the intended use (purpose) of my medication(s); (3) The pharmacist helped me to understand the intended results (goals of therapy) of my medication(s); (4) The pharmacist helped me understand how to take my medication(s) safely and correctly; (5) I feel that my overall health and well-being improved because of my MTM visit; (6) Health care benefits should include MTM services; and (7) I would recommend this MTM service to my family and friends. Beneath the 7 statements, there is room for respondents to write comments and suggestions about the MTM program.

In 2008, only patients newly enrolled in the MTM program were surveyed after 2 visits with the MTM pharmacist. Patients received the surveys in the mail along with a pre-addressed postage-paid envelope. For the purposes of the present study, the results of the surveys administered from July to December 2008 were analyzed.

Results
From 1998 to 2008, there were 33,706 documented encounters in a cohort of 9,068 patients, yielding an average of 3.72 visits per patient. The patients ranged in age from 21 to 102 years with 55.5% of patients younger than age 65 years (Table 1). Females constituted 75.9% of the patients.

Medical Conditions and Drug Therapies Used
The average number of medical conditions being treated or prevented per patient through September 2008 was 6.8; 72.4% of patients had 5 or more conditions, and 23.0% had more than 10 conditions. The most frequent indications for drug therapy were hypertension (8.4%), hyperlipidemia (7.9%), nutritional/vitamin supplements (7.3%), diabetes (6.5%), osteoporosis (4.1%), depression (3.7%), and esophagitis (3.5%; data not shown).

The number of medications per patient ranged from 1 to 52. The mean (SD) number of medications per patient encounter was 12.4 (5.9). Forty-five percent of the patients (n = 4,081) were taking 59,427 different OTC medications, and 633 patients (7.0%) were also using 1,783 different sample products.

Drug Therapy Problems Identified and Addressed
The number of drug therapy problems identified and addressed by MTM pharmacists from 1998 to 2008 was 38,631. At the first MTM visit, 7,708 (85.0%) of patients had 1 or more drug therapy problems, and 2,630 (29.0%) had 5 or more drug therapy problems. The most frequent drug therapy problem was the need for additional drug therapy (28.1% of all drug therapy problems; Table 2). The majority of these problems involved patients who required preventive aspirin, oral calcium supplements, oral hypoglycemics, statins, or insulin. The second most common drug therapy problem category was subtherapeutic dosage (26.1% of all drug therapy problems). The top 5 categories of medications that were most commonly used in subtherapeutic dosages included oral hypoglycemics, insulin, calcium, statins, and angiotensin-converting enzyme (ACE) inhibitors. Only 16.5% of drug therapy problems were attributed to nonadherence. In the pharmacist’s assessment of the single main cause for nonadherence, the most frequent cause of patients being unable or unwilling to take medications as intended was that the patient could not afford to purchase the medication or could not afford the copayment required to obtain the prescription (36.2% of 6,379 nonadherent patients; Table 3). The next most frequent reason identified for nonadherence was that the patient did not understand the instructions (24.8% of nonadherent patients). The top 5 categories of medications associated with nonadherence were

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### Table 1: Patient Population Receiving Medication Therapy Management

<table>
<thead>
<tr>
<th>Gender Characteristics</th>
<th>Number of Patients (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2,184 (24.1)</td>
</tr>
<tr>
<td>Female</td>
<td>6,884 (75.9)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>21-50</td>
<td>2,018 (22.3)</td>
</tr>
<tr>
<td>51-64</td>
<td>3,019 (33.3)</td>
</tr>
<tr>
<td>65 or more</td>
<td>4,031 (44.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of medications at baseline&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35 (0.4)</td>
</tr>
<tr>
<td>1-2</td>
<td>130 (1.4)</td>
</tr>
<tr>
<td>3-4</td>
<td>248 (2.7)</td>
</tr>
<tr>
<td>5-6</td>
<td>444 (4.9)</td>
</tr>
<tr>
<td>7-8</td>
<td>716 (7.9)</td>
</tr>
<tr>
<td>9-10</td>
<td>844 (9.3)</td>
</tr>
<tr>
<td>More than 10</td>
<td>6,651 (73.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of medical conditions&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>217 (2.4)</td>
</tr>
<tr>
<td>1-2</td>
<td>1,015 (11.2)</td>
</tr>
<tr>
<td>3-4</td>
<td>1,269 (14.0)</td>
</tr>
<tr>
<td>5-6</td>
<td>1,741 (19.2)</td>
</tr>
<tr>
<td>7-8</td>
<td>1,605 (17.7)</td>
</tr>
<tr>
<td>9-10</td>
<td>1,135 (12.5)</td>
</tr>
<tr>
<td>More than 10</td>
<td>2,086 (23.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of drug therapy problems</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1,360 (15.0)</td>
</tr>
<tr>
<td>1</td>
<td>1,405 (15.5)</td>
</tr>
<tr>
<td>2</td>
<td>1,469 (16.2)</td>
</tr>
<tr>
<td>3</td>
<td>1,451 (16.0)</td>
</tr>
<tr>
<td>4</td>
<td>753 (8.3)</td>
</tr>
<tr>
<td>5 or more</td>
<td>2,630 (29.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reflects patients who chose participation after receiving a mailed invitation from the MTM program. Columns may not sum to 100% due to rounding.
<sup>b</sup> Total medication count includes chronic and acute prescription drugs, over-the-counter drugs, supplements, and herbal products.
<sup>c</sup> Count of medical conditions was based on the number of different International Classification of Diseases, Ninth Revision, Clinical Modification codes contained in the patient’s electronic medical record.
Eighty percent of drug therapy problems identified in Fairview’s MTM program were resolved without the direct involvement of patients’ physician(s), perhaps because the MTM program has collaborative practice agreements signed with physicians in Fairview Health Services. The most common resolutions of drug therapy problems with patients were education (35.8%), elimination of a barrier to access a medication (26.8%), initiation of a new drug therapy (11.8%), and change in dose (10.5%). The most frequent resolutions of drug therapy problems with patients were initiation of a new drug therapy (32.4%), change in drug dosage (25.2%), change in drug product (14.7%), and discontinuation of a drug therapy (12.1%).

Clinical Outcomes
In the clinical status assessment of the 12,851 medical conditions in 4,849 patients who were not at goal when they enrolled in the MTM program, 7,068 conditions (55.0%) improved, 2,956 (23.0%) were unchanged, and 2,827 (22.0%) worsened during the course of MTM services. Of the 31,858 medical conditions evaluated on at least 2 occasions in 5,054 patients, 17,203 (54.0%) conditions were unchanged, 10,513 (33.0%) improved, and 4,141 (13.0%) declined in clinical status during MTM therapy.

In the subset of patients with diabetes (110 employees of a self-funded employer), 47 (42.7%) reached all D5 goals for diabetes (A1c less than 7%, blood pressure less than 130/80 mmHg, LDL-C less than 100 mg per dL, no tobacco use, and daily aspirin use) at the last MTM visit. At baseline, only 19 (17.3%) of these patients were reaching all goals, representing an absolute 25.4% change. By comparison, in Minnesota as a whole, only 8% and 13% of patients with diabetes who were covered by public and private payers, respectively, were reaching all these goals in 2008.\(^{36}\)

Economic Outcomes
Over the 10-year study period, pharmacist-estimated direct savings to Fairview Health Services were $2,913,850 ($86.45 per encounter for 33,706 encounters; Table 4). The average cost of an MTM visit for Fairview was $67.00 in the last quarter of 2008, for a total MTM programmatic cost of $2,258,302 and an estimated ROI of $1.29 per $1 in MTM costs.

Patient Satisfaction
From July to December 2008, 317 patients responded to the patient satisfaction survey (28.0% response rate of 1,132 surveys mailed), expressing a generally high level of satisfaction with the program: 97.1% of respondents agreed or strongly agreed that the pharmacist provided them with the education that will help them to achieve their goals of therapy; 95.3% of respondents agreed or strongly agreed that their overall health and well-being had improved because of MTM; 98.1% of patients agreed or strongly agreed that they would recommend this service to their family and friends; 99.0% of respondents agreed or strongly agreed that the pharmacist helped them to understand the intended use (purpose) of their medications; 99.9% of patients agreed or strongly agreed that the pharmacist helped them to understand the intended results (goals of therapy) of their medications; 99.0% of respondents agreed or strongly agreed that the pharmacist helped them to understand how to take their medication(s) safely and correctly; and 98.1% of patients agreed or strongly agreed that health care benefits should include the MTM program. Moreover, the patients’ comments about the MTM program were overwhelmingly positive, including a patient who commented that the MTM service had changed her life by permitting her to gain control of her diabetes.

Discussion
In a large integrated health care system, MTM was provided to a diverse group of 9,068 patients, using a standardized patient care process to address numerous drug therapy problems identified by pharmacists. In this population, patients rarely experienced a single medical condition, and 72% had 5 or more medical conditions. The high level of comorbidities makes patients’ drug regimens complex, which can make adherence difficult and confusing for patients. Focusing on only a single disease state is unlikely
to adequately meet all of a patient’s drug-related needs. Moreover, despite extensive use of nonprescription medications (OTC, supplements, herbal medicines, etc.) by this population, those drug products are usually not recorded in standard payer claims database systems or pharmacy dispensing systems. MTM is an effective mechanism to facilitate assessment of the indications, effectiveness, and safety of OTC products, especially in patients who are using multiple prescription medications. More than one-half (54.2%) of drug problems involved the need for a new medication or dosage increase. The medical conditions associated with these most common drug therapy problems were diabetes and hyperlipidemia. These results suggest that when pharmacist practitioners work closely and over time with patients to facilitate reaching the goals of therapy, there is usually an increase in medication use. These results are consistent with those of previous research that assessed the clinical outcomes of pharmaceutical care services.\(^{10,31,39,40}\) For example, Welch et al. found that Medicare Part D beneficiaries who opted in to receive MTM were more likely to incur an increase in medication costs than were those who opted out of MTM.\(^{39}\) These results also indicate that health care providers might choose nonpharmaceutical interventions when drug therapy is needed or use a dose that is too low to control the patient’s medical condition. Other studies have shown a failure to titrate medications, such as statins, to effective doses in patients at risk of complications.\(^{41,42}\) Some authors who stress the importance of using more aggressive therapy, such as higher doses or introducing combination therapy to get patients to goal, have described “clinical inertia,” a failure of health care providers to initiate or intensify therapy when indicated.\(^{43,44}\)

Even though most work conducted within pharmacy has focused on adverse drug effects, drug interactions, duplicate therapy, and compliance, our data suggest that the major problem related to medications can be attributed to underuse of potentially efficacious drug therapy. As stated by O’Connor et al. (2005), failure to intensify therapy in patients with chronic conditions and suboptimal biomarker readings for blood glucose, blood pressure, or serum lipids represents a type of medication error as defined by the Institute of Medicine by leading to adverse events.\(^{45}\) O’Connor et al. assert that the main distinction between the adverse events caused by overuse or misuse of therapies, and adverse events caused by underuse of therapies in chronic disease care, is the time frame over which the adverse event occurs. Clinical inertia, or the underuse of efficacious drug therapy, “may take years or even decades for the consequent adverse event to declare itself.”\(^{45}\)

The Fairview MTM program’s experience suggests that patients often have good reason for not adhering or persisting with drug treatment. As discussed by Ramalho de Oliveira and Shoemake (2006), pharmacists should look at noncompliance from the perspective of the patients, taking into consideration their subjective experiences with their illnesses and medications.\(^{45}\) In this context, it is essential to understand the patient’s unique medication experience, which is connected with patients’ previous experiences with medications, what they think and feel about their medications, and their concerns and beliefs about them.\(^{46}\) This experience will influence the patient’s decisions about whether to take the medication, to decrease or increase the dose, or to make necessary modifications to the drug regimen. In a recent review on compliance and adherence, Tuchette and Shapiro (2008) suggested that because adherence is a multifaceted issue, programs designed to impact adherence should focus on identifying patient-specific adherence barriers and tailor interventions to eliminate or reduce these barriers.\(^{47}\) The authors emphasize that tailoring interventions to meet each patient’s needs will bring about better outcomes than offering the same blanket intervention to all patients.\(^{47}\) This review corroborates the approach of using the patient’s unique medication experience to assist him or her to achieve therapeutic goals.

Stiebbs et al. (2005) examined pharmacists’ interventions that combined drug utilization review with patient and physician education in a medical clinic for low-income elderly patients.\(^{48}\) In this study, pharmacists’ interventions increased the use of generic drugs, decreased out-of-pocket drug expenses by patients, and promoted use of needed treatments. Another study by Barnett et al. (2009) that analyzed 7 years of MTM claims from an MTM administrative services company suggested that from 2000 to 2006, there was a shift in the type of pharmacists’ interventions from patient education involving acute medications to prescriber consultation for chronic medications.\(^{49}\) Barnett et al. also found an increase in the MTM reimbursement over time, from $7.65 to $12.28 per intervention. As underscored by Benner and Kocot (2009), we are moving towards a health care system that will emphasize and reward quality and high value, and pharmacists must take the opportunity to redefine themselves as medication therapy managers who will add significant value by improving medication outcomes.\(^{50}\) The

<table>
<thead>
<tr>
<th>TABLE 4  Estimated Health Care Savings*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Care Savings</td>
</tr>
<tr>
<td>Clinic outpatient visit avoided</td>
</tr>
<tr>
<td>Specialty office visit avoided</td>
</tr>
<tr>
<td>Employee work days saved</td>
</tr>
<tr>
<td>Laboratory service avoided</td>
</tr>
<tr>
<td>Urgent care visit avoided</td>
</tr>
<tr>
<td>Emergency room visit avoided</td>
</tr>
<tr>
<td>Hospital admission avoided</td>
</tr>
<tr>
<td>Nursing home admissions</td>
</tr>
<tr>
<td>Home health visit</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
*Reflects services provided to 9,068 patients in 33,706 encounters from September 1998 through September 2008. Savings were calculated as the number of events avoided by MTM, as estimated by the MTM pharmacist and validated by external review, times the average costs of services at Fairview Health Services in the second quarter of 2008.

MTM = medication therapy management.
profession of pharmacy must focus on the unmet needs of patients and provide consistent and standardized services that can be recognized, measured, and paid for.

The economic results of this study were positive as the calculated ROI suggests that MTM services decreased the total cost of health care in Fairview Health Services. Our results are similar to those of other studies that also indicated potential cost-saving effects of MTM services.34,40

This study is an important step in the direction of examining the outcomes of a comprehensive, standardized, and holistic approach to MTM. As stressed by Doucette et al. (2005),39 policy makers seeking models of MTM services for Medicare beneficiaries should consider a model as comprehensive as pharmaceutical care for patients at high risk of developing drug-related problems.

Currently, MTM pharmacists are considered an indispensable part of the health care team in Fairview Health Services because they assume responsibility for patients’ drug therapy outcomes and collaborate with other providers to facilitate high-quality patient care. In 2010, Fairview’s MTM program is expanding to 6 additional clinics, and 3 MTM pharmacists are providing care on-site at major employers’ headquarters in the Twin Cities area.

Limitations

First, the lack of a comparison group makes this a descriptive study without the ability to attribute outcomes to the MTM interventions. Participating patients opted into the program and therefore might be especially motivated to comply with medical and drug treatments. Second, the economic outcomes described here are the result of a process of estimation and documentation by MTM pharmacists, which is based on clinical judgment instead of a thorough analysis of medical claims. Third, our programmatic cost estimates do not include additional costs associated with added medications or increased dosages. Fourth, because our survey response rate was low, the satisfaction level and drug treatments.

Second, the economic outcomes described instead of a thorough analysis of medical claims. Third, our results may be partly attributable to the collaborative practice agreements that permitted pharmacists to make 80% of interventions without physician involvement. A final limitation is the inability to generalize the findings outside of the health system environment where access to needed patient information is not as readily available.

Conclusion

The pharmaceutical care-based MTM services assessed in this study identified numerous drug therapy problems; 85% of patients had 1 or more drug therapy problems, and 29% had 5 or more drug therapy problems. Because the most prevalent drug therapy problems were related to the underuse of effective medications, the number of medications used by patients tends to increase with MTM services. However, MTM may save total health care costs by helping patients avoid office visits, ER visits, and hospitalizations.

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DISCLOSURES

There was no external funding for this manuscript. The 3 authors are employees of Fairview Pharmacy Services. Ramalho de Oliveira had primary responsibility for the concept and design, writing, and revision of the manuscript, with the assistance of Brummel and Miller. Ramalho de Oliveira performed the data collection, and all 3 authors shared equally in data interpretation.

REFERENCES


Medication Therapy Management: 10 Years of Experience in a Large Integrated Health Care System


Geographic Variation in Drug Safety: Potentially Unsafe Prescribing of Medications and Prescriber Responsiveness to Safety Alerts

Richard A. Feifer, MD, MPH, and Jason M. James

ABSTRACT

BACKGROUND: Drug safety issues represent a major cause of morbidity and mortality. Alerting programs are intended to identify patients at potential risk for adverse drug reactions and may provide relevant information to prescribers to support their decision making about clinically appropriate risk reduction. Geographic differences in the incidence of drug safety issues and the responsiveness of prescribers to alerting systems have not been previously studied.

OBJECTIVE: To measure geographic differences in the rates of alerting events for potential drug safety issues, communicated to prescribers by mail or fax, and the responsiveness of prescribers to such alerts.

METHODS: All alerts generated by a commercially available drug safety alerting program were evaluated for calendar year 2008 and were classified geographically based on patient residence. Primary study measures were (a) number of alerting events per 1,000 members (i.e., covered beneficiaries of all ages whose plan sponsor was enrolled in the alerting program service), and (b) therapy change rate (defined as the percentage of alerts that were followed by therapy modification consistent with the clinical alert).

RESULTS: The program-wide aggregate rate of alerting events across all regions was 128 per 1,000 members, with the state-specific range from 78 to 240. The program-wide aggregate rate of drug therapy change across all regions was 54.0%, with the state-specific range from 48.1% to 59.5%.

CONCLUSIONS: The rates of potential drug safety issues (alerting events) and the responsiveness of prescribers to drug safety alerts vary considerably by region and state. States with high issue rates and low therapy change rates may require additional prescriber outreach.

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What this study adds

• In an analysis of 1.6 million drug safety alerts generated by a large pharmacy benefits management company for 12.6 million eligible members of all ages in 2008, state-by-state alert rates ranged from 78 to 240 alerts per 1,000 eligible beneficiaries.
• Variation was also seen in the regional rates of physician responsiveness to drug safety alerts, with success (therapy change) rates per alerting event ranging from 48.1% to 59.5% across states in the United States.

According to the Institute of Medicine, “Pharmaceuticals are the most common medical intervention, and their potential for both help and harm is enormous.” More than 3.8 billion prescriptions are dispensed in the United States each year, costing over $291 billion. These medications sometimes lead to significant unintended consequences, which are termed “adverse drug events” (ADEs). The Institute of Medicine estimates that over 1.5 million preventable ADEs occur in the United States each year. As many as 28% of emergency room visits are drug related—of which 70% are preventable—with 24% resulting in hospital admission. A systematic review and meta-analysis reported a median of 7.1% (interquartile range 5.7%-16.2%) of all hospital admissions resulted from ADEs, of which 59% were considered preventable. Howard et al. (2006) found in a systematic review of 13 prospective observational studies that the median percentage of admissions due to preventable ADEs was 3.7% (range = 1.4% to 15.4%). From an economic perspective, the cost of addressing ADE-related morbidity was over $177 billion in 2000, which exceeded the total cost of outpatient prescribed medication sales in that year.

Many factors contribute to these high rates of ADEs. Each year, prescribers are confronted with having to master the complexities of various new medications, as well as new data on the safe and effective use of thousands of existing drugs. Furthermore, patients increasingly require multiple medications to treat various conditions and comorbidities, increasing the potential for drug interactions, drug-disease conflicts, and ADEs.

Relying on physicians and other prescribers to maintain mastery of this increasingly complex situation from memory alone is an inadequate strategy. Furthermore, prescribers often do not have access to relevant patient information, including key diagnoses, because of inadequate coordination of care across multiple

What is already known about this subject

• Drug safety is a critical issue, with preventable adverse drug events contributing to significant unnecessary morbidity, mortality, and health care costs. As many as 28% of emergency room visits and 16.2% of hospital admissions are drug-related, with the majority being preventable. In a systematic review, Howard et al. (2006) found that a median of 3.7% (range 1.4% to 15.4%) of hospital admissions were attributable to preventable drug-related causes.
• Medical decision making and medical care exhibit large regional variation, including hospitalization rates, procedures, and adherence to national guidelines. The magnitude of this variation is often by a factor of 3 to 5. However, geographic variation in the United States related to drug safety has not previously been described.

Note: This article is the subject of a commentary that appears on pages 231-232 of this issue.
health care providers and inadequate integration of medical and pharmacy data.11,12

Automated alerting systems have been developed to help mitigate this problem, using patient-specific data that have been integrated from a variety of medical and pharmacy sources. One such alerting system is provided by a pharmacy benefits management company (PBM), Medco Health Solutions, Inc., under the name RationalMed. This program includes thousands of algorithms that continuously analyze patient-level data to identify potential drug safety issues. When a potential problem is identified, such as a drug that is contraindicated when a patient has a particular disease as indicated by that patient's claims record, prescribers are alerted to the issue by mail or fax and provided with the relevant scientific evidence and patient-level data. One example of this intervention is the prescribing of medications for attention deficit hyperactivity disorder (ADHD) to a child with comorbid structural heart disease. The alert for this situation would describe the potential interaction, cite the relevant external sources including citations from the medical literature, and provide a summary of the patient's medical and pharmacy claims record, including contact information for other prescribers and pharmacies involved in the prescribing conflict.

In these alerting situations, the ultimate decision maker remains the physician or other prescribing health care professional. The alert itself has no role in any determination of drug coverage or copayment and is purely for the informational use of the prescriber. The role of the alerting system is to provide a complete view of the patient, as well as up-to-date literature-based recommendations, to facilitate improved decision making.

By virtue of having national reach, the largest drug safety alerting systems also provide an opportunity to undertake a geographic comparison of regions and states, exploring differences in prescribing and responsiveness to care-improvement alerts. Geographic variations in many elements of medical care have previously been reported, including the likelihood of hospitalization, procedure rates, prescribing of medications, and adherence with national care-improvement guidelines.15-18 For example, the proportion of children with persistent asthma receiving influenza vaccination has been observed to vary regionally by a factor of 2, from 12.1% to 23.8%.15

In contrast to the above examples, variations related to drug safety have not been sufficiently studied. This analysis describes the findings of a large-scale alerting program and explores geographic variation to help guide future prescriber outreach and support efforts.

Methods

RationalMed, the source of the drug safety alerts evaluated in the present study, integrates outpatient pharmacy and medical claims data to identify potential drug safety issues. RationalMed also alerts on other issues, such as coordination of care (e.g., polypharmacy in seniors) and omission of essential care (e.g., omission of guideline-based drug therapy such as inhaled corticosteroids for severe asthma), although the focus of the present analysis was specifically on the subset of alerts pertaining to potential ADEs.

The algorithms are developed and maintained by a team of physicians and pharmacists that has responsibility for ongoing surveillance to identify new clinical issues warranting incorporation into the program and necessary changes to existing algorithms and messages. Active surveillance is focused on FDA alerts, manufacturer alerts, product labeling changes, major national guidelines, and the peer-reviewed medical literature. The algorithms and messages are all based directly and entirely on those external sources, with explicit citations provided to prescribers who receive the alerts. Pharmacists then test each of these algorithms by performing detailed reviews of a sufficiently powered sample of individual patient profiles to assess the targeting accuracy based on their professional judgment in the context of the entire medical and pharmacy claims record.

The evaluation period for this analysis was calendar year 2008. During this time, roughly 12.6 million members throughout the United States were enrolled in the alerting program. Pharmacy claims were available for all members, since the study PBM directly provided their pharmacy benefits. Medical claims were provided to the PBM by all participating plan sponsors on a frequent basis, typically monthly, and were integrated with pharmacy claims. Pharmacy claims were present in 2008 for 60.3% of eligible members, and medical claims were present for 62.9% of eligible members.

All alerting events pertaining to potential ADEs for these 12.6 million members were included in the analysis. An alerting event was defined as a potential drug safety issue that generated an alert to 1 or more prescribers. The event count excludes the very small fraction of possible safety issues (1.47%) that could not be communicated to the prescribers for administrative reasons, such as invalid contact data. These alerting events were classified based on each patient’s residence according to U.S. Census regions, divisions, and states.

Two key measures were evaluated for each geographic area. The first, the number of alerting events for potential safety issues identified per 1,000 members, is the prevalence rate of potentially unsafe prescribing situations. By dividing the observed number of alerting events by the number of members whose plan sponsors were enrolled in the program (which varies from region to region), the reported alerting event rate was adjusted for differences in population size as well as differences in the percent of the region’s population enrolled in the alerting program. In calculating this rate, multiple discrete issues and alerting events for the same member were counted separately. Members who were potentially candidates for an alert, should their clinical situation warrant, included people of all ages regardless of any prior drug utilization.

The rates of safety alerting events were reported without
**TABLE 1** Types of Drug Safety Issues Addressed, with Illustrative Examples

<table>
<thead>
<tr>
<th>Type of Drug Safety Issues Identified</th>
<th>Therapy Change That Would Qualify as an Alerting Successa</th>
<th>Clinical Issue Summary</th>
<th>Illustrative Examplesb</th>
<th>Primary Sources</th>
<th>Alerting Successa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse drug-disease interaction</strong></td>
<td>Discontinuation of the conflict medication or (when clinically applicable) reduction to a safer dose</td>
<td>Attention deficit hyperactivity disorder medication for a child with a significant cardiac structural or rhythm abnormality Risk of sudden death</td>
<td>Sudden death has been reported with stimulants given at usual doses to youth with structural cardiac abnormalities or other serious heart problems. Atomoxetine, amphetamines and methylphenidate should generally not be used in children or adolescents with serious cardiac structural or rhythm abnormalities.</td>
<td>Vetter et al., 200839\footnote{39} FDA, 201020\footnote{20} Perrin et al., 200821\footnote{21}</td>
<td>Central nervous system stimulant is discontinued.</td>
</tr>
<tr>
<td><strong>Adverse drug interaction</strong></td>
<td>Discontinuation of either of the conflict medications or (when clinically applicable) reduction of either of the conflict medications to a safer dose</td>
<td>Concomitant use of azole antifungal medications and amiodarone Risk of serious cardiac arrhythmias</td>
<td>Cases of QT prolongation with or without torsades de pointes have been reported in patients taking amiodarone concomitantly with azole antifungals. The decision to administer amiodarone with other drugs that prolong the QTc interval must be based on careful assessment of the potential risks and benefits for each patient.</td>
<td>Amiodarone product label, 200922</td>
<td>Azole antifungal is discontinued.</td>
</tr>
<tr>
<td><strong>Dose duration issue</strong></td>
<td>Discontinuation of the conflict medication, reduction to a safer dose, or (when clinically applicable) addition of a protective agent</td>
<td>Prolonged (&gt; 30 days) NSAID use at or above the maximum recommended daily dose in patients aged 65 years or older, with no cytoprotective agent Risk of gastrointestinal hemorrhage</td>
<td>Older patients are at high risk of gastrointestinal bleeding with non-steroidal anti-inflammatory medications. Consider using the lowest effective dose for the shortest duration consistent with the patient’s treatment goals. If ongoing NSAID therapy is required, consider adding a cytoprotective agent.</td>
<td>FDA, 201023\footnote{23} ACR, 200024</td>
<td>NSAID dose is lowered (or proton pump inhibitor is added).</td>
</tr>
<tr>
<td><strong>Drug-age conflict</strong></td>
<td>Discontinuation of the conflict medication or (when clinically applicable) reduction to a safer dose</td>
<td>Topical immunomodulatory eczema treatment for patients younger than 2 years of age Risk of infection, skin malignancies, and lymphoma</td>
<td>Topical calcineurin inhibitors carry a black box warning that use in children under 2 is not indicated because long-term safety has not been established. Effects on the developing immune system are unknown. Rare cases of malignancy have been reported.</td>
<td>FDA, 200925\footnote{25} FDA, 201026\footnote{26} ACAAI/AAAAI, 200627 \footnote{27}</td>
<td>Topical calcineurin inhibitor is discontinued.</td>
</tr>
<tr>
<td><strong>Drug-pregnancy consideration</strong></td>
<td>Discontinuation of the conflict medication</td>
<td>Angiotensin-converting enzyme inhibitors during pregnancy Risk of congenital malformations</td>
<td>Oligohydramnios, limb contractures, hypoplastic lung development, and renal failure have been reported with angiotensin-converting enzyme inhibitor use during the second and third trimester. First trimester exposure may be associated with defects of the cardiac septum, central nervous system, and urologic system. Discontinue the angiotensin-converting enzyme inhibitor as soon as possible in pregnant women.</td>
<td>FDA, 201028\footnote{28} Cooper et al., 200629\footnote{29}</td>
<td>Angiotensin-converting enzyme inhibitor is discontinued.</td>
</tr>
<tr>
<td><strong>Drug therapy duplication</strong></td>
<td>Discontinuation of either of the conflict medications</td>
<td>Concomitant use of atenolol and metoprolol Increased risk of heart block</td>
<td>Atenolol and metoprolol have similar pharmacologic effects. Patients who receive duplicative therapy may exhibit additive side effects without further therapeutic benefit.</td>
<td>Metoprolol tartrate product label, 200930\footnote{30} Atenolol product label, 200831</td>
<td>Atenolol is discontinued or metoprolol is discontinued.</td>
</tr>
</tbody>
</table>
adjustment for any regional differences in age or disease burden because the intent of this analysis was to be fully descriptive of the extent of the potential safety issues identified and of regional differences attributable to all causes, including demographics as well as prescribing practice patterns.

The second key measure, success per alerting event, is the frequency of therapy changes that were consistent with the safety alert sent to the prescriber. In the example of a drug contraindicated in the context of a patient’s disease, a success would be a change to a safer medication (i.e., without the contraindication), or drug discontinuation. Similarly, the success of alerts on dose-related issues would be defined by a change in the patient’s prescription to a safer dose (calculated as strength times quantity divided by days supply). Changes in therapy were determined through systematic monitoring of each patient’s prescription claims record during a specific window of time after each alert was sent to the prescriber. A success was recorded for the alert if, during that particular window, (a) neither the offending medication nor other medications with the same clinical concern were filled, or (b) the medication was not filled at an unsafe dose for dose-related alerts. For most prescriptions, that window begins on the earliest date that refills can be processed under most plans (when 75% of the alerted-upon medication would be used), and extends for 52 days thereafter. The window for 30-day fills begins on day 23 (75% of 30) and extends 52 days from then, ending on day 75. The window for 90-day fills begins on day 68 (75% of 90) and extends 52 days from then, ending on day 120. For prescriptions where the earliest next refill date is less than 15 days from the alert being generated, the start date of the measurement window is fixed at day 15 after the alerting event to ensure that the prescriber had likely received the alert prior to counting any change as an alerting success.

The types of drug safety issues and alerts that were included in this analysis are described in Table 1, with specific illustrative clinical examples from among the thousands of program algorithms, as well as the associated therapy changes that would define a success according to the methodology above.

Approval or exemption from an institutional review board (IRB) was not sought for this study. The analyses were conducted entirely from claims related to the pharmacy programs that the PBM routinely delivers on behalf of its clients. This manuscript does not include any individually identifiable health information. The authors and the PBM are authorized to use protected health information (PHI) in administering the RationalMed program under the “treatment, payment, and health care operations” provision of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The authors and the PBM are bound to the covered entity by privacy and security standards that protect PHI, including HIPAA-compliant procedures for storage, transmission, release, and disposal of PHI.

### Results

Table 2 describes by state the eligible population and the alerting events for potential safety issues identified in 2008. These

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**TABLE 1** Types of Drug Safety Issues Addressed, with Illustrative Examples (continued)

| Type of Drug Safety Issues Identified | Therapy Change That Would Qualify as an Alerting Success | Illustrative Examples
|-------------------------------------|--------------------------------------------------------|----------------------|
| **Duration issue**                  | Discontinuation of the conflict medication             | Long-term use of depot medroxyprogesterone may cause a significant decrease in bone density during the initial years of treatment. Recovery of bone mass after drug discontinuation may be prolonged and incomplete. Medroxyprogesterone product label, 2006.32
|                                    |                                                        | Depot medroxyprogesterone is discontinued. Medroxyprogesterone product label, 2009.35
|                                    | Discontinuation of the conflict medication or reduction to a safer dose | High doses of sedative hypnotic drugs may be associated with dizziness, drowsiness, headache, abdominal pain, nausea, and falls. Patients may develop dependence. Consider whether dose adjustment is warranted for your patient. Zolpidem tartrate product label, 2009.35

**a**Reflects therapy changes made within a window that begins on the fill date plus 75% of the dispensed days supply (e.g., fill date plus 23 days for a 30-day supply) and ends 52 days later. See Methods section for detailed description.

**b**From among the thousands of specific clinical issues alerted upon.

ACAAI/AAAAI = American College of Allergy, Asthma & Immunology/American Academy of Allergy, Asthma & Immunology; ACOG = American College of Obstetricians and Gynecologists; ACR = American College of Rheumatology; FDA = U.S. Food and Drug Administration; NSAIID = nonsteroidal anti-inflammatory drug.
## Geographic Variation in Drug Safety: Potentially Unsafe Prescribing of Medications and Prescriber Responsiveness to Safety Alerts

### TABLE 2

Overview of Members Eligible for Alerting and Safety Issues Identified in 2008

<table>
<thead>
<tr>
<th>State</th>
<th>Number of Alerting Events</th>
<th>Number of Members*</th>
<th>Potential Safety Issues (Alerting Events) Per 1,000 Members*</th>
<th>Successes (Therapy Change) Per Alerting Event</th>
<th>Mean Age of Members*</th>
<th>Average Number of Distinct Drug Classes Per Member*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AK</td>
<td>1,158</td>
<td>14,786</td>
<td>78</td>
<td>53.5%</td>
<td>37</td>
<td>1.90</td>
</tr>
<tr>
<td>AL</td>
<td>21,384</td>
<td>119,102</td>
<td>180</td>
<td>57.5%</td>
<td>44</td>
<td>4.18</td>
</tr>
<tr>
<td>AR</td>
<td>12,148</td>
<td>86,889</td>
<td>140</td>
<td>53.4%</td>
<td>42</td>
<td>3.96</td>
</tr>
<tr>
<td>AZ</td>
<td>21,410</td>
<td>156,381</td>
<td>137</td>
<td>54.4%</td>
<td>44</td>
<td>3.80</td>
</tr>
<tr>
<td>CA</td>
<td>144,762</td>
<td>1,221,379</td>
<td>119</td>
<td>52.7%</td>
<td>42</td>
<td>3.70</td>
</tr>
<tr>
<td>CO</td>
<td>16,162</td>
<td>146,843</td>
<td>110</td>
<td>52.1%</td>
<td>40</td>
<td>3.27</td>
</tr>
<tr>
<td>CT</td>
<td>9,316</td>
<td>90,886</td>
<td>103</td>
<td>53.7%</td>
<td>41</td>
<td>3.47</td>
</tr>
<tr>
<td>DC</td>
<td>4,035</td>
<td>16,846</td>
<td>240</td>
<td>51.8%</td>
<td>43</td>
<td>3.09</td>
</tr>
<tr>
<td>DE</td>
<td>8,700</td>
<td>53,161</td>
<td>164</td>
<td>53.4%</td>
<td>51</td>
<td>4.81</td>
</tr>
<tr>
<td>FL</td>
<td>84,046</td>
<td>528,345</td>
<td>159</td>
<td>56.8%</td>
<td>48</td>
<td>3.37</td>
</tr>
<tr>
<td>GA</td>
<td>48,409</td>
<td>372,944</td>
<td>130</td>
<td>57.3%</td>
<td>41</td>
<td>3.87</td>
</tr>
<tr>
<td>HI</td>
<td>1,164</td>
<td>9,998</td>
<td>116</td>
<td>52.3%</td>
<td>50</td>
<td>3.45</td>
</tr>
<tr>
<td>IA</td>
<td>11,607</td>
<td>133,083</td>
<td>87</td>
<td>49.4%</td>
<td>37</td>
<td>2.14</td>
</tr>
<tr>
<td>ID</td>
<td>5,923</td>
<td>43,991</td>
<td>120</td>
<td>49.9%</td>
<td>39</td>
<td>2.62</td>
</tr>
<tr>
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<tr>
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<tr>
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<tr>
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<td>2.81</td>
</tr>
<tr>
<td>TOTAL</td>
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<td>12,555,993</td>
<td>128</td>
<td>54.0%</td>
<td>43</td>
<td>3.91</td>
</tr>
</tbody>
</table>

*A member is an enrolled person of any age whose plan sponsor uses the safety alerting program, regardless of whether the member filled any prescriptions during 2008.
alerting events were the basis for the success analysis. Table 2 also reveals the variation in the average number of distinct drug classes per member, using the Specific Therapeutic Class framework provided by First DataBank (San Bruno, CA).  

Table 3 provides the rates of alerting events and the mean age for the program-eligible population in each of the U.S. Census regions and divisions. These data reveal that 13.2% of division-level variation in alerting events is explained by eligible member age.

Figures 1 and 2 show each geographic region plotted on a 2-by-2 chart. The x-axis reflects the prevalence of potential safety issues (alerting events) per 1,000 members. The y-axis reflects success per alerting event, which is the rate of therapy change in response to the alert. Each chart also includes dotted lines to indicate the program-wide aggregate rates across all members in all regions and states. The aggregate rate of potential safety issues (alerting events) was 128 per 1,000 members. The aggregate rate of success per alerting event was 54.0%.

The full extent of the regional variation is demonstrated by the state-level data in Figure 2. Potential safety issues per 1,000 members ranged from the lowest rate in Alaska (78) to the highest rates in Washington, DC (240), followed by Louisiana, Michigan, and Alabama (180-182). Success per alerting event ranged from the lowest in North Dakota (48.1%) to the highest in Ohio (59.5%).

Figure 2 graphically displays which quadrant each state falls into, based upon whether it is above or below the program-wide rates for each of the measured variables. These quadrant assignments are also depicted in a map of the United States in Figure 3, which shows the proximity of states with similar measured characteristics.

### Discussion

Geographic variation in medical decision making and patient management has been widely reported. Prior research has extended from the utilization rates of certain procedures, such as back surgeries, to the likelihood of being prescribed narcotics or stimulant medications. Studies also have measured geographic differences in clinical quality, largely defined as physician adherence to national guidelines for conditions such as asthma and heart disease, and differences in the rates of preventive health services. In contrast, little previous attention has been given to geographic variation related to drug safety issues. This study reveals considerable variation.

The data in figures 1 and 2 can be interpreted best by quadrant, based on the divisions provided by the program-wide (weighted average) values for each measure. The “High Potential Safety Issues (Alerting Events), Low Success” quadrant is perhaps the most concerning, since the extent of the potential patient safety problem is the greatest, and the prescribers appear to be relatively resistant to addressing care improvement opportunities. The “Low Potential Safety Issues (Alerting Events), High Success” quadrant is the most reassuring. In these regions, fewer safety issues are identified, and of those that do arise, prescribers are more responsive to alerts to address them. The “High Potential Safety Issues (Alerting Events), High Success” quadrant may reflect a greater degree of provider reliance on alerting programs. In the “Low Potential Safety Issues (Alerting Events), Low Success” region, fewer events suggest fewer potential drug safety improvement opportunities, although prescribers are less responsive to alerts on the safety issues that do arise. One possible explanation could be that the most straightforward clinical situations are addressed by prescribers up-front, with the alerted-upon issues representing more complex patient cases that reflect medical management challenges.

The map-based representation of these quadrants by state (Figure 3) reveals that many states in close proximity tend to demonstrate similar patterns, suggesting that the variation may be related to pervasive regional factors such as prescribing practice patterns, disease prevalence, and demographics.

One of the contributors to the varying rates of potential safety issues is the underlying variation in rates of prescribing, which has previously been reported for several classes of medications. The underlying reasons for these differences in prescribing rates have also been explored and fall into 4 major categories: physician characteristics, patient characteristics, regulations, and clinical management programs. Physician characteristics include specialty training, practice habits, and association with medical leaders who are “enthusiasts” about certain practice patterns.
Patient characteristics include age, gender, social environment, income, and race. Regulations include state-specific monitoring programs. Clinical management programs include those that help guide prescribers in their prescribing decisions and that sometimes influence the patient’s medication coverage.

The relative contributions of differences in prescribing rates and other factors to the frequency of safety issues have not been well studied. Researchers in Scotland, Clark et al. (2007), provided insight into this question in association with the reporting of suspected adverse drug reactions (ADRs) to the National Health Service. They concluded that approximately 44% of the variation in reports of certain ADRs can be explained by variations in prescribing rates after controlling for differences in regional population size. Therefore, roughly 56% of the ADR variation was unexplained by population size and prescribing rates and was attributable to other factors. Investigation of these other causes, at the physician and patient level, is an opportunity for further research so that interventions can be deployed accordingly.

The Institute of Medicine has called for sweeping changes in health care processes to reduce ADEs. Among these recommendations is the expanded use of integrated data and coordination of care among physicians, using information technology and alerting systems such as the one described by this study.4

Focused efforts to adopt these recommendations should use geographic and local data, such as those reported here, to target program enhancements and physician outreach.

**Limitations**

First, the safety alerting program described in this study treated all alerts equally regardless of potential seriousness, without differentiating among various drugs and safety concerns. Therefore, possible explanations for our findings include underlying...
Geographic Variation in Drug Safety: Potentially Unsafe Prescribing of Medications and Prescriber Responsiveness to Safety Alerts

FIGURE 2 Potential Safety Issues and Prescriber Responsiveness to Alerts by State

- Differences in clinical issues or in the populations in the various regions. Second, we did not age- and gender-adjust our estimates. Tables 2 and 3 do show variation in average age, which can be viewed as a proxy for overall illness burden, although age variation does not explain 100% of the observed rate of drug safety issues. Table 1 also shows variation in the number of drug classes utilized per member, as another marker for overall disease burden. Because both patient factors and prescriber factors affect the rates of safety alerts, the findings of the present study should not be viewed as a simple reflection of the quality of individual prescribing decisions. However, the differences in rates are still meaningful because they may quantify differences in the opportunity for programmatic intervention.

Third, prescribers could have received the same alert for the same patient on multiple occasions. The effect of this limitation on our success rate is unknown. Fourth, 100% success may not be a reasonable or clinically appropriate target for many alerts. In real-world medical care, patient-specific circumstances and exceptions may arise that warrant careful oversight without therapy modification. Furthermore, some data elements in medical or pharmacy claims may have been erroneously coded and processed. Therefore, the interpretation of success rates in this study should focus on the regional variation and not on the absolute values. Sixth, because market penetration for the program may vary by state, the degree to which our results represent actual statewide differences, as opposed to differences unique to members of our program, is unknown.

Conclusions

Potential safety issues associated with prescription medications are common. Geographic variation exists in the rates of alerting events for such issues and in the success rates of alerts aimed at helping

\*A member is an enrolled person of any age whose plan sponsor uses the safety alerting program, regardless of whether the member filled any prescriptions during 2008.
prescribers reduce the risk of ADEs for their patients. Opportunity exists to collaborate with local and regional medical organizations, in addition to those who pay for the high costs of medical care associated with ADEs, to help improve both measures.

ACKNOWLEDGEMENTS

The authors thank Susan Anselmi, RPh, Barbara Piercy, RPh, and Emily Stefanelli, PharmD, for their invaluable assistance in providing the detailed examples and explanations of the RationalMed development and management processes within this manuscript.

REFERENCES


Geographic Variation in Drug Safety: Potentially Unsafe Prescribing of Medications and Prescriber Responsiveness to Safety Alerts


Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

Anna Vlahiotis, MA; Rebecca Sedjo, PhD; Emily R. Cox, PhD; Thomas E. Burroughs, PhD; Amy Rauchway, DO; and Rebecca Lich, PharmD

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is a chronic, neurodegenerative inflammatory disease that affects approximately 400,000 Americans, the majority of whom are female. Although MS prevalence is higher among females, males are more likely to have a more progressive clinical course. For both genders, use of disease-modifying medications (DMMs) in the clinical management of MS is pivotal in altering the natural course and diminishing progressive disability over time.

OBJECTIVES: To evaluate gender differences in self-reported symptom awareness and perceived ability to manage therapy among MS patients taking a DMM.

METHODS: During February 2008, a self-administered, 42-item survey was mailed to 4,700 commercially insured patients taking a DMM to treat MS. Survey items measured self-reported clinical characteristics, symptom awareness, and perceived ability to manage therapy. Bivariate analyses assessed associations of gender with other predictor and outcome variables, including demographic characteristics, clinical disease characteristics, specific DMM used at the time of the survey, self-reported symptom awareness, and perceived ability to manage therapy. Logistic regression analyses further assessed the associations of gender with symptom awareness and perceived ability to manage MS after adjustment for relevant covariates (age at diagnosis, educational level, income, current DMM, type of pharmacy where drug was dispensed, frequency of flare-ups, and clinical course of disease).

RESULTS: The response rate was 44.1% (n = 2,074). Of the 2,022 respondents with useable surveys, 80.6% were female; 82.3% had relapsing-remitting MS; and 83.1% were taking one of the most commonly used DMMs (intramuscular interferon beta-1a 33.4%, subcutaneous interferon beta-1a 15.9%, and glatiramer acetate 33.8%). Compared with female patients, males were older and a greater proportion had a more progressive clinical course of disease. In multivariate models, female patients were more likely than males to report recognition of a relapse/exacerbation (odds ratio [OR] = 1.37, 95% CI = 1.03-1.82) and to report knowing what to do when experiencing a relapse/exacerbation (OR = 1.34, 95% CI = 1.01-1.77) or if they missed a dose of medication (OR = 1.78, 95% CI = 1.08-2.43). Females were also more likely to report awareness of treatment options (OR = 1.48, 95% CI = 1.07-2.07) and to think that DMMs were helping their MS (OR = 1.32, 95% CI = 1.02-1.77).

CONCLUSIONS: Female MS patients report better awareness of disease symptoms and have more positive perceptions of their ability to manage therapy with DMMs than male MS patients. These findings suggest that male MS patients may require additional education and support to manage their disease and therapy needs. Knowledge of these gender differences potentially could help managed care organizations to improve therapy adherence by guiding gender-specific patient support programs.

What is already known about this subject

• Adherence to disease-modifying medications (DMMs) for multiple sclerosis (MS) is particularly challenging because these drugs are injectable rather than oral medications. Mohr et al. (2001) showed that nonadherence to weekly intramuscular injections of interferon beta-1a was related to patients’ low expectations of their ability to self-inject medication and that patients whose medication was administered by another individual, such as a spouse or a visiting nurse, had an increased risk of discontinuation. These medications also have side effects that reduce adherence to therapy.

• Female MS patients are more optimistic and confident about their ability to function with MS than are males. In a study population (n = 556) of 124 males (73 with relapsing-remitting MS [RRMS] and 51 with progressive MS) and 432 females (348 with RRMS and 84 with progressive MS), Fraser and Polito (2007) found that females had significantly higher scores than males (P = 0.001) on a 9-item function subscale of the Multiple Sclerosis Self-Efficacy Scale (MSSE), a validated and reliable tool. Although the MSSE’s creators suggested its use in research investigating adherence to treatment and health, the MSSE does not capture information about DMMs or patient perception of ability to manage therapy with DMMs.

• Female MS patients are better able than males to manage the emotions related to MS disabilities. Miller and Dishon (2006) found that the negative correlation between a Health Related Quality of Life (HRQOL) Scale (MSQOL-54 with Fatigue Severity Scale) and physical sequelae of MS as measured by the Expanded Disability Status Scale was smaller for females than for males. However, this survey did not capture information about perceived ability to manage therapy with a DMM.
Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

What this study adds

- Patient perceptions about ability to manage MS therapies and symptom awareness, which are essential for optimal long-term disease management, differ by gender. Female patients have greater self-reported symptom awareness and more positive perceptions of ability to manage therapy.
- Most respondents to a mailed survey of commercially insured MS patients (N=2,022) were female (n=1,629, 80.6%); most had relapsing-remitting MS (n=1,493 of 1,813, 82.3%); and most were using subcutaneous glatiramer acetate (n=680 of 2,011, 33.8%) or intramuscular interferon beta-1a (n=672 of 2,011, 33.4%) to treat MS.
- After controlling for relevant covariates, such as frequency of flare-ups, clinical course of disease, and type of pharmacy where medications were dispensed, female MS patients had greater odds of reporting that they know what to do when experiencing any MS symptom (odds ratio [OR]=1.42, 95% CI=1.08-1.88); that they recognize a disease relapse or exacerbation (OR=1.37, 95% CI=1.03-1.82); and that they know what to do if a relapse or exacerbation occurs (OR=1.34, 95% CI=1.01-1.77). Female patients were also more likely to perceive that the DMM they were taking was helping their MS (OR=1.32, 95% CI=1.02-1.77) and were more likely to report being aware of treatment options (OR=1.48, 95% CI=1.07-2.07).

Multiple sclerosis (MS) is a chronic, neurodegenerative inflammatory disease of the central nervous system that affects an estimated 400,000 Americans.1 This disease is categorized into 4 forms or subtypes by clinical course: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive-relapsing MS (PRMS). At the onset of the disease, approximately 85% of all MS patients have RRMS, of whom almost one-half will experience a gradual progression of disability within 10 years of their initial attack,2 and 90% will develop worsening disease within 25 years.3 Multiple sclerosis affects females at 2 to 3 times the rate it affects males,4,5 but males have a later average onset of disease and a faster progression to disability than do female patients.5-7

Altering the natural course of MS and diminishing the risk of progressive disability over time are pivotal in the clinical management of MS. Accordingly, the Multiple Sclerosis Council for Clinical Practice Guidelines and the National Multiple Sclerosis Society recommend the early use of disease-modifying medications (DMMs) in patients who have relapsing forms of MS.8,9 Of the 6 immunomodulatory therapies approved for treatment in MS patients, there are 3 beta-interferons: intramuscular interferon beta-1a (Avonex, IM IFN β-1a), subcutaneous interferon beta-1a (Rebif, SC IFN β-1a), and subcutaneous interferon beta-1b (Betaseron and newly released Extavia, SC IFN β-1b); glatiramer acetate, a synthetic protein; intravenous natalizumab (Tysabri), a monoclonal antibody; and the antineoplastic mitoxantrone for intravenous infusion (Novantrone). The interferons and glatiramer acetate are recommended for treatment in patients with RRMS.3 Natalizumab is recommended primarily for patients who are unable to tolerate or have not responded adequately to other DMMs.8 Mitoxantrone is recommended for worsening relapsing disease but is also used in patients with worsening SPMS with or without relapses.9 Although clinical trials of some DMMs in patients with progressive forms of MS have failed to provide conclusive evidence of disease modification, DMMs are still used in these patients.10,11 Despite the recommendation for the initiation of treatment after confirmed diagnosis,8,9 only about one-half of all MS patients currently use a DMM.12

Although DMM use is important for optimal health management, MS patients face many challenges in adhering to the recommendations. These include the chronicity of the disease, high cost of therapies, injection anxiety, injection site and post-injection reactions, and adverse side effects of the DMMs.13,14 Reports suggest that the chronic and disabling nature of the disease may lead to depression in some patients,15,16 which may be associated with decreased adherence to DMMs.17 In addition, the costs of DMMs present an additional burden. Unemployment rates of 41% to 60% have been reported in MS patients, which may lead to difficulty affording prescription medications.18,19 In a study of MS patients aged 21 to 64 years, lezzeni et al. (2008) reported that even among patients with prescription drug coverage, 20% reported the level of difficulty in paying for medications as somewhat or very difficult.19 Furthermore, the interferons and glatiramer acetate are injectable medications, and self-injection is frightening to some patients. Mohr et al. (2001) found injection anxiety in 44% of a survey sample of 101 MS patients and suggested that negative perceptions of injection of DMMs are significantly related to discontinuation of therapy.20,21 Injections may also lead to injection site reactions ranging from mild bruising to the development of ulcers and granulomas.21 The interferons used to prevent disease progression in MS are often also associated with such side effects as flu-like symptoms, muscle spasticity, and fatigue.22,23 Such adverse effects are often cited as reasons for discontinuation of therapy.24 Other factors that decrease adherence include perceived lack of efficacy and suboptimal patient-health care provider relationship.20,25-26

In addition to effective management of and adherence to DMM therapy, awareness of MS symptoms and the ability to respond to them appropriately are important factors in the successful self-management of MS.27 Symptom awareness as part of self-monitoring in other chronic diseases has also been associated with fewer physician visits and hospitalizations.28,29 Disease self-management is in turn thought to be an important factor in the psychological adjustment or adaptation to being diagnosed and living with a chronic disease.30

It has been well established that, in general, male and female patients experience health and disease differently.31,32 Although
some of the gender differences in MS patient health can be attributed to clinical course of disease,\textsuperscript{3,6} these differences may also be attributable to psychological adjustment. Studies have suggested that female MS patients are more optimistic about their ability to function with the disease.\textsuperscript{18,32} In a study by Fraser and Polito (2007) of 556 patients with MS, average scores on the functional subscale of the Multiple Sclerosis Self-Efficacy Scale were significantly higher for females (n = 348 with RRMS and 84 with progressive MS) than for males (n = 73 with RRMS and 51 with progressive MS).\textsuperscript{33} Miller and Dishon (2006) evaluated the impact of gender and disability on quality of life in MS patients. The authors found that the relationship between physical disability and diminished quality of life was weaker among females than males, leading them to conclude that females are better able than males to manage the emotions related to MS disabilities.\textsuperscript{18}

Although studies using existing survey instruments that measure disability and quality of life have reported gender differences in patient psychology, these existing survey instruments do not capture information about symptom awareness or the perceptions of various aspects of therapy with a DMM. Specifically, no study has addressed the impact of gender on self-reported symptom awareness or perceived ability to manage therapy with DMMs, factors that are essential for optimal long-term disease management. Therefore, the purpose of this study was to examine self-reported symptom awareness and perceived ability to manage therapy with DMMs, comparing females with males in a commercially insured population of MS patients who were currently taking a DMM. We hypothesized that female patients would have greater self-reported symptom awareness and a more positive perception of ability to manage therapy than male patients.

**Methods**

Patients receiving pharmacy benefits through a large pharmacy benefits management company (PBM) and using a DMM for MS as indicated by the PBM’s administrative claims data were asked to complete a survey detailing their perceptions of their overall health, their disease, and the DMMs that they were taking. The survey was designed to identify potential gaps in care upon which managed care organizations (MCOs) could potentially intervene.

**Patients**

Data were extracted from a 1-year database (2007) constructed for research purposes by Express Scripts, Inc. The database was composed of administrative pharmacy claims and eligibility information (including age, gender, and mailing address) for a random sample of approximately 14 million enrollees, representing all 50 states, from the more than 55 million enrollees in 578 commercially insured (i.e., not Medicare or Medicaid) health plans using the PBM to manage their pharmacy benefits. Health plan sponsors included private and public sector employer groups, MCOs, third-party administrators, self-insured employers, and union groups. The target population consisted of all patients identified as having MS as indicated by the purchase of at least 2 prescriptions for 1 of the 6 biologic agents used to treat the disease during the first 6 months of 2007, identified by generic product identifier (GPI, Medi-Span, Inc., Indianapolis, IN) code beginning with 62-40. These drugs included IM IFN β-1a, SC IFN β-1b, SC glatiramer acetate, mitoxantrone, SC IFN β-1a, and IV natalizumab.

Additional study inclusion criteria were (a) at least 1 pharmacy claim for a DMM between July 1, 2007, and December 15, 2007; (b) aged 18 years or older when the survey was mailed; and (c) continuous enrollment with the study PBM for pharmacy benefits between January 1, 2007, and January 31, 2008 (Figure 1). This study protocol was determined to be exempt by the Institutional Review Board at Saint Louis University in Saint Louis, Missouri.

**Survey Development and Administration**

A single, self-administered survey was mailed to each targeted

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**FIGURE 1** Flow Chart of Sample Selection

- **Targeting Criteria**
  - Aged 18 years or older in February 2008 (n = 11,122,415)
  - Continuously eligible throughout study period\textsuperscript{a} (n = 7,941,367)
  - At least 2 DMM claims\textsuperscript{b} in first 6 months of 2007\textsuperscript{c} (n = 4,936)
  - At least 1 DMM\textsuperscript{b} claim from July 1, 2007, through December 15, 2007 (n = 4,700)

- **Inclusion Criteria**
  - Valid mailing address (n = 4,679)
  - Returned survey (n = 2,074)
  - Valid age (n = 2,036)
  - Valid gender (n = 2,032)
  - Valid DMM\textsuperscript{b} (n = 2,022)

- **Included in sample**
  - (n = 2,022)

\textsuperscript{a}From January 1, 2007, through January 31, 2008.

\textsuperscript{b}Medi-Span GPI code beginning 62-40, including intramuscular interferon β-1a, subcutaneous interferon β-1b, subcutaneous glatiramer acetate, mitoxantrone, subcutaneous interferon β-1a, and intravenous natalizumab.

\textsuperscript{c}January 1, 2007, through June 30, 2007. DMM = disease-modifying medication; GPI = generic product identifier.
patient during the first week of February 2008. Because the survey was anonymous, it was not possible to identify initial nonrespondents. Thus, no follow-up with nonrespondents was performed. Responses were captured through April 25, 2008.

The 42-item self-report survey collected standard demographic and MS-specific clinical characteristics, such as clinical course of disease and frequency of exacerbations or relapses, in addition to information about therapy with DMMs and utilization of physician services. Although a previously validated MS-specific survey instrument has been used to measure some constructs of patient perception of disease impact and ability to function with the disease,\textsuperscript{33} the instrument was not used for this study because it did not specifically capture information about DMMs. Our survey measured self-reported physical and mental health status using the Medical Outcomes Short Form 12 (SF-12), a validated health outcomes instrument that has been used in previous MS surveys.\textsuperscript{35}

Additional questions about utilization of physician services and reasons for lack of physician care were also asked in an attempt to capture information about potential gaps in care. These questions were not part of a previously validated instrument. The survey also captured information about symptom awareness, which DMMs were currently being used, where the medications were being obtained (through a mail order pharmacy, specialty pharmacy, or community pharmacy), and how positively or negatively the patients perceived their ability to manage therapy with those medications. The perception questions included items measuring the perceived efficacy of medications, drug administration skill and knowledge, and adherence to prescribed drug therapy. Factual and behavioral questions involving clinical disease characteristics, physician care, MS medications, and demographic characteristics were measured with multiple-choice responses tailored for each question. Knowledge and attitudinal questions (e.g., perceived self-care ability) were measured on 5-point Likert scales ranging from 1 (strongly agree) to 5 (strongly disagree) to provide a representative set of response options, maximize discrimination, and maintain a consistent number of response options with the SF-12 that served as a foundation for the current instrument.

The survey was developed through an iterative process that involved 6 experts in neurology, pharmacy, epidemiology, and survey design and validation, following the industry standard approach developed by Dillman and colleagues and recommended in survey methodology textbooks.\textsuperscript{36} This multi-step process included (a) definition of the primary aims of the study; (b) identification and operational definition of the relevant constructs to be measured; (c) detailed literature search for existing validated instruments; (d) interviews with patients, family members, and clinicians caring for patients with MS to establish core survey content; (e) drafting the initial item set, including any questions from existing instruments; (f) structured review for appropriateness of response options and understandable terminology by 2 external survey methodologists who were not associated with the current study; (g) item revisions or reductions; (h) pilot testing in a convenience sample of 8 individual MS patients; (i) additional item revisions; and (j) administration of instrument to the full study sample. The revisions to the survey instrument included a reordering of the survey to include general health questions from the SF-12 as the first set of questions and moving questions about physician care to the middle of the instrument; changing the clinical terminology from “exacerbation” to “flare-up” in all questions asking about disease exacerbations; and deletion of the term “benign MS” as a clinical subtype of the disease. Questions were worded at the sixth-grade reading level, with the exception of commonly used MS clinical terminology. The questionnaire is available by request from the corresponding author.

Measurement of Outcomes

The primary outcomes for this study were self-reported symptom awareness and perceived ability to manage therapy. Questions were designed to capture information about perceptions of disease and therapy with DMM in order to identify where managed care pharmacy could intervene on behalf of the patient. Three items on the survey measured self-reported symptom awareness, that is, whether patients felt they could recognize when disease relapses or exacerbations were occurring and how to respond to these and other general disease symptoms. Additional questions measured perceived ability to manage therapy and included 2 questions about patient perception of managing dosing regimens, a single question about perception of adverse effects, 3 questions about medication adherence, and 2 questions measuring perceived efficacy of DMMs. Questions also asked about the perceived ease of self-administering, obtaining, and paying for medications, and another question measured whether or not patients were aware of the treatment options for MS.

Statistical Analysis

Post hoc reliability analyses using the Cronbach’s alpha coefficient were performed to determine the internal consistency of identified constructs. The constructs tested for reliability included symptom awareness (relapse recognition, management of relapses, and management of general MS symptoms); dosing regimens; adherence; and perceived efficacy of DMMs.

The responses to all statements measuring symptom awareness and perceived ability to manage therapy were dichotomized by combining the responses “strongly agree” or “agree” into the category “agree” versus any other response (i.e., “neither agree nor disagree,” “disagree,” or “strongly disagree”) as “did not agree.” Bivariate analyses assessing the relationship between gender and a number of survey measures, including clinical course of disease, DMM, self-reported health status, self-reported symptom awareness, and perceived ability to manage therapy, were computed using the Pearson chi-square test.

Separate multivariate logistic regression models were
Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

developed to further assess the relationship of gender with measures of symptom awareness and perceived ability to manage therapy after adjustment for other covariates. Bivariate comparisons with gender with P values less than 0.25 and variables that theoretically would be expected to affect measured outcomes were included as covariates in the multivariate models. A more liberal critical value than the traditional value of $P \leq 0.05$ was used as a criterion for covariate inclusion to account for complex relationships or variables that may become significant only in the presence of other variables. All models controlled for educational level (high school diploma or less as the referent category, associates’ degree, bachelor’s degree, post-graduate education); age at the time of the survey (less than 43 years of age as the referent category, ages 43 through 49 years, ages 50 through 55 years, age 56 years or older); annual household income (less than $50,000 as referent category, $50,000 to $74,999, $75,000 to $99,999, $100,000 to $149,999, $150,000 or more); type of pharmacy where DMM was dispensed (mail order pharmacy as the referent category, retail pharmacy, specialty pharmacy); clinical course of disease (RRMS disease type as the referent category, SPMS, PPMS, PRMS); frequency of flare-ups or exacerbations in the previous 12 months (none as the referent category, 1 to 2, 3 to 5, 6 or more); and DMM used by the patient at the time of the survey (IM IFN β-1a as the referent category, SC IFN β-1b, SC glatiramer acetate, SC IFN β-1a). Patients using natalizumab or mitoxantrone were excluded from the models because of small patient counts.

Two variables meeting the covariate inclusion criteria were excluded from the models. First, because age at the time of diagnosis and age at the time of the survey were strongly correlated (Pearson’s $r = 0.60$, $P < 0.01$), only age at time of survey was included as a covariate. Second, although theoretically important, self-reported health status was strongly correlated with number of flare-ups (Spearman’s rho = 0.78, $P < 0.001$) and was therefore excluded from the models.

Although we computed models evaluating the relationship between gender and all of the items measuring symptom awareness and perceived ability to manage therapy, model results are reported only for outcomes in which gender was a statistically significant predictor. All analyses were conducted using a 2-sided alpha of 0.05 in SPSS 17.0 (SPSS Inc., Chicago, IL). Other data captured by the survey but not significantly related to gender and self-reported symptom awareness or perceived ability to manage therapy are available by request from the authors.

Results

Of the 4,700 patients who were mailed a survey in February 2008, 2,074 (44.1%) returned a survey by April 25, 2008 (Figure 1). Of those who returned a survey, respondents with invalid or missing values for age at the time of the study ($n = 38$), gender ($n = 4$), or type of DMM ($n = 10$) were excluded. The final analytic sample included 2,022 respondents. Respondents who were using natalizumab ($n = 37$) or mitoxantrone ($n = 2$) were included in the analytic sample but were excluded from multivariate analysis because of small sample size.

Assessments of Questionnaire Response Rates and Reliability

Some respondents did not answer all of the questions, and rates of item nonresponse differed by question but were less than 2% of the responses for most survey items. An error in a questionnaire skip pattern, intended to direct respondents not to complete items about lack of physician care if they were currently seeing a physician for their MS, also directed respondents who were seeing a physician not to answer questions about use of physician services. However, nearly all (98.7%) respondents reported being under a physician’s care in responding to the questions in that section, and only those who reported that they were not currently under a physician’s care responded to questions about why they were not receiving care.

There were no significant differences in age, gender, DMM, disease type, or frequency of relapses or exacerbations between respondents included in the final analysis sample and the 52 respondents who were excluded. As survey participation was anonymous, making analysis of nonrespondents impossible, potential nonresponse bias was measured only by comparing the 4,700 targeted patients with the 2,022 respondents on key demographic and clinical characteristics. The total targeted sample and the respondents were similar with respect to distributions of gender, DMM type, DMM-related monthly out-of-pocket costs, and the average age of patients by gender (data not shown but available from authors on request).

In post hoc reliability tests, the Cronbach’s alpha coefficient for measures of symptom awareness (relapse recognition, management of relapses, and management of general MS symptoms) was 0.88, indicating that the constructs consistently measured the same concept. Post hoc reliability tests suggested some internal consistency on questions related to the concept of dosing regimens ($\alpha = 0.64$), low internal consistency on questions related to adherence ($\alpha = 0.35$), and sufficient internal consistency on questions related to perceived efficacy of DMMs ($\alpha = 0.76$).

Patient Characteristics

The majority (80.6%) of respondents were female (Table 1). Compared with female respondents, male respondents were older when the survey was completed ($P = 0.009$), were diagnosed with MS at an older age ($P = 0.006$), and were more likely to have a progressive clinical course of disease ($P < 0.001$), although the majority of respondents, regardless of gender, did not have the more progressive forms of MS. In addition, a greater portion of male respondents were taking SC IFN β-1a at the time of the study (19.5% vs. 15.0% for males and females, respectively), and a smaller portion were taking IM IFN β-1a, (25.7% vs. 35.3%, $P = 0.008$). Differences in the proportions of males and females filling prescriptions for DMMs through retail pharmacies, the
### TABLE 1  Characteristics of Female and Male Patients Using Disease-Modifying Medication for Multiple Sclerosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Females</th>
<th>Males</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole sample n (percent of sample)</strong></td>
<td>1,629 (80.6)</td>
<td>393 (19.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of years since diagnosis mean [SD]</strong></td>
<td>10.8 [9.0]</td>
<td>10.7 [8.8]</td>
<td>0.747</td>
</tr>
<tr>
<td><strong>Age at time of diagnosis (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 31</td>
<td>419 (26.7)</td>
<td>71 (18.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>32 to 38</td>
<td>370 (23.6)</td>
<td>91 (23.8)</td>
<td></td>
</tr>
<tr>
<td>39 to 45</td>
<td>409 (26.0)</td>
<td>108 (28.3)</td>
<td></td>
</tr>
<tr>
<td>46 or older</td>
<td>373 (23.7)</td>
<td>112 (29.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at time of survey (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 42</td>
<td>405 (24.9)</td>
<td>81 (20.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>43 to 49</td>
<td>401 (24.6)</td>
<td>78 (19.8)</td>
<td></td>
</tr>
<tr>
<td>50 to 55</td>
<td>405 (24.9)</td>
<td>106 (27.0)</td>
<td></td>
</tr>
<tr>
<td>56 or older</td>
<td>418 (25.7)</td>
<td>128 (32.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td>0.927</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1,498 (92.1)</td>
<td>361 (92.6)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>74 (4.6)</td>
<td>16 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>54 (3.3)</td>
<td>13 (3.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Educational attainment</strong></td>
<td></td>
<td></td>
<td>0.130</td>
</tr>
<tr>
<td>HS/GED or less</td>
<td>651 (40.5)</td>
<td>148 (38.2)</td>
<td></td>
</tr>
<tr>
<td>Associate’s degree</td>
<td>279 (17.4)</td>
<td>54 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>376 (23.4)</td>
<td>96 (24.8)</td>
<td></td>
</tr>
<tr>
<td>Post-graduate degree</td>
<td>302 (18.8)</td>
<td>89 (23.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Annual household income</strong></td>
<td></td>
<td></td>
<td>0.169</td>
</tr>
<tr>
<td>$49,999 or less</td>
<td>498 (32.8)</td>
<td>102 (27.5)</td>
<td></td>
</tr>
<tr>
<td>$50,000 to $74,999</td>
<td>395 (26.0)</td>
<td>102 (27.5)</td>
<td></td>
</tr>
<tr>
<td>$75,000 to $99,999</td>
<td>263 (17.3)</td>
<td>73 (19.7)</td>
<td></td>
</tr>
<tr>
<td>$100,000 to $149,999</td>
<td>243 (16.0)</td>
<td>55 (14.8)</td>
<td></td>
</tr>
<tr>
<td>$150,000 or more</td>
<td>121 (8.0)</td>
<td>39 (10.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical course of disease</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapsing-remitting</td>
<td>1,238 (84.5)</td>
<td>255 (73.3)</td>
<td></td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>166 (11.3)</td>
<td>47 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Primary progressive</td>
<td>45 (3.1)</td>
<td>33 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Progressive relapsing</td>
<td>16 (1.1)</td>
<td>13 (3.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Flare-ups experienced in previous year</strong></td>
<td></td>
<td></td>
<td>0.225</td>
</tr>
<tr>
<td>None</td>
<td>661 (42.5)</td>
<td>169 (44.5)</td>
<td></td>
</tr>
<tr>
<td>1 to 2</td>
<td>636 (40.9)</td>
<td>140 (36.8)</td>
<td></td>
</tr>
<tr>
<td>3 to 5</td>
<td>199 (12.8)</td>
<td>49 (12.9)</td>
<td></td>
</tr>
<tr>
<td>6 or more</td>
<td>59 (3.8)</td>
<td>22 (5.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Self-reported overall health status</strong></td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>Excellent, very good, or good</td>
<td>1,324 (84.0)</td>
<td>296 (78.1)</td>
<td></td>
</tr>
<tr>
<td>Fair or poor</td>
<td>252 (16.0)</td>
<td>83 (21.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Steroids to treat symptoms</strong></td>
<td></td>
<td></td>
<td>0.726</td>
</tr>
<tr>
<td>Not using steroids</td>
<td>976 (80.9)</td>
<td>229 (79.5)</td>
<td></td>
</tr>
<tr>
<td>Oral steroids (scheduled or for flare-ups)</td>
<td>135 (11.2)</td>
<td>37 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Intravenous steroids (scheduled or for flare-ups)</td>
<td>96 (8.0)</td>
<td>22 (7.6)</td>
<td></td>
</tr>
<tr>
<td><strong>DMM currently used by patient</strong></td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>IM interferon beta-1a</td>
<td>572 (35.3)</td>
<td>100 (25.7)</td>
<td></td>
</tr>
<tr>
<td>SC interferon beta-1a</td>
<td>244 (15.0)</td>
<td>76 (19.5)</td>
<td></td>
</tr>
<tr>
<td>IV natalizumab</td>
<td>28 (1.7)</td>
<td>9 (2.3)</td>
<td></td>
</tr>
<tr>
<td>SC interferon beta-1b</td>
<td>233 (14.4)</td>
<td>67 (17.2)</td>
<td></td>
</tr>
<tr>
<td>SC glatiramer acetate</td>
<td>543 (33.5)</td>
<td>137 (35.2)</td>
<td></td>
</tr>
<tr>
<td>IV mitoxantrone</td>
<td>2 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>
Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

TABLE 1  Characteristics of Female and Male Patients Using Disease-Modifying Medication for Multiple Sclerosis (continued)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Females</th>
<th>Males</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of pharmacy where DMM is dispensed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community retail</td>
<td>102 (6.6)</td>
<td>18 (4.8)</td>
<td>0.442</td>
</tr>
<tr>
<td>Mail order pharmacy</td>
<td>348 (22.5)</td>
<td>86 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Specialty</td>
<td>1,095 (70.9)</td>
<td>269 (72.1)</td>
<td></td>
</tr>
<tr>
<td>Survey Items</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported symptom awareness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I know when I am experiencing a relapse or exacerbation.</td>
<td>1,159/1,538 (75.4)</td>
<td>255/370 (68.9)</td>
<td>0.011</td>
</tr>
<tr>
<td>I know what to do when I am experiencing a relapse or exacerbation.</td>
<td>1,124/1,534 (73.3)</td>
<td>244/367 (66.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>I know what to do when I experience any MS symptom.</td>
<td>1,164/1,541 (75.5)</td>
<td>257/371 (69.3)</td>
<td>0.013</td>
</tr>
<tr>
<td>Perceived ability to manage therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I know what to do if I miss a dose.</td>
<td>1,462/1,583 (92.4)</td>
<td>338/374 (90.4)</td>
<td>0.204</td>
</tr>
<tr>
<td>I know what to do if there is an injection site reaction.</td>
<td>1,347/1,572 (85.7)</td>
<td>312/373 (83.6)</td>
<td>0.317</td>
</tr>
<tr>
<td>I take my medication as prescribed by my physician</td>
<td>1,517/1,584 (95.8)</td>
<td>363/376 (96.5)</td>
<td>0.496</td>
</tr>
<tr>
<td>I forget to take my medications.</td>
<td>348/1,566 (22.2)</td>
<td>85/375 (22.7)</td>
<td>0.853</td>
</tr>
<tr>
<td>I take medications only when symptoms appear.</td>
<td>19/1,578 (1.2)</td>
<td>9/376 (2.4)</td>
<td>0.081</td>
</tr>
<tr>
<td>The benefits I receive from taking the medication are worth the costs.</td>
<td>1,202/1,582 (76.0)</td>
<td>255/372 (68.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>I believe that the medication helps my MS.</td>
<td>1,250/1,580 (79.1)</td>
<td>270/376 (71.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>The medication gives me unwanted side effects.</td>
<td>740/1,579 (46.9)</td>
<td>157/375 (41.9)</td>
<td>0.081</td>
</tr>
<tr>
<td>I have trouble administering the medication to myself.</td>
<td>464/1,578 (29.4)</td>
<td>95/376 (25.3)</td>
<td>0.111</td>
</tr>
<tr>
<td>I have trouble paying for my medication.</td>
<td>336/1,576 (21.3)</td>
<td>80/376 (21.3)</td>
<td>0.985</td>
</tr>
<tr>
<td>I have trouble getting the medications I need for my MS.</td>
<td>87/1,580 (5.5)</td>
<td>26/375 (6.9)</td>
<td>0.287</td>
</tr>
<tr>
<td>I am aware of my treatment options for MS.</td>
<td>1,327/1,562 (85.0)</td>
<td>303/378 (80.2)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

*For categorical variables, P values are derived from Pearson’s chi-square test. For number of years since diagnosis, P values are derived from Student’s t-test. All tests compared males with females.

For these survey items, numerators are counts of respondents who answered “strongly agree” or “agree” on a 5-point Likert-type scale, on which the remaining options were “neither agree nor disagree,” “disagree,” and “strongly disagree.” Denominators are counts of respondents answering the question.

DMM = disease-modifying medication; HS/GED = high school/general education diploma; IM = intramuscular; IV = intravenous; MS = multiple sclerosis; SC = subcutaneous; SD = standard deviation.

PBM’s mail order pharmacy, or specialty pharmacies were not significant (P = 0.442). A significantly greater proportion of male respondents reported fair or poor overall health compared with females (21.9% vs. 16.0%, respectively, P = 0.008).

Relationship of Gender with Measures of Symptom Awareness and Perceived Ability to Manage Therapy

Multivariate models controlling for clinical course of disease, frequency of flares or exacerbations, DMM type, pharmacy where medications were dispensed, income, age, and educational attainment reflected significant differences in self-reported symptom awareness and some perceptions of ability to manage therapy between males and females (Table 2). Compared with male respondents, females had 42% greater odds of agreeing with the statement “I know what to do when I experience any MS symptom” (odds ratio [OR] = 1.42, 95% confidence interval [CI] = 1.08-1.88). Female respondents also had greater odds of reporting that they know when they are experiencing a disease exacerbation (OR = 1.37, 95% CI = 1.03-1.82) and that they know what to do when they experience a disease exacerbation (OR = 1.34, 95% CI = 1.01-1.77). In addition, female respondents had greater odds of responding optimistically to several statements related to perception of ability to manage therapy. They had 78% greater odds of reporting that they know what to do if they miss a dose of medication (OR = 1.78, 95% CI = 1.08-2.43), 32% greater odds of believing that the medications they were taking were helping their disease (OR = 1.32, 95% CI = 1.02-1.77), and 38% greater odds of believing that the benefits of taking the medications were worth the costs (OR = 1.38, 95% CI = 1.04-1.84). Finally, female respondents also had 48% greater odds of reporting awareness of all treatment options for MS (OR = 1.48, 95% CI = 1.07-2.07). Measures that were not significantly associated with gender included taking prescriptions as prescribed, forgetting to take medications, taking medications only when symptoms appeared, having trouble self-administering medications, having trouble paying for medications, perceiving unwanted side effects from the medications, and having trouble obtaining the medications.

Discussion

Among commercially insured MS patients who were currently taking a DMM, the results of this survey suggest that a gender
difference may exist in self-reported symptom awareness and perceived ability to manage DMM therapy among MS patients. The present study is the first, to our knowledge, to report that female MS patients had significantly greater self-reported symptom awareness than males, even after controlling for clinical course of disease and frequency of flare-ups. Female survey respondents also had more optimistic perceptions of efficacy with DMMs compared with male respondents and reported greater awareness
of treatment options, both of which are important factors in the perception of ability to manage therapy. Such factors have been shown to be important for long-term adherence to drug therapy in a variety of disease states.25,37,38

Our findings are consistent with those of previous research that reported gender differences in illness perception and symptom awareness among females as compared with males. Previous research suggests that female patients, because of greater selective attention to their bodies and an increased attribution of bodily sensations to physical illness, have historically perceived an excess of symptoms compared with males, even when both sexes are healthy.39 Coping skills are also an important factor in patients’ adaptation to and self-management of their chronic diseases, including MS. Structured interviews with male and female patients and their partners suggested that the ability to integrate various dimensions of the disease into their daily lives is associated with gender. Female patients had greater coping skills compared with male patients.40 In similar studies of patients with heart failure, females scored higher on measures of health satisfaction and generally had more positive perceptions of the impairment, limitations, loss, and emotional burden associated with living with heart failure.41

The present study’s findings may play an important role in enhancing patients’ adherence to DMMs. The perception of lack of efficacy accounts for as many as one-half of treatment discontinuations,26 and perceiving efficacy from DMM therapy may be associated with better adherence.25,42,43 Patients may also assume that their DMM is ineffective when their current MS symptoms persist or new symptoms arise.44 Although this perceived lack of efficacy may be accurate in patients who develop neutralizing antibodies after beginning therapy or in patients with nonresponsive disease,45 it may also be the result of unrealistic treatment expectations or lack of symptom awareness46 and may lead to detrimental discontinuations, nonadherence, or costly medication waste.

Eliminating barriers to adherence with DMM is therefore key in the clinical management of MS patients, as is increasing awareness of relapses and disease symptoms. In MS, patients’ awareness of symptoms and appropriate expectations of treatment are an important part of the patient-provider relationship.45,47 While the causes of patient nonadherence are still an area of study and debate, it has been suggested that health care providers play a critical role in recognizing medication nonadherence and identifying solutions that improve patient adherence.46

Findings of the present study suggest that it may be necessary for health care providers and MCOs to tailor messages and programs to male and female MS patients differently in order to optimize therapy. Health care providers and MCOs should consider offering male MS patients additional education on the clinical course of their disease and the benefits of taking a DMM, in addition to steering them toward clinical support programs that teach them to identify when an exacerbation is occurring and how to handle exacerbations and other disease symptoms. Although the MS literature contains no studies of the effectiveness of such gender-tailored psychosocial interventions, a patient education program for males that better explains the goals of treatment with DMMs, emphasizing delay or prevention of disease progression, may have potential success.

Limitations

First, the potential for reporting biases and misclassification is always present in surveys, especially when gathering self-reported medication use data from patients. In this study, responses were anonymous to minimize any social desirability response bias; however, it is possible that some patients reported better symptom awareness or perceived ability to manage DMM therapy partly because of social desirability concerns. Second, potential self-selection bias may have led to selective reporting of results; that is, more optimistic patients or patients with less disability might have been more likely to respond to the survey. Third, the c-statistics for the logistic regression analyses were modest, ranging from 0.58 to 0.66 on a scale of 0.5 to 1.0 where 0.5 indicates predictive ability no better than random assignment.

A fourth limitation was the absence of medical claims data to confirm a diagnosis of MS. Although the DMMs used to treat MS are not often cited as medications with common off-label uses,48 patients could have been incorrectly identified as MS patients from inclusion criteria based solely on pharmacy claims. Fifth, an error in survey construction may have prevented the capture of important information about the use of physicians for MS care and potentially threatened the results of the survey. Specifically, a section of the survey contained questions about whether or not a patient was receiving physician care and reasons for lack of physician care, but the survey instructed patients not to answer any of the questions in the section if they were currently being seen by a physician. However, the vast majority of respondents (98.7%) positively answered the question of whether they were currently under care, suggesting that the erroneous instruction did not affect survey responses. Sixth, the sample of patients was identified from a commercially insured population of patients currently using DMMs, whose outcomes may not represent those of the general population of MS patients in the United States or of commercially insured patients not taking DMMs.

Conclusions

This survey of a commercially insured sample of MS patients using DMMs found that female respondents had greater self-reported symptom awareness and more positive perceptions of their ability to manage therapy with DMMs than did male MS patients. These data suggest that males with MS may benefit from additional education and support to manage their disease and therapy needs. Increased education about drug administration and appropriate efficacy expectations may lead to increased adherence, which can prevent disease progression.
Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

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DISCLOSURES

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Burroughs was responsible for concept and design, with the assistance of Vlahiotis and Rauchway. Data collection was performed by Cox and Lich, with the assistance of Burroughs and Rauchway. Cox, Lich, Sedjo, and Vlahiotis shared in the data interpretation. The manuscript was written primarily by Vlahiotis and Sedjo and revised primarily by Vlahiotis and Lich.

REFERENCES


Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

ABSTRACT

BACKGROUND: Vaccines have demonstrated cost-effectiveness in managed care through the prevention of disease. As new vaccines for previously untargeted conditions are developed, pharmacoeconomic modeling is becoming even more critical for the quantification of value in the health care industry. Two recently developed vaccines aimed at prevention of infection from human papillomavirus (HPV) types 16 and 18 have proven to be highly efficacious. HPV 16 and 18 are the 2 most common oncogenic strains of HPV and are responsible for 70% of cervical cancer cases worldwide. Persistent infection with an oncogenic HPV type is a known cause of cervical cancer. Therefore, prevention of cervical cancer via HPV vaccination may have a significant financial impact.

OBJECTIVE: To qualitatively review existing mathematical models of the cost-effectiveness of prophylactic HPV vaccination, with an emphasis on the impact on managed care in the United States.

METHODS: Mathematical models of the cost-effectiveness of HPV vaccination based on U.S. data were reviewed. A search of the PubMed database was conducted using the search terms “HPV,” “vaccine,” and “cost-effectiveness” for articles published before February 22, 2010. Studies employing mathematical models to estimate the cost-effectiveness of HPV vaccination in healthy subjects from the United States were included. Models based on data or populations from outside of the United States were excluded. Outcomes were measured with incremental cost-effectiveness ratios (ICERs), typically in units of quality-adjusted life expectancy (quality-adjusted life years [QALYS]) gained. Most studies included in this review modeled vaccination of a cohort or population of females aged 12 years. Assessment of catch-up vaccination in females (through aged 24 to 26 years) was included in a couple of reports. One study examined vaccination in older females (aged 35, 40, and 45 years). Models typically compared a strategy of HPV vaccination with the current practice of cervical screening (sampling of cervical cells for disease detection) alone.

RESULTS: 11 studies of cost-effectiveness modeling of HPV vaccination were included in this review. A direct quantitative comparison of model results is challenging due to the utilization of different model types as well as differences in variables selected within the same model type. Each model produced a range of cost-effectiveness ratios, dependent on variables included in sensitivity analyses and model assumptions. Sensitivity analyses revealed the lowest ICER to be $997 per QALY gained and the highest ICER to be $12,749,000 per QALY gained. This enormous range highlights the need to clarify what model assumptions are being made. The 2 studies that included modeling of catch-up vaccination scenarios in females older than 12 years also produced a wide range of ICERs. One study, assuming 90% efficacy, 100% coverage, and lifelong immunity, modeled catch-up vaccination in all females aged 12 to 24 years and yielded an ICER of $4,666 per QALY. The other study modeling catch-up HPV vaccination assumed 100% efficacy, 75% coverage, and lifelong immunity. ICERs in this study for outcomes relating to cervical cancer ranged from $43,600 per QALY in the base model vaccinating only 12 year olds with no catch-up vaccination, to $152,700 in a model including catch-up vaccination through age 26 years. Although catch-up to age 21 years resulted in a cost of $120,400 per QALY, the ICER decreased to $101,300 per QALY if model outcomes related to prevention of genital warts were also included. The lone study modeling vaccination in women aged 35 to 45 years resulted in an ICER range of $116,950 to $272,350 per QALY when compared with annual and biennial cytological screening.

Cost-effectiveness was defined as an ICER at or below $100,000 per QALY gained. All models of female adolescent vaccination were able to produce vaccination strategies that would be cost-effective according to this definition in addition to many strategies that would be cost-prohibitive. Variables influential in determining cost-effectiveness of HPV vaccination included the frequency of accompanying cervical screening, the age at which screening is initiated, vaccination efficacy, duration of vaccine protection, and the age range of females to be vaccinated. The actual effectiveness of HPV vaccination in the female population will also depend on levels of vaccine uptake or coverage and compliance in completing all vaccine doses.

CONCLUSION: Clinical studies have shown HPV vaccination to be highly efficacious and potentially lifesaving if administered to females naïve or unexposed to vaccine HPV types. Modeling studies have also shown that HPV vaccination can be cost-effective with an ICER of $100,000 or less per QALY gained if administered to females aged 12 years in the context of cervical screening intervals typically greater than 1 year. Catch-up vaccination through 21 years of age increases the cost per QALY to more than $100,000. Until real-world coverage rates increase, cost-effectiveness modeling of HPV vaccination underestimates the actual cost per QALY.

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What this review adds

- This is the first qualitative review of cost-effectiveness models of HPV vaccination based solely on U.S. data. All models examined have determined that HPV vaccination in females aged 12 years can be cost-effective in comparison with the current practice, which consists of cervical screening alone beginning no later than 21 years of age.
- Cost-effectiveness models of HPV vaccination may underestimate actual costs due to assumptions about efficacy and coverage (i.e., vaccination rate in the population) that may not be realized in the real world. Efficacy is based on completion of 3 doses, which probably occurs in no more than 75% of females who initiate vaccination. For coverage, Centers for Disease Control and Prevention (CDC) survey data for 2008 showed that only 37% of females between 13-17 years of age and 10% of women between 18-26 years of age had taken at least 1 of the 3 recommended vaccine doses.
- Cost-effectiveness will be lower (more favorable) when the HPV vaccine is universally administered to 12-year-old females. Even with high coverage, the cost per QALY is greater than $100,000 when catch-up HPV vaccination is extended to females aged up to 21 years and more than $150,000 per QALY when extended to females aged up to 26 years. Nevertheless, managed care organizations might consider providing full benefits coverage for the cost of HPV vaccination for all females aged 9 to 26 years, the age range currently recommended for vaccination by the CDC Advisory Committee on Immunization Practices.

In 1999, the Centers for Disease Control and Prevention (CDC) deemed universal vaccinations of children as one of the 10 greatest achievements in public health during the 20th century. In the United States, routine vaccinations have led to the eradication of 2 diseases once considered scourges of society: smallpox and polio. Since 1900, morbidity or disease incidence from 7 other vaccine-preventable diseases (diphtheria, pertussis, tetanus, measles, mumps, rubella, and Haemophilus influenzae type b) has also decreased by 95% or better.1 Vaccination prevents an estimated 3 million deaths annually worldwide, including nearly 1.8 million from hepatitis B and measles combined.2 Reductions in morbidity and mortality as a result of vaccination have had a significant economic impact as well: in most cases, the savings provided by vaccines far exceed their cost. For example, for every dollar spent on the measles-mumps-rubella, diphtheria-tetanus-acellular pertussis, and Haemophilus influenzae type b vaccines, more than $21, $24, and $2 are saved in direct medical costs, respectively.2 Notably, global savings in direct medical costs related to the eradication of smallpox in 1977 are estimated to exceed $300 million per year.2

Managed care organizations should recognize that while vaccines provide optimal value, vaccines continue to be underused and undervalued.2 This value is derived from the fact that most vaccines provide benefits that exceed both the direct medical and indirect societal costs of disease management, making these agents an obvious choice for implementation in the cost-driven managed care setting.2 The administration of traditional childhood vaccines has demonstrated substantial cost savings.2 However, as the paradigm for vaccine use in managed care moves toward prevention of diseases more typical of the adolescent and adult population, the cost offsets may be less obvious. The advent of newer vaccines aimed at previously untargeted infectious agents may require more involved pharmacoeconomic analyses in order to establish definitive value. Thus, complex mathematical models have been employed so that government agencies and health care payers can evaluate whether newer vaccines should be widely administered and subsidized.

HPV Vaccination Is an Opportunity for Managed Care

Perhaps the most talked about of the newer vaccines are those aimed at prevention of infection from the human papillomavirus (HPV).3 In the cervix, HPV is typically transmitted through microabrasions that may occur as a result of sexual intercourse.4 Persistent infection with an oncogenic strain of HPV is the known cause of cervical cancer,5 the second most common cancer in women worldwide. Of the 40 HPV types that affect the genital area, at least 15 types are known to be oncogenic (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82).6 The strength of the association between HPV and cervical cancer is at least 10 times greater than the association between smoking and lung cancer.3 HPV infection is also associated with other genital cancers (e.g., vaginal, vulvar, anal, and penile) as well as non–life-threatening diseases, such as genital warts.

Prophylactic vaccines for cervical cancer target HPV 16 and 18, the most common oncogenic types of HPV. In the United States, there are currently 2 HPV vaccines available for use, quadrivalent HPV vaccine (Gardasil, Merck) and bivalent HPV vaccine (Cervarix with AS04, GlaxoSmithKline).7 Both vaccines offer protection against HPV types 16 and 18, which are associated with 70% of invasive cervical cancer cases worldwide.9 Quadrivalent HPV vaccine also protects against nononcogenic HPV types 6 and 11, which are responsible for benign anogenital warts.7 When administered to females previously unexposed to vaccine HPV types, both HPV vaccines have demonstrated greater than 90% efficacy against the incidence of high-grade precancerous cervical lesions (Table 1).7,8,10,11 The CDC Advisory Committee on Immunization Practices recommends HPV vaccination for all females aged 11 to 12 years and as young as 9 years.12 This age recommendation is aimed at vaccinating females before sexual debut. Catch-up vaccination is also recommended for all females aged 13 to 26 years who have not been previously vaccinated.12

Since cervical screening only detects neoplastic changes after they have occurred, HPV vaccination is considered to be the primary form of cervical cancer prevention. Because prophylactic HPV vaccination is not effective against infection from all 15 oncogenic HPV types, regular cervical screening is still necessary. However, only about 82% of privately insured women and 65% of women enrolled in Medicaid received a Papanicolaou (Pap) screening test in 2007.13 This lack of adherence implies that secondary prevention alone is not adequate in addressing the disease burden associated with cervical cancer. Poor screening compliance inevitably results in cervical cancer cases going undetected until later stages when the prognosis is far graver and the disease is more costly to treat.

Prophylaxis of Cervical Cancer and Related Cervical Disease: A Review of the Cost-Effectiveness of Vaccination Against Oncogenic HPV Types
Although widespread cervical screening is largely responsible for an approximate 74% decrease in U.S. cervical cancer deaths over the past 50 years,14 the sensitivity of conventional cytologic cervical screening is only about 50% for detection of moderate to severe precancerous lesions.15 Use of newer and more expensive liquid-based cytology (LBC) screening has not definitively improved sensitivity.15 However, the sample collected for LBC may concurrently be used for HPV deoxyribonucleic acid (DNA) testing that may confirm the presence of an oncogenic HPV type. While this combination testing is more sensitive than traditional Pap screening, it is less specific and may lead to more false-positive results and unnecessary follow-up testing.16 One recent meta-analysis found specificity of traditional cytology in identifying low-grade cervical lesions (96%) to be significantly higher than that of HPV DNA testing (86.5% to 94.7%). It was estimated that the lower sensitivity translated to a false-positive rate of nearly 10%.17

Current screening guidelines endorsed by the American Cancer Society recommend beginning screening about 3 years after first vaginal intercourse and no later than age 21 years.18 Annual screening with the Pap test is recommended, while bimannual screening is allowed when using LBC. At 30 years of age, women who have had 3 consecutive normal Pap screens may begin screening every 2 or 3 years. Alternatively, these women may be screened every 3 years in conjunction with HPV DNA testing.18 The American College of Obstetricians and Gynecologists (ACOG) revised its screening guidelines in December 2009. ACOG now recommends beginning biennial screening at age 21, regardless of sexual history. At age 30, screening every 3 years is recommended for women who have had 3 consecutive negative cytology screenings.19

It is estimated that in the United States, 1 in 4 women between the ages of 14 and 59 years is infected with HPV; oncogenic HPV types 16 and 18 have prevalence rates of 1.5% and 0.8%, respectively.20 An estimated 11,270 new cases and 4,070 deaths still occur annually,14 and total direct medical costs related to cervical cancer prevention and treatment have been estimated at approximately $6 billion.21-23 In one health plan in the northwestern United States, nearly two-thirds of these direct costs were allocated to routine screening, with 10% allocated to treatment of invasive cervical cancer, 17% to precancerous lesions, and 9% to follow-up care of false-positive Pap tests.24 Indirect costs associated with cervical cancer are even higher than direct costs, as more than 75% of the total economic burden of cervical cancer is attributed to decreased productivity, lost future earnings, and other related factors.25 HPV vaccination may help to diminish the total direct and indirect costs by preventing infection and subsequent development of precancerous lesions and invasive cancer, providing a long-term return on investment by avoiding cervical cancer treatment.

**Modeling the Cost-Effectiveness of HPV Vaccination**

It can take years to decades for an HPV infection to progress to cervical cancer. Due to this practical limitation, and because cancer incidence cannot be ethically used as an endpoint for vaccine evaluation (i.e., subjects cannot be denied treatment upon detection of cytologic abnormalities or precancerous lesions in order to establish vaccine efficacy against cancer), mathematical modeling is employed to simulate outcomes. Three types of models have been employed: static Markov, transmission dynamic, and hybrid models combining features of both Markov and dynamic models.

Results of HPV vaccine cost-effectiveness studies modeled with U.S. data are summarized in Table 2. These outcomes are typically measured with an incremental cost-effectiveness ratio (ICER), determined by dividing the difference in cost between 2
strategies (e.g., HPV vaccination vs. current screening practices) by the difference in health outcomes. Typically, the unit of measurement for the ICER is the difference in life expectancy (life years saved [LYS]) or quality-adjusted life expectancy (including utilities defined on a scale of 0 [death] to 1 [perfect health], quality-adjusted life years [QALY] saved) is a measure of disease burden that accounts for years lived in less than perfect health.

It is important to understand that all mathematical models are based on assumptions and predictions that may or may not always be accurate. Therefore, the utility of conclusions drawn by mathematical models is constrained by the need for subsequent validation of these assumptions. Model outcomes of the cost-effectiveness of HPV vaccination are constrained by assumptions of vaccine efficacy, duration of vaccine protection, and level of vaccine coverage in the population among other variables. Although data exist on vaccine efficacy, duration of protection is yet to be determined, and there are uncertainties about how fast vaccine uptake will occur. Therefore, the accuracy of model assumptions and subsequent model outcomes can only be validated over time.

Model Types
Markov models simulate disease progression for a particular cohort (e.g., females aged 11 years) over an expected lifetime (Figure 1). These models are typically probabilistic and linear and follow the susceptible cohort through subsequent disease stages or compartments (e.g., HPV infected, cervical intraepithelial neoplasia, cervical cancer, and death). Probabilistic models allow for events to occur by chance, and the probability that any individual will transition from one compartment to the next is drawn from a probability distribution. Transition probability parameters (p), based on established clinical morbidities, are constant over time and determine what proportion of the cohort advances to various disease states during a model cycle. Use of a prophylactic HPV vaccine should reduce the number of patients in the original cohort that will develop HPV infections and lower the proportion of patients developing subsequent HPV-related disease states. The Markov cycles are run until all the members of the original cohort have died, either from HPV-related disease or natural causes, based on the model parameters. The time spent in each stage over the lifetime of the cohort is then used to measure both the survival time and health care costs accrued.

Transmission dynamic models examine a whole population over time. These models are typically deterministic and nonlinear. These models are deterministic in that there is an average rate of transition between disease stages that is the same for each individual at a given time, as opposed to being drawn from a probability distribution for each person. Individuals enter this type of model at birth and exit the model at death. In contrast to cohort models where transition parameters between disease states are constant over time, the parameters in dynamic models can change if HPV prevalence changes. For example, transmission dynamic models can take herd immunity into account, whereby vaccination of a large segment of the population will decrease the transmission parameter between the HPV-susceptible stage and HPV-infected stage by having fewer individuals infected with HPV able to transmit the virus. Since the rate at which individuals become infected is dependent on the number of infectious individuals, this type of model is inherently nonlinear. Although this type of model is more “real world” in that more variables are considered, it is also prone to greater uncertainty based upon an increased number of parameter assumptions that must be made.

Hybrid models combine properties of the Markov and dynamic models. The hybrid model follows a single cohort rather than the whole population but allows for changes in the transmission parameters between disease states over time. In this way, the benefits of herd immunity can be modeled by simulating a decrease in disease transmission over time.

Model Selection
Models included in this review were found by searching the PubMed database using the terms “HPV,” “vaccine,” and “cost-effectiveness.” Only primary research studies focusing on the economic impact of HPV vaccination on cervical cancer that were modeled using U.S. data and published before February 22, 2010, were included in this review. Studies based on data from outside the United States were excluded, as were studies
## TABLE 2  Overview of Published HPV Vaccination Cost-Effectiveness Models

<table>
<thead>
<tr>
<th>Authors/Model Type/Funding</th>
<th>Model Subjects</th>
<th>Vaccine Characteristics</th>
<th>Baseline Screening Characteristics</th>
<th>Cost-Effectiveness Point Estimates</th>
<th>Treatment Comparators</th>
<th>Sensitivity Analyses</th>
<th>Model Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulasingam and Myers (2003)(^{12})</td>
<td>100,000 females aged 12 years</td>
<td>70% of oncogenic HPV types (including 16 &amp; 18) 90% efficacy 100% coverage</td>
<td>Biennial Pap screening initiated at age 24 years</td>
<td>$44,889 per QALY</td>
<td>Biennial Pap screening at age 18 years</td>
<td>CE range = $44,889 per LYS to $236,250 per LYS</td>
<td>1. Vaccine costs $200 2. Duration of protection 10 years 3. Progression from low- to high-grade cervical lesion not differentially affected by the vaccine 4. Age-specific risks of infection, regression, and disease incidence modeled 5. Future costs and life years discounted at 3% 6. Disutility of precancerous lesions about 1 month, for cancer for 5 years of follow-up</td>
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<td>Markov model type Funded by Merck Research Laboratories</td>
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<tr>
<td>Goldie et al. (2004)(^{33})</td>
<td>100,000 females aged 12 years</td>
<td>HPV 16/18 90% efficacy 100% coverage</td>
<td>Lifelong protection</td>
<td>Current practice: Pap screened 70.5% in last year, 12.6% in last 2 years, 4.3% in last 3 years, and 3.0% in last 5 years, 5.2% never screened</td>
<td>$24,300 per QALY</td>
<td>Current screening practice alone</td>
<td>CE range = $17,200 per QALY to $3,867,500 per QALY</td>
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<tr>
<td>Markov model type Funded by GlaxoSmithKline Biologics, NCI</td>
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<tr>
<td>Rogoza et al. (2008)(^{34})</td>
<td>100,000 females aged 12 years</td>
<td>HPV 6/11/16/18 95% efficacy (vaccine HPV types), 53% efficacy (HPV 31), 88% efficacy (HPV 45) 100% coverage</td>
<td>Current practice: annual screening for females aged 15-89 years, coverage rate 3%-60%</td>
<td>$7,828 per QALY</td>
<td>Current screening practice</td>
<td>CE range = $7,828 per QALY to $79,581 per QALY</td>
<td>1. Vaccine costs $474 2. Costs and outcomes discounted 3% 3. Utilities (0.92-0.99 for precancerous lesions; 0.73 for treated cancer; 0.62-0.97 for cancer follow-up)</td>
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<tr>
<td>Markov model type Funded by GlaxoSmithKline Biologics</td>
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<tr>
<td>Goldhaber-Fiebert et al. (2008)(^{36})</td>
<td>1,000,000 females aged 9 years, vaccinated by age 12 years</td>
<td>HPV 16/18 100% efficacy 100% coverage</td>
<td>Current screening practice based on “large population-based studies with various levels of screening coverage and frequency for different sub-populations”</td>
<td>$41,000 per QALY with screening every 5 years beginning at age 25 years, HPV DNA testing beginning at age 35 years</td>
<td>Next best strategy defined as screening every 5 years beginning at age 25 and no HPV DNA testing</td>
<td>CE range = $6,000 per QALY to $12,749,000 per QALY</td>
<td>1. Vaccine costs $402 2. Costs and outcomes discounted 3% annually 3. Utilities decrease with increasing age 4. Utilities for cancer (0.48-0.68)</td>
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</tbody>
</table>
### TABLE 2  
Overview of Published HPV Vaccination Cost-Effectiveness Models (continued from previous page)

<table>
<thead>
<tr>
<th>Authors/Model Type/Funding</th>
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<th>Treatment Comparators</th>
<th>Sensitivity Analyses</th>
<th>Model Assumptions</th>
</tr>
</thead>
</table>
| Sanders and Taira (2003)47 | All U.S. females aged 12 years | 13 oncogenic HPV types including 16 & 18 | Current standard of care: routine biennial Pap for compliant patients (71% of females) starting at age 16 years | ~$22,755 per QALY | Biennial screening starting at age 16 years | CE range = $12,682 per QALY to $52,398 per QALY | 1. Vaccine cost $300, booster cost $100  
2. 10-year duration of protection with booster shots  
3. Annual infection incidence at age 15 years (10%), peaks at age 19 years (18%).  
4. Discounting at 3%  
5. No utility decrement for undiagnosed infection or lesion, diagnosed lesions measured at 0.97 |
| Markov model type | | | | | | | Same assumptions as Sanders and Taira (2003)47 |
| Funded by Stanford Cancer Council | | | | | | | |
| Taira et al. (2004)38 | All U.S. females aged 12 years accounting for herd immunity | HPV 16/18 90% efficacy 70% coverage | Current practice: biennial Pap for compliant patients (71% of females) | ~$14,583 per QALY | Current screening practice | CE range = $14,583 per QALY to about $800,000 per QALY | 1. Vaccine cost $300, booster cost $100  
2. Costs and QALY discounted at 3%  
3. Utility for precancerous lesions (0.87-0.91); for cancer (0.48-0.76); for cancer survivors (0.76) |
| Hybrid model type | | | | | | | |
| Funded by SSMMSA; V Foundation; Stanford Cancer Council | | | | | | | |
| Elbasha et al. (2007)42 | Whole population of U.S. females aged 12 years, catch-up to 24 years | HPV 6/11/16/18 90% efficacy 100% coverage | Current practice: routine Pap; age-stratified data used to estimate cytology screening rates | ~$4,666 per QALY | Current screening practice | CE range = $997 per QALY to $124,063 per QALY | 1. Vaccine cost $300  
2. Costs and QALY discounted at 3%  
3. Age-specific cancer incidence rates from 2003; population-based registries |
| Dynamic model type | | | | | | | |
| Funded by Merck Research Laboratories | | | | | | | |
| Adding male vaccination aged 12-24 years | HPV 6/11/16/18 90% efficacy 100% coverage | Current practice: routine Pap; age-stratified data used to estimate cytology screening rates | ~$45,056 per QALY | Current screening practice | CE range = $997 per QALY to $124,063 per QALY | 1. Vaccine cost $300  
2. Costs and QALY discounted at 3%  
3. Age-specific cancer incidence rates from 2003; population-based registries |
| Chesson et al. (2008)43 | Whole population of U.S. females | HPV 6/11/16/18 100% efficacy 100% coverage | Current practice: not defined, as the incidence rates of cervical disease used in the model occurred in the context of current screening practices | ~$5,336 per QALY | Current screening practice | CE range = <$0 per QALY to $122,976 per QALY | 1. Vaccine cost $300  
2. Costs and QALY discounted at 3%  
3. Age-specific cancer incidence rates from 2003; population-based registries |
| Dynamic model type | | | | | | | |
| Funded by CDC | | | | | | | |
| Adding male vaccination aged 12-24 years | HPV 16/18 100% efficacy 100% coverage | Current practice: routine Pap; age-stratified data used to estimate cytology screening rates | ~$10,318 per QALY | Current screening practice | CE range = <$0 per QALY to $122,976 per QALY | 1. Vaccine cost $300  
2. Costs and QALY discounted at 3%  
3. Age-specific cancer incidence rates from 2003; population-based registries |
Prophylaxis of Cervical Cancer and Related Cervical Disease:
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**TABLE 2** Overview of Published HPV Vaccination Cost-Effectiveness Models (continued from previous page)

<table>
<thead>
<tr>
<th>Authors/Model Type/Funding</th>
<th>Model Subjects</th>
<th>Vaccine Characteristics</th>
<th>Baseline Screening Characteristics</th>
<th>Cost-Effectiveness Point Estimates</th>
<th>Treatment Comparators</th>
<th>Sensitivity Analyses</th>
<th>Model Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim and Goldie (2008)**</td>
<td>Whole population of U.S. females vaccinated at age 12 years</td>
<td>HPV 6/11/16/18 100% efficacy 75% coverage</td>
<td>Current practice: starting average age 20 years; either Pap or LBC according to U.S. guidelines; 53% screened annually; 17%, 11%, and 14% screened every 2, 3, 5 years; 5% never screened</td>
<td>$43,600 per QALY</td>
<td>Current screening practice</td>
<td>CE range = $34,900 per QALY to $324,200 per QALY</td>
<td>1. Vaccine cost $360; booster cost $250</td>
</tr>
<tr>
<td><strong>Adding catch-up vaccination to 18 years of age</strong></td>
<td>HPV 6/11/16/18 100% efficacy 75% coverage</td>
<td>Current practice</td>
<td>$97,300 per QALY</td>
<td>Current screening practice</td>
<td>1. Vaccine cost $360; booster cost $250</td>
<td>2. Costs and QALY discounted at 3%</td>
<td>3. Utility for cancer (0.48–0.76); warts (0.91)</td>
</tr>
<tr>
<td><strong>Adding catch-up vaccination to 21 years of age</strong></td>
<td>HPV 6/11/16/18 100% efficacy 75% coverage</td>
<td>Current practice</td>
<td>$120,400 per QALY</td>
<td>Current screening practice</td>
<td>1. Vaccine cost $360; booster cost $250</td>
<td>2. Costs and QALY discounted at 3%</td>
<td>3. Utility for cancer (0.48–0.76); warts (0.91)</td>
</tr>
<tr>
<td><strong>Adding catch-up vaccination to 26 years of age</strong></td>
<td>HPV 6/11/16/18 100% efficacy 75% coverage</td>
<td>Current practice</td>
<td>$152,700 per QALY</td>
<td>Current screening practice</td>
<td>1. Vaccine cost $360; booster cost $250</td>
<td>2. Costs and QALY discounted at 3%</td>
<td>3. Utility for cancer (0.48–0.76); warts (0.91)</td>
</tr>
<tr>
<td>Kim and Goldie (2009)**</td>
<td>Whole population of U.S. females and males vaccinated at age 12 years</td>
<td>HPV 6/11/16/18 100% efficacy against infection from vaccine-targeted HPV types 75% coverage</td>
<td>Current practice: starting average age 20 years; either Pap or LBC according to U.S. guidelines; 53% screened annually; 17%, 11%, and 14% screened every 2, 3, 5 years; 5% never screened</td>
<td>$290,290 per QALY</td>
<td>Current screening practice</td>
<td>CE range = $88,930 per QALY to $390,440 per QALY</td>
<td>1. Vaccine cost $360; booster cost $250</td>
</tr>
</tbody>
</table>
based solely on regional U.S. data. A total of 15 studies met these criteria. A total of 4 studies were excluded. Two excluded studies presented additional data from a previously published model; and 1 study was excluded because it was based solely on data from Kentucky; and 1 study was excluded because it was focused on the cost-effectiveness of HPV vaccination in the prevention of recurrent respiratory papillomatosis. Because the 11 included studies used varying assumptions in their models, this review is a comparative review rather than a quantitative meta-analysis.

**Model Results**

Three studies have examined cost-effectiveness of an HPV vaccine administered to a modeled cohort of 100,000 girls at age 12 years. Ku: Kulasingam and Myers (2003) assumed that their model vaccine offered 10-year protection and was targeted to 70% of oncogenic HPV types, including types 16 and 18. Every female in the cohort was assumed to have been administered the vaccine (100% coverage). The vaccine was assumed to be 90% efficacious and priced at a cost of $200 per series. Compared with biennial screening beginning at age 18 years, a strategy of vaccination at age 12 combined with delayed biennial screening starting at age 24 years resulted in a cost of $44,889 per LYS. By contrast, the strategy of vaccination plus annual screening beginning at age 18 resulted in a cost of $236,250 per LYS. These findings suggest that a delay in cervical screening initiation in addition to a longer interval between screenings would be most cost-effective when vaccinating against HPV.

Goldie et al. (2004) also modeled cost-effectiveness in a cohort of 100,000 females aged 12 years based on a bivalent vaccine protecting against HPV types 16 and 18 only. Cost-effectiveness in this model was measured compared with current U.S. cervical screening practices as determined by data from the CDC’s Behavioral Risk Factor Surveillance System (detailed in Table 2). The vaccine in this model was assumed to cover 100% of the target cohort and to have 90% efficacy and lifetime protection, at a cost of $377 per series. Administration of this vaccine would reduce the lifetime incidence of cervical cancer by 58% and would cost $24,300 per QALY gained. When efficacy was set at 100%, the ICER decreased to $20,600 per QALY gained. Model results were most sensitive to changes in duration of vaccine protection, whether persistent HPV infections after age 30 years were newly acquired or reactivations of latent infections, and to variables related to screening (e.g., age at initiation, frequency). The most expensive strategy modeled by Goldie et al. combined vaccination at age 12 years with annual cervical screening and LBC initiated at age 18. This strategy cost more than $3.5 million per QALY compared with the next best strategy, which used the same parameters with annual Pap screening rather than LBC. However, the annual reduction in lifetime risk was only 2% more than biennial screening strategies.

Finally, Rogoza et al. (2008) analyzed cost-effectiveness in the
same cohort of 100,000 females aged 12 years given a quadrivalent vaccine protecting against nononcogenic HPV types 6 and 11 in addition to oncogenic types 16 and 18. This vaccine was estimated to have 100% coverage, 95% efficacy, and lifetime protection. Sensitivity analyses related to properties of the vaccine were not conducted for this model. The vaccine was also modeled to have some protective efficacy for nonvaccine HPV types: efficacy against HPV 31 was set at 53%, and efficacy against HPV 45 was set at 88%. HPV 31 and 45 combined are associated with another 7% of cervical cancer cases. Compared with current U.S. screening practices, vaccination in this model resulted in a cost per QALY gained of $7,828.

Goldhaber-Fiebert et al. (2008) used a Markov model to estimate cost-effectiveness of HPV vaccination in a larger cohort of 1 million females 9 years of age who were to be vaccinated by age 12 years. Their model also allowed for individual variation in life history to be accounted for. Rather than using population-based averages to determine transition probabilities between disease states (i.e., between HPV infection and cervical intraepithelial neoplasia [CIN]), this model simulated all possible individual clinical pathways. In their model, the whole cohort was assumed to be vaccinated by age 12, and the vaccine was assumed to be 100% effective against HPV 16 and 18 with lifelong duration of protection. The model also simulated the effects of varying the starting age of cervical screening and screening frequency interval. If this cohort began 5-year interval cervical screening at age 25, switching to HPV DNA testing at age 35, the cost per QALY gained was $41,000 compared with a strategy with the same screening parameters but without the switch to HPV DNA testing. Switching to HPV testing at age 30 increased the ICER to $126,000 per QALY, while increasing screening frequency to a 3-year interval increased ICER to $188,000 per QALY. The most expensive vaccination strategy (more than $12 million per QALY) included annual Pap screening at age 18 years that switched to LBC at 25 years of age.

Sanders and Taira (2003) measured cost-effectiveness of HPV vaccination in 2 ways: in a Markov model following a cohort of all U.S. 12 year olds and also in a hybrid model that accounted for disease transmission rate changes due to herd immunity. The authors modeled a vaccine that was 75% efficacious against a set of 13 oncogenic HPV types including HPV 16 and 18. This model also assumed 70% coverage, 10-year protection (at a cost of $300 per series) with booster injections every 10 years (at a cost of $100 per booster). In the cohort model, compared with biennial Pap screening beginning at age 16 years, the addition of HPV vaccination resulted in an incremental cost per QALY gained of $22,755. Vaccine efficacy was shown to be the parameter with the greatest influence on cost-effectiveness. For example, at 35% efficacy, cost-effectiveness increased to $52,398 per QALY.

Taira et al. (2004) amended this cohort model to include changes in HPV prevalence resulting from widespread immunization (herd immunity) as well as to model the cost-effectiveness of male vaccination. In this hybrid model, the vaccine had 90% efficacy against HPV 16 and 18, with 70% coverage. The inclusion of herd immunity (as well as the increase in efficacy) decreased the cost per QALY gained to $14,583. When the hybrid model was altered to include male vaccination, the cost per QALY gained jumped to $442,039. Although males may also develop penile and anal cancers as a result of HPV infection, the incidence rates are much lower compared with cervical cancer. For example, about 1 in 100,000 men infected with HPV will develop penile cancer, and 2,100 cases of anal cancer are diagnosed in men annually. By comparison, 94% of all HPV-related cancers affect women. Therefore, the cost-effectiveness of vaccinating males will largely result from the indirect benefits of increasing herd immunity. Taira et al. found that vaccinating males would decrease cancer incidence only slightly for such a high cost.

Transmission dynamic models have also simulated the effects of HPV vaccination in the whole U.S. female population. Elbasha et al. (2007) examined the cost-effectiveness of a vaccine protecting against infection from HPV types 16, 18, 6, and 11. Vaccine efficacy against incident infection was set at 90%, and efficacy against HPV-related disease was 100%. Vaccine cost was set at $360 for the 3-dose series and produced lifelong protection. Coverage of 12-year-old females increased from 0% to 70% over the first 5 years and was set at 70% thereafter. Coverage in a catch-up vaccination program for those aged 12 to 24 years increased from 0% to 50% over the first 5 years and was then eliminated from the model. Compared with current practice, female-only vaccination before age 12 with the catch-up program resulted in a cost of $4,666 per QALY gained. However, if duration of protection was limited to 10 years, then costs increased to $21,121 per QALY. The most effective strategy in terms of disease reduction included the additional vaccination of boys and men with lifelong protection at a cost of $45,056 per QALY. Limiting duration of protection to 10 years while vaccinating males and females increased costs to $54,928 per QALY.

Chesson et al. (2008) also examined the cost-effectiveness of the same quadrivalent HPV vaccine as well as a bivalent vaccine (protecting against HPV 16 and 18 only) using a dynamic model. In this study, efficacy was assumed to be 100% against HPV infection and disease. Although no catch-up vaccination was modeled, the coverage of 12 year olds, vaccine cost, and duration of protection were the same as the Elbasha et al. study detailed above. Chesson et al. found that a vaccine targeting HPV 16, 18, 6, and 11, or only HPV 16 and 18, resulted in estimated costs of $5,336 and $10,318 per QALY gained respectively when examining cervical abnormalities (i.e., not including anal, vaginal, vulvar, and oropharyngeal cancers), compared with existing cervical cancer screening. Sensitivity analyses produced a worst-case scenario cost-effectiveness estimate of $122,976 per QALY, including parameters such as a lower incidence of HPV-related diseases and a smaller reduction in quality of life resulting from HPV-related diseases.

Kim and Goldie (2008) also utilized a dynamic model with some modifications to allow for individual variations in behavior to examine cost-effectiveness of a vaccine targeting HPV 16, 18, 6, and 11. In addition to evaluating population dynamics that varied transmission rates over time, this model also allowed for differences in individual history (e.g., vaccination, screening,
 treatment, and past abnormalities) thereby accommodating complexities in screening strategies. Kim and Goldie examined the cost-effectiveness of vaccinating all 12 year olds alone, as well as the cost-effectiveness of adding catch-up vaccinations through ages 18, 21, and 26 years. Coverage was assumed to be 75% within the first 5 years, at a coverage rate of 25% per year. In the base-case scenario, efficacy was assumed to be 100% with lifelong duration of protection. Compared with current screening practices, vaccination of 12 year olds alone resulted in a cost of $43,600 per QALY gained for outcomes solely related to cervical cancer (i.e., not including genital warts). A number of sensitivity analyses were conducted by the authors, including evaluation of the assumption of duration of protection. If duration of protection was limited to 10 years, costs increased to $144,100 per QALY. Use of a booster shot at 10 years resulted in an ICER of $83,300 per QALY. Under the base assumption of lifelong protection, ICERs increased incrementally when extending the age range of females to be vaccinated to $97,300 per QALY for catch-up through age 18, $120,400 through age 21, and $152,700 through age 26. Vaccinations of all age ranges were more cost-effective if prevention against nonvaccine HPV types were included. Studies of both HPV vaccines have demonstrated some level of cross-protection against nonvaccine oncogenic HPV types. Kim and colleagues (2009) also used this model to examine cost-effectiveness of HPV vaccination in 2 other populations: all 12 year olds including boys and women aged 35 to 45 years. In the analyses of 12 year olds, vaccination of girls at 75% coverage with 100% lifelong efficacy against infection and disease related to HPV 16 and 18 resulted in an ICER of $40,310 per QALY compared with current screening practices for outcomes related to cervical disease. Vaccinating 12-year-old boys at 75% coverage with lifelong 85% efficacy against HPV 16/18 infection and 90% efficacy against HPV 16/18-related disease increased the ICER to $290,290 per QALY for cervical disease outcomes. When HPV 16/18-related noncervical male and female cancer outcomes were added into the model (50% vaccine efficacy), the ICER for vaccinating girls only decreased to $27,370 per QALY, while the addition of male vaccination resulted in a cost of $164,580 per QALY. When lower efficacy, waning immunity, or higher vaccine costs were assumed, the incremental cost of vaccinating boys consistently exceeded $250,000 per QALY. A strategy vaccinating older women was also modeled and found to not be cost-effective (more than $100,000 per QALY). Neither HPV vaccine has been indicated for use for women older than 26 years of age. In the model of HPV vaccination in older females, women aged 35, 40, and 45 years were given the complete 3-dose series. The cost-effectiveness of vaccination was compared with a baseline of women practicing annual or biennial screening and also with the more variable and infrequent screening rate of current practice. Compared with annual or biennial screening, vaccination with 100% lifetime efficacy resulted in an ICER range from $116,950 to $272,350 per QALY gained. Compared with current screening practice, vaccination at any age resulted in ICERs of more than $125,000 per QALY.

### Discussion and Limitations

Whether or not females will choose to be vaccinated may depend on their awareness of the benefits and risks of HPV vaccination. Given that most infections resolve without intervention, Haug (2009) questioned the necessity of HPV vaccination, concluding that the HPV infection “does not appear to be very harmful.” Haug also states that it is impossible to determine in which females HPV infection will persist, leading to disease progression, and in which females the infection will regress. These arguments raise the issue of the clinical value of HPV vaccination. However, HPV is a common infection in U.S. females, and natural immune responses are not reliably protective against infection. Although 91% of HPV infections regress within 2 years, for women with persistent HPV 16 or 18 infection the risk of developing precancerous lesions is 169 times greater than for those who are uninfected. HPV vaccination targets the 2 most common HPV types associated with approximately 3 out of every 4 cases of cervical cancer in the United States. Furthermore, the vaccines may provide additional protection against nonvaccine HPV types that are phylogenetically related to HPV 16 and 18.

Assumptions about the HPV vaccine affect modeling estimates of the cost-effectiveness of HPV vaccination. Efficacy rate, duration of protection, and rates of vaccine coverage or uptake are critical variables that will impact the cost-effectiveness of HPV vaccination. Most models assumed vaccine characteristics of 90% or 100% efficacy against vaccine HPV types, consistent with the currently available data from the controlled clinical trials for the 2 HPV vaccines. Phase III studies of quadrivalent HPV vaccine revealed 98% protection against high-grade precancerous lesions, whereas for bivalent HPV vaccine 93% efficacy has been demonstrated in females naive to HPV 16 and 18 who completed the 3-dose vaccine series. However, while these studies have demonstrated high vaccine efficacy rates, it must be kept in mind that patients and their providers must be compliant with prescribing and receiving the vaccination regimen to achieve these high vaccination protection rates. Initial data suggest that adolescents may often not receive the vaccine when eligible and that when the vaccine regimen is started, only 58% to 75% of patients complete the entire 3 injection series. If fewer patients complete the entire vaccination series than what was estimated by a cost-effectiveness model, the “real world” cost per QALY results would be worse than what was predicted by the model.

Based on clinical trials, HPV vaccination is efficacious against the occurrence of precancerous lesions, which suggests that vaccination is likely to be effective. However, real-world effectiveness of the vaccine will be contingent upon actual levels of vaccine coverage, compliance, and duration of protection. One assumption common to all models is a high level of vaccine coverage (at least 70% of the target population is assumed to receive the vaccination). However, recent CDC survey data reveal that only 37% of females between 13-17 years of age and 10% of women between 18-26 years of age had taken at least 1 of the 3 recommended vaccine doses. Until coverage levels increase in the target population, cost-effectiveness model estimates may underestimate
actual costs. Unfortunately, no model has estimated the cost-effectiveness of vaccination with coverage levels at 37% or lower. Therefore, the modeling of beneficial effects from herd immunity is only speculative until vaccine uptake increases. Regarding vaccine compliance, not everyone who initiates the vaccine series completes all 3 doses or completes all doses in the recommended 6-month time frame, and it is presently unknown how noncompliance affects vaccine efficacy and duration of protection.

Concerns over vaccine safety may be contributing to the low coverage rates observed thus far. Yet, a recent analysis of the quadrivalent vaccine found that the overall rates of adverse events were not greater after HPV vaccination compared with background rates following other types of vaccination. However, a disproportionate number of syncope and venous thrombotic events were observed after HPV vaccination. The venous thrombotic events reported fell within a large time window post-vaccination, and 90% of subjects reported having pre-existing risk factors. As such, venous thrombotic events were not clearly linked to vaccination. For the bivalent vaccine, local reactions (pain, redness, swelling) were reported more frequently after vaccine injection compared with control injection. However, incidence of new onset autoimmune diseases was comparable between vaccine and control groups. Among females aged 10 through 25 years, 6.4% of subjects who received the bivalent vaccine and 7.2% of subjects who received the control reported at least 1 adverse event (without regard to causality) during a 7.4 year follow-up period.

For questions regarding duration of protection, most models assumed that the vaccine provided either 10-year or lifetime protection. At this time, the minimum antibody titer level that confers protective efficacy has not been determined. For the quadrivalent HPV vaccine, titers specific to vaccine HPV types (6, 11, 16, 18) peaked at month 7 after the initial vaccine dose, declined through month 24, and stabilized at levels above baseline. Anti-HPV titers remained similar at month 60. For the bivalent HPV vaccine, antibody titers for both HPV 16 and 18 peaked at month 7 after the initial dose and reached a plateau that was sustained from month 18 through month 76. A recent mathematical model of the immunological data from the bivalent HPV vaccine predicts that antibody titers above baseline may be observed 20 years post-vaccination. It is presently unknown if model assumptions of duration of protection will be validated. Until long-term studies of efficacy have been completed, the use of ICERs based on the conservative estimate of 10-year protection may be warranted rather than the use of ICERs based on lifetime protection.

Other model assumptions that impacted cost-effectiveness were the inclusion or exclusion of herd immunity effects, the amount of discounting assumed, and the setting of disease-related utilities. The major shortcoming of studies using Markov models is the exclusion of herd immunity effects. The inclusion of herd effects in hybrid and dynamic models should decrease modeled ICERs, although the specific contribution of herd immunity is difficult to quantify across models with different assumptions. The closest comparison that can be made among the studies currently examined is between the Markov model of Sanders and Taira and the Taira et al. hybrid model. The hybrid model added herd immunity to the original Markov model, resulting in a decrease of about $8,000 per QALY. However, the direct comparison is complicated by the fact that Taira et al. assumed 90% efficacy while Sanders and Taira assumed 75% efficacy. Although some models varied the discount rate of future costs in sensitivity analyses, all models set discounting of the base case analysis at 3%. By contrast, the quality of life utility scores for cervical disease progression varied across studies. Again, it is difficult to isolate the singular effect of these different utility scores on the ICERs across studies.

Typically, an intervention is deemed cost-effective if the ICER is within or below the range of $50,000 to $100,000 per QALY gained. By this standard, all models presented above have determined that HPV vaccination in females can be a cost-effective intervention in comparison with the current practice of cervical screening alone. However, broad ranges of ICERs were produced from sensitivity analyses. The highest estimates typically resulted from vaccination strategies that included annual cervical screening initiated at age 18 years. The Kim and Goldie model was especially useful as the authors incorporated several additional variables, including vaccination, screening, treatment, past abnormalities, and the implications of catch-up vaccinations. Including these additional variables makes the results more "real world" and may explain why the cost per QALY results for certain patient subgroups were often higher than $100,000 per QALY gained (e.g., $120,000 per QALY for vaccination catch-up for women through 21 years of age).

Cervical screening is still a necessary preventive procedure, as the currently developed HPV vaccines do not protect against all oncogenic HPV types. However, HPV vaccination may allow for potential revisions in the current screening guidelines. Although it is beyond the scope of this review to recommend revisions to current screening guidelines, cervical screening is most inefficient in younger women, when HPV infections are most likely to be transient, and 1 report suggests that screening should not begin until age 25. If widespread HPV vaccination could decrease the incidence of oncogenic HPV infection during the peak ages of infection (late adolescence and early adulthood), it may be feasible to begin screening later and/or increase the interval between screenings. For example, Goldhaber-Fiebert et al. estimated in their model that screening alone every 3 years beginning at 25 years of age would decrease cervical cancer risk by 71%. Vaccination in combination with these screening parameters was estimated to decrease cervical cancer risk by 93%. Increasing the interval between screenings to every 5 years still resulted in a decrease in cervical cancer risk of 91%-92%, at a substantial cost savings. However, in this model, vaccination was assumed to have 100% efficacy against infection with HPV 16 and 18 with a lifetime duration of protection. Therefore, the reduction in cervical cancer risk and the cost savings may be lower than estimated, as efficacy is not 100% and duration is yet to be determined.
The 3 studies modeling cost-effectiveness of HPV vaccination in males produced mixed results. Compared with the cost-prohibitive projections (more than $400,000 per QALY) of the Taira et al. model, cost estimates of vaccinating males in the Elbasha et al. study were much lower (approximately $50,000 per QALY). Differences in the modeled vaccines and model assumptions may have contributed to this large disparity. The study vaccine in the model described by Taira et al. did not protect against HPV types 6 and 11, responsible for genital warts, and included higher utility scores for precancerous lesions compared with the Elbasha et al. model. The most recent model including male vaccination, by Kim and Goldie, found that male vaccination was not cost-effective under most scenarios. The addition of male vaccination fell below the $100,000 per QALY threshold only when high, lifelong vaccine efficacy against all HPV-related diseases, including other noncervical cancers and genital warts, was included, or if lower efficacy was modeled with lower coverage or lower vaccine costs. Further clinical and modeling studies should be conducted before conclusions can be drawn about the cost-effectiveness of male vaccination. Data on the clinical efficacy of quadrivalent HPV vaccine in males show that the vaccine is 76% effective against the incidence of external genital lesions and 80% effective against the incidence of genital warts.

Elbasha et al. and Kim and Goldie were the only investigators to model the costs of catch-up vaccination. In addition to modeling the whole population of 12-year-old females and males, respectively, the Elbasha et al. model included catch-up vaccination up through age 24 years. In females only compared with current screening practices, the Elbasha et al. model produced a relatively low ICER of less than $5,000 per QALY. Kim and Goldie’s ICER estimates were much higher by comparison. One factor contributing to this disparity is the lower vaccine coverage rate modeled by Kim and Goldie (75% compared with 100%). Kim and Goldie examined female vaccination of 12-year olds with catch-up through 26 years of age, matching the catch-up range of current CDC recommendations. Although their results suggested that vaccination of all 12-year-old females can be cost-effective ($43,600 per QALY compared with current screening practice), catch-up vaccination becomes more expensive as older cohorts are added. Assuming lifelong immunity, adding catch-up vaccination through age 18, 21, and 26 years increased the ICER to approximately $100,000 per QALY, $120,000 per QALY, and $150,000 per QALY, respectively. These estimates decreased if cross-protection against nonvaccine HPV types was included in the model. The inclusion of cross-protection lowered the costs of catch-up vaccination through age 21 years to just over $100,000 per QALY. Although this model did not support catch-up vaccination through the CDC’s recommended age of 26 years from a cost-effectiveness perspective, the clinical risk of HPV infection and disease progression remains lifelong. The only study to examine vaccination in older females found that HPV vaccination was not cost-effective for women 35 to 45 years of age. For this age range, the probability of HPV vaccination being cost-effective for women was 0% with biennial screening and less than 5% with triennial screening.

Above and beyond the costs of vaccination, the implications of HPV vaccine-derived protection affect the primary goal of disease prevention in managed health care. Although covering the costs of HPV vaccination may be initially cost-prohibitive for managed care organizations, coverage of HPV vaccination and cervical screening should result in noticeable improvements in clinical outcomes, which should over the long term lead to some cost offsets. As health plans continue to expand and meet the changing needs of their customers and society, financial implications must be weighed against clinical benefit to arrive at the best decisions. Economic models are necessary for managed care organizations to evaluate the different options and design benefits to include in their health plans. Plan stakeholders have different options for approaching the issue of HPV vaccine coverage. Full coverage of these products under a standard vaccination benefit is 1 option, as is a “nonstandard” vaccination benefit where health plan members pay a portion (e.g., 20%) of the costs for vaccines deemed optional (e.g., rotavirus, palivizumab, and HPV vaccine). Given available cost-effectiveness data, full coverage may be the more appropriate option, and this option has already been adopted by at least 1 managed care organization.

The direct cost of HPV vaccine ($375) is high compared with other vaccines and may be prohibitively expensive for a large percentage of females. Therefore, full coverage should help to increase HPV vaccine uptake, thereby increasing herd immunity effects. However, these financial incentives must be accompanied by public health initiatives that help to educate the public about the consequences of HPV infection as well as the benefits of HPV vaccination. Although the cost-effectiveness of HPV vaccination may be questionable above the age of 21 years, to best meet the goal of disease prevention, managed care organizations might extend full coverage to all females between 9 and 26 years to encourage vaccination according to the schedule recommended by the CDC.

## Conclusion

Comprehensive health benefits coverage of vaccines has been a mainstay of virtually all managed care benefits and has proven to be a wise investment from clinical, societal, and economical perspectives. As newer vaccines come to market that are targeted to morbidity more than mortality, quantification of disease burden and modeling of the cost-effectiveness of intervention options are becoming more important when determining how best to allocate scarce health care dollars. Although the current models predict cost-effectiveness of HPV vaccination, emerging clinical data for quadrivalent HPV vaccine and bivalent HPV vaccine may require revisions in ICER estimates to reflect demonstrated long-term efficacy. Models will underestimate actual costs per QALY if real-world vaccination series completion rates do not match those of controlled clinical trials or if coverage of HPV vaccination is less than assumed.
Prophylaxis of Cervical Cancer and Related Cervical Disease: A Review of the Cost-Effectiveness of Vaccination Against Oncogenic HPV Types

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Variation in Prescriber Responses to Drug Safety Alert Messages: Disease, Symptom, or Red Herring?

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In this issue of JMCP, Feifer and James provide significant food for thought in their examination of geographic variation in the rate of automated drug safety alerts as well as prescriber response to such alerts. Findings from this study suggest that the major influences on this variation are uncertain, as member demographics explained a relatively small proportion of the observed variance in alerting rates. The authors conclude that outreach and education are necessary to improve prescriber behavior where warranted.

When broken down into the study’s constituent parts, however, both measures of variation are linked to much broader considerations regarding the state of American health care practice. The rates of “alerting events” in this study varied considerably by state, ranging from 78 to 240 per 1,000 members. However, is this variation really surprising? After all, small-area variation in health care utilization and clinical practice is a well-documented phenomenon; why should awareness of potential drug safety concerns be subject to any less variation?

As an example, consider one of the clinical situations that Feifer and James present in Table 1 of their study report—the prescribing of stimulants for children with attention deficit hyperactivity disorder (ADHD) and significant cardiac structural or rhythm abnormalities. This is indeed a significant concern, but its calculus involves more than simple variation in prescriber awareness of the clinical problem. Indeed, the documented geographic variation in both the prevalence of diagnosed ADHD and receipt of ADHD medication is significant, with 2- to 3-fold variation reported in each measure by state of residence. While there are no published data on variation in the prevalence of co-diagnosed ADHD and structural/rhythm abnormalities in children, it is not unreasonable to imagine this prevalence to be (a) relatively low; and (b) distributed in some disproportionate fashion regionally, perhaps in relation to the location of advanced pediatric cardiology services and/or children’s hospitals.

Variability in inappropriate prescribing is therefore likely to be a result of a complex interaction of disease epidemiology, practice variation, the likelihood of a given clinician encountering a relatively rare safety issue in practice, and many other concerns. As a clue for the development and targeting of a programmatic intervention to change prescribing behavior, it is also a red herring.

Why? The answer can perhaps be found in the examination of Feifer and James’ second key measure, the rate of successful therapy change per alerting event. The geographic variation in this measure was actually fairly small—from 48.1% to 59.5% when examined by state. Small variation, but universally poor results—essentially, a flip of the coin as to whether a given alert would effect the appropriate change in therapy. In contrast to alerting event rates, these results get us closer to the true nature of a systematic and widespread problem that in actuality has relatively little to do with geographic variation.

On the surface, the availability of an automated alerting system such as the one described by Feifer and James would appear to have great utility to the overworked clinician. Findings from an empirical model of the potential downstream impact of an automated alert system suggested that, for every quarter-million prescriptions, more than 400 adverse drug events would be averted, preventing death or disability in nearly 50 patients, and substantially reducing numbers of unplanned hospitalizations as well as emergency department and office visits. Physicians also appear to support the concept of such a system; survey responses from 184 physicians suggest that the majority feel that electronic prescribing improves quality of care, prevents medical errors, and enhances both patient satisfaction and clinician efficiency, and nearly two-thirds of survey participants reported modifying practice in some way in response to automated alerts.

Despite these positive signals, the clinician response to alerting systems in practice has been underwhelming. The 184 physician respondents in the above-mentioned survey were generally unsatisfied with drug interaction and allergy alerts, citing outdated information, failure to account for appropriate drug combinations, and an excessive volume of alerts. Findings from another survey-based study indicated strong prescriber preference for use of printed material and pharmacist consults over electronic alerts for drug-drug interactions. Not surprisingly then, rates at which automated alerts have been ignored or overridden are reported to be 90% or greater in studies of e-prescribing systems, even when such alerts are stratified by potential severity.

In the current environment, it is clear that any outreach tied to better response to alerts at the point of prescribing (the aforementioned red herring) will have limited utility at best. So too would outreach aimed at improving prescriber response to alerts, given the number of administrative burdens that the typical clinician already must deal with, the lack of coordination and communication between health care providers, and the absence of comprehensive primary patient care that is typical of health care practice in the United States.

Lack of response to electronic alerts is therefore a symptom
Interestingly, e-prescribing is one of the strategies included for any clinical practice to implement, as presented in Table 1. Jenkins and Vaida describe a list of low-cost strategies feasible for any clinical practice to implement, as presented in Table 1. Interestingly, e-prescribing is one of the strategies included. However, other approaches, such as highlighting whether a patient has a diagnosis critical to medication selection, dosing, and frequency (i.e., diabetes, kidney disease, liver disease, mental illness) or is in receipt of a “high-alert” medication with known precautions (e.g., warfarin, insulin, opiates), may provide benefits similar to those of automated alerts. Importantly, many of these strategies involve enhanced communication within and across practices, something that is hard to argue with and would not be improved by automated message systems.

In conclusion, while it is well and good to highlight variation in prescriber practice and response to messages regarding inappropriate prescribing, true system change will require improvements in infrastructure and communication to reduce the likelihood of medication errors and correct such errors when they do occur.

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DISCLOSURES

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REFERENCES