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COVER IMPRESSIONS

About our cover artist

Where Words Go Once We Have Used Them (1999) ■ Hans Breiter, MD

Hans Breiter, MD, has been chosen as the winner of *JMCP*'s 2003 Annual Call for Entries. He is a psychiatrist and co-director of the Motivation Emotion Neuroscience Collaboration (MENC) at the Athinoula Martinos Center for Biomedical Imaging and Harvard Medical School, Massachusetts General Hospital, in Charlestown, Massachusetts. He is involved in the mapping of the circuitry of the human brain and how it translates into motivation, behavior, and emotion. He received both his bachelor of science and medical degrees from Northwestern University.

[These] disjointed letters form a symbolic "junkyard" of conversations already spoken.

Breiter has participated in many studies on human behavior and written numerous papers. According to *Popular Science*'s Web site, he "has recently published some of the most tangible evidence yet that certain pathological human behaviors travel the same biological pathways as addictive drugs. Using brain-imaging technology, Breiter demonstrated that gamblers at slot machines show increased blood flow in the same brain areas where cocaine produces a surge in dopamine—the transmitter that carries neural messages relating to pleasure and pain." In another study, "Beautiful Faces Trigger Reward Center of Brain," (from ABCNEWS.com), Breiter stated, "There are lots of myths that people have [surrounding] . . . beauty and attraction, and part of the issue is to stop thinking about things in terms of myth, but to use the tools of neuroscience, and start dissecting and understanding how things actually function."

Born and reared in Schenectady, New York, Breiter was introduced to art at an early age because his mother was an art teacher. One lesson he remembers quite vividly was the assignment to "draw what is beneath the cloth." For this lesson, his mother took various objects and draped cloth over them. He learned to draw using light and shadow to depict solid mass. Breiter later came to appreciate his early art training, and he now devotes much of his free time to painting. He has furthered his art education by enrolling in classes at the Museum of Fine Arts School in Boston. Most of his subjects contain text, although he also paints figures and abstracts. Breiter plans to launch his own Web site, called Art Without Walls, in the near future.

Breiter's 2003 showing of artwork at Newtonville Books, located just outside of Boston, consisted of (appropriately enough) his "word" art compositions. In his artist's statement for the installation, he wrote, "*Views of Well-Intentioned Words* is an installation juxtaposing text catalogued on the bookshelf, with words used purely as a visual enterprise. On these canvases and photo collages, you will observe a twisting and turning matrix of words. Some works refer to phrases from conversations, or psychotherapy sessions, swirling around each other in space to demonstrate the flow of emotion between individuals. Words, in this way, appear to loop around their speakers and form the emotional framework within which the speakers operate as physical entities."

In his painting, *Where Words Go Once We Have Used Them,* Breiter explained that his intention was to "paint emotion"—using the words that are spoken by all of us on a daily basis and subsequently appear to vanish into a void. These words, represented here as disjointed letters, form a symbolic "junkyard" of conversations already spoken. By composing a picture such as this, he has abstracted words into their components—letters—encouraging the viewer to appreciate the letters for their individual aesthetic shapes.

Breiter painted *Where Words Go Once We Have Used Them* over the course of a year, because his studio is located in an unheated barn on his property in Lincoln, Massachusetts, and the cold weather limited his painting time. The painting itself is quite large, "about the size of a door," he said. When asked to explain the process of executing this work, he said that he made a pile of unpainted wooden letters, and drew that image onto the canvas, adding the color to the letters afterward. He applied the color boldly, using lighter colors such as yellow to portray light cast upon a letterform, and darker colors such as navy blue to indicate depth and shadow. In addition to the primary colors, Breiter included a few unexpected colors in the painting, such as pink and lilac. He incorporated whole and partial letters in the composition, creating the illusion that the letters are endless in number, floating in an infinite universe.

It is clearly evident that Breiter's medical profession and artistic career share a common theme—human emotion.

Sheila Macho
JMCP Contributing Editor

COVER CREDIT

Hans Breiter, MD, *Where Words Go Once We Have Used Them*, acrylic, alkyd, graphite on canvas. Lincoln, Massachusetts. Copyright© 1999.

SOURCES

Interview with the artist.
http://www.popsci.com/popsci/medicine
http://abcnews.go.com/sections/living

Could *you* be *JMCP's* next cover artist?
To inquire, contact Sheila Macho at jmcpcoverart@amcp.org.

ORIGINAL RESEARCH

Acute Uncomplicated UTI and *E. coli* Resistance: Implications for First-Line Empirical Antibiotic Therapy

ELEANOR M. PERFETTO, PhD, MS; KAREN KEATING, RPT, MBA; SANJAY MERCHANT, MBA, PhD; and BRIAN R. NICHOLS, MS

ABSTRACT

BACKGROUND: Uncomplicated urinary tract infection (uUTI) typically affects immunocompetent, anatomically normal women. *Escherichia coli (E. coli)* accounts for approximately 80% of cases. Given increased *E. coli*-trimethoprim-sulfamethoxazole (TMP-SMX) resistance, practice guidelines advocate first-line alternatives based on local resistance rates above 10%. This paper provides a model incorporating use of a new extended-release formulation of ciprofloxacin, used once daily, to facilitate revision of uUTI treatment policies by managed care organizations (MCOs) and practitioners.

METHODS: A cost-minimization model was designed from the MCO perspective, assuming an initial office visit with a urinalysis and empiric, 3-day treatment (TMP-SMX 800/160 mg twice daily or ciprofloxacin XR 500 mg once daily). Persistent infections were assumed to require a second visit. Costs were provided by a major employee health and benefit plan provider; clinical data were based on published information. Five case scenarios were used to compare average treatment costs based on varying *E. coli* resistance rates to therapy and to identify rates of TMP-SMX resistance where total treatment costs are equal.

RESULTS: Using national surveillance resistance data, Case 1 demonstrated average cost savings of $9.59 to $10.21 with ciprofloxacin XR. In Case 2, treatment costs ($49.19) were equal at an *E. coli* resistance rate of 4.3% for TMP-SMX and 1.0% for ciprofloxacin. Case 3 assumed empiric telephone prescribing, demonstrating that, at 4.3% TMP-SMX resistance, costs are equal for both treatments ($4.19). Case 4 used real-world data on therapy duration, demonstrating that, at 2.8% TMP-SMX resistance, costs are equal for both treatments ($54.87). Case 5 assumed 10% ciprofloxacin-*E. coli* resistance; at 13.3% TMP-SMX resistance, treatment costs were equal ($57.50). Results from all cases demonstrate that while the per-dose cost of ciprofloxacin XR far exceeds TMP-SMX, average total treatment costs are lower for ciprofloxacin XR at expected local levels of *E. coli* resistance to TMP-SMX.

CONCLUSIONS: The results suggest that in areas where local TMP-SMX *E. coli* resistance exceeds 10% and resistance to ciprofloxacin remains low, (0.5% to 6%) ciprofloxacin XR is an appropriate alternative to standard empiric treatment. The data provide evidence to MCOs that switching to a more expensive per-dose alternative will not necessarily increase total costs when guideline recommendations are followed. Responsible use of antibiotics for uUTI requires selection and administration of the right dosage of the most suitable antibiotic for an appropriate time period to eliminate pathogens quickly and successfully. The decision to use an alternative first-line therapy for uUTI should be driven by local resistance and susceptibility data—not simply per-dose drug acquisition costs.

KEYWORDS: Acute cystitis; Urinary tract infection, uncomplicated; Bacterial resistance; *E. coli* resistance; Antibiotic therapy; Fluoroquinolones; Ciprofloxacin; Trimethoprim/sulfamethoxazole; Cost-effectiveness

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Urinary tract infection (UTI) is the most common kidney and urologic disease in the United States.[1] UTIs affect approximately 8 million American women and account for approximately the same number of ambulatory care visits per year, making it one of the most common conditions encountered by clinicians.[1-3] UTIs account for more than 100,000 hospital admissions, presumably from acute pyelonephritis.[1] It is estimated that 11% of women report at least 1 physician-diagnosed UTI per year, and between 40% and 50% of women report at least 1 UTI in their lifetimes.[2,4] Uncomplicated UTI (uUTI) typically affects young women who are immunocompetent and have anatomically normal physiology.[5] The most common clinical manifestation is painful urination stemming from uncomplicated urethritis or cystitis.[6]

In addition to the tremendous personal and public health burden, the financial costs associated with UTI are significant. Direct costs are estimated to be more than $1 billion per year.[7] Additional costs stem from lost productivity and reduced quality of life. An epidemiologic study found that a UTI episode prior to treatment with an antibiotic accounts for 6.1 symptom days, 2.4 days of restricted activity, and 1.2 days away from school or work.[4]

The spectrum of causative pathogens for uUTI is well known. *Escherichia coli (E. coli)* is the most common, accounting for approximately 80% of cases. *Staphylococcus saprophyticus (S. saprophyticus)* is the second most common pathogen, accounting for another 5% to 15% of cases.[8-13] A 5-year, cross-sectional survey of antimicrobial susceptibilities in health maintenance organization-enrolled women (aged 18 to 50 years) with acute cystitis, found that *E. coli* and *S. saprophyticus* accounted for 90% of urine isolates studied.[9]

Until recently, the empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) for uUTI was based on the high

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TABLE 1 2001 U.S. Susceptibility Profile for Uncomplicated Urinary Tract Infection in Women of All Ages (38 states reporting)

State	Number of Isolates	TMP-SMX* % Resistant	Ciprofloxacin % Resistant
Alaska	90	17.78	1.11
Alabama	23	13.04	4.35
Arkansas	51	31.37	0.00
California	788	20.81	2.28
Colorado	133	18.80	0.00
DC	34	17.65	0.00
Delaware	1	0.00	0.00
Florida	1,455	15.40	1.51
Hawaii	231	36.36	1.30
Illinois	270	13.70	1.11
Indiana	156	12.18	1.92
Kansas	1,207	14.00	0.50
Kentucky	204	21.08	0.49
Louisiana	610	15.90	0.33
Massachusetts	157	16.56	1.27
Maryland	11	27.27	27.27
Michigan	4,000	11.30	0.75
Minnesota	44	18.18	2.27
Missouri	331	12.39	1.51
North Carolina	41	12.20	0.00
North Dakota	165	16.36	0.00
Nebraska	124	11.29	0.00
New Jersey	205	10.24	0.98
New Mexico	4,450	17.08	0.65
Nevada	1	0.00	0.00
New York	504	18.65	1.59
Ohio	1,698	9.60	1.06
Oklahoma	275	16.73	2.18
Oregon	1,212	21.62	1.32
Pennsylvania	966	12.42	0.21
South Carolina	104	6.73	0.96
Tennessee	1	100.00	100.00
Texas	324	22.53	4.94
Utah	159	22.01	0.63
Vermont	13	30.77	0.00
Washington	2,592	15.16	1.08
Wisconsin	510	21.96	2.16
West Virginia	378	7.94	0.53
Total	**23,518**	**15.31**	**1.03**

Source: The Surveillance Network, Focus Technologies, 2001.
**TMP-SMX = trimethoprim/sulfamethoxazole.*

level of certainty surrounding both the distribution of causative pathogens involved and the susceptibility patterns of these pathogens.[10] While there is little evidence to suggest that the distribution of causative pathogens has changed appreciably, there are ample data to suggest that resistance to TMP-SMX has risen significantly. Salient risk factors for TMP-SMX resistance include previous exposure to TMP-SMX and other antibiotics.[10,14,15]

The results of several individual studies suggest that TMP-SMX resistance approaches or exceeds 20% in many parts of the United States.[16,17] In a cross-sectional study conducted by Gupta et al., *E. coli* resistance to TMP-SMX increased from 9% in 1992 to 18% in 1996.[9] Similarly, a retrospective cohort study of women with acute cystitis seen at a university health center and primary care clinics showed that the prevalence of TMP-SMX resistance increased significantly ($P = 0.01$) from 8.1% in 1992 to 15.8% in 1999.[14] Recently, one managed care organization (MCO) in California reported a 38% TMP-SMX *E. coli* resistance rate.[18]

Given the marked increase in *E. coli*-TMP-SMX resistance occurring over the last decade, authoritative medical bodies have released evidence-based guidelines advocating a change in first-line therapy of uUTIs based specifically on local resistance rates. The Infectious Diseases Society of America (IDSA) recommends that alternatives to TMP-SMX should be used in communities where resistance rates exceed 10% to 20%.[1] Others have recommended that the threshold level of resistance for abandoning TMP-SMX as a first-line therapy for uUTI should be even lower than the range proposed by IDSA.[19] In addition, the Sanford Guide specifically recommends ciprofloxacin as a treatment alternative in areas of high TMP-SMX resistance.[20]

Resistance patterns are known to vary geographically. To develop guidelines to inform the practice of a particular provider, local data on TMP-SMX resistance data are needed. The Surveillance Network (TSN; MRL, Herndon, VA), a nationwide effort to pool susceptibility data from laboratories across the United States, provides information to clinicians regarding resistance rates in their geographic region of practice.[10] In 2001, there were 270 participating laboratories, up from 43 in 1995.[21] As shown in Table 1, data from the participating 38 states indicate that the average TMP-SMX resistance rate for uUTI specifically was 15.31% in 2001.[22] Table 2 shows resistance rates from another analysis of TSN data in which a broader definition of UTI was used.[21]

The availability of local TMP-SMX resistance data, coupled with the advent of guidelines recommending the use of these data to select the most appropriate first-line therapy for uUTI, means that most MCOs must now determine the level of community resistance at which their current empirical-treatment policies should be modified. They should identify the point at which first-line empirical treatment with TMP-SMX is no longer the most clinically appropriate and cost-effective approach.

To assist managed care professionals in this decision, a number of models have been published addressing the cost-effectiveness of TMP-SMX versus fluoroquinolones at various levels of TMP-SMX-*E. coli* resistance. Le and Miller (2001) found the threshold resistance rate for a switch to a fluoroquinolone was 22%.[23] In a second model, Perfetto and Gondek (2002) identified a threshold TMP-SMX resistance rate between 19% to 21% and included copayments (ranging from $5 to $20) for office visits and prescription drugs.[24] These models, as well as others,[17,18,25,26] demonstrated that, while cost per dose was higher among fluoroquinolone patients, the lower rate of resistance in

these patients rendered this drug more cost effective in average total treatment costs. The models identified the significant cost factors—the direct drug cost of the fluoroquinolone alternative and follow-up care required after a treatment failure occurs.

This paper provides an important update to assumptions used in previously reported analyses to aid MCOs and physician leaders in the formulation of treatment policies pertaining to uUTI in light of rising *E. coli* resistance. The model incorporates the use of a new formulation of ciprofloxacin extended-release tablet (Cipro XR), given in 3 single 500 mg doses across 3 days. Since the cost of the fluoroquinolone was identified as a cost driver in previous models, it was hypothesized that the new formulation would lower the total cost for treatment and decrease the threshold rate of TMP-SMX-*E. coli* resistance at which the alternative becomes cost effective.

Methods

Model Perspective

Using a Microsoft Excel spreadsheet, a cost-minimization model was designed from the perspective of an MCO. The structure of the model, in which empiric TMP-SMX was compared with empiric ciprofloxacin XR for the treatment of uUTI, is depicted in Figure 1. Five clinical scenarios are analyzed, including 2 base cases using national averages for *E. coli* resistance, a financial break-even assessment, the use of a telephone treatment protocol, and a worst-case scenario for ciprofloxacin resistance. An effort has been made to provide MCOs with an easy-to-use and transparent model that can be customized to reflect their unique set of clinical and economic conditions.

Model Assumptions

Consistent with a similar model developed by Le and Miller (2001),[23] the model assumed an initial office visit that included an in-office urinalysis but no culture and sensitivity testing. Each initial empiric treatment was given over a period of 3 days, after which all infections were either cured or persistent. As recommended, double-strength TMP-SMX was used twice daily and ciprofloxacin XR was used once daily. Persistent infections were assumed to require a second visit either back to the physician's office or to an emergency room (ER). This return visit was assumed to include a second urinalysis, an initial urine culture and sensitivity test sent to a lab, and a successful 7-day regimen of another antibiotic.

Cost Data

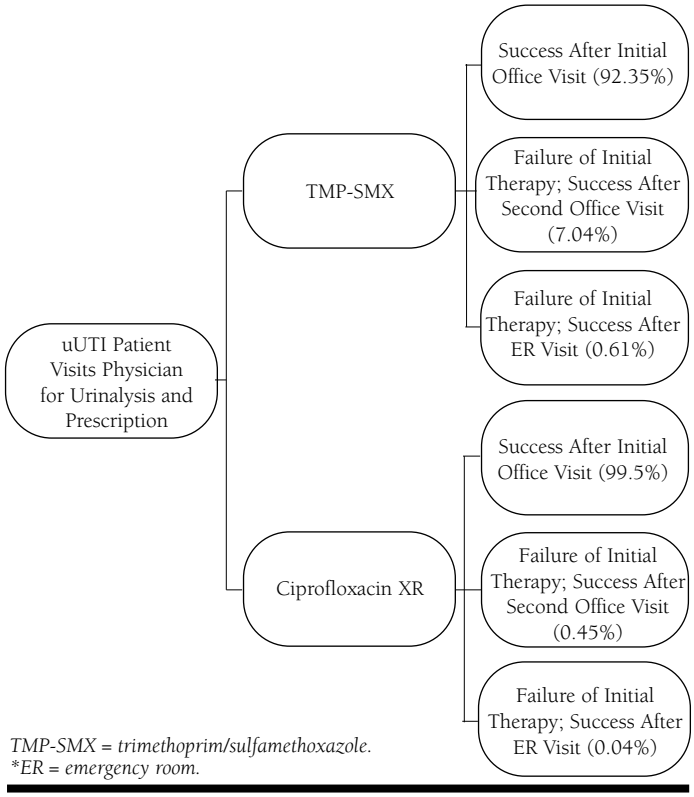
The model incorporates only direct medical costs paid by the MCO or insurer. The cost-related parameters used in the model (Table 3) were derived from reimbursement amounts provided by a major employee health and benefit plan provider (HBPP) based in the mid-Atlantic region of the United States. Using its claims databases, the HBPP reported the range of reimbursements paid, based upon the most common ICD-9 codes for

TABLE 2 2001 U.S. Susceptibility Profile for *E. coli* Urinary Tract Infection Isolates Among Outpatient Women of All Ages

U.S. Census Bureau Region	TMP-SMX* % Resistant	Ciprofloxacin % Resistant
New England (ME, NH, VT, MA, RI, CT)	13.9	1.9
Mid-Atlantic (NY, NJ, PA)	12.7	2.3
South Atlantic (DE, MD, DC, VA, WV, NC, SC, GA, FL)	15.9	6.0
East North Central (OH, IN, IL, MI, WI)	11.8	1.8
East South Central (KY, TN, AL, MS)	17.7	2.0
West North Central (MN, IA, MO, ND, SD, NE, KS)	13.7	1.3
West South Central (AR, LA, OK, TX)	21.8	3.2
Mountain (MT, ID, WY, CO, NM, AZ, UT, NV)	18.3	2.0
Pacific (WA, OR, CA, AK, HI)	20.3	2.3
Nationwide average	**16.1**	**2.5**

Source: Karlowsky et al. 2002.
**TMP-SMX = trimethoprim/sulfamethoxazole.*

FIGURE 1 Flow Chart of Treatments and Outomes Incorporated in Model



TMP-SMX = trimethoprim/sulfamethoxazole.
**ER = emergency room.*

TABLE 3 Medical Care Resource Costs Utilized in an Uncomplicated Urinary Tract Infection Treatment Model

Resource	Cost ($)	Copayment ($)	Final MCO Cost After Copayment ($)
Generic TMP-SMX* 800 mg/160 mg bid for 3 days	5.21	5.00	0.21
Ciprofloxacin XR for 3 days	18.23	15.00	3.23
Office visit—physician fee	60.00	20.00	40.00
Urinalysis—physician fee	5.00	0.00	5.00
Urinalysis—physician office processing fee†	5.00	0.00	5.00
Laboratory fee—urinalysis	35.00	0.00	35.00
Laboratory fee—culture and sensitivity	70.00	0.00	70.00
Emergency department visit	145.00	50.00	95.00
Emergency department lab fees—urinalysis	80.00	0.00	80.00
Emergency department lab fees—culture and sensitivity	120.00	0.00	120.00
Second drug for 7 days	38.87	15.00	23.87

** TMP-SMX = trimethoprim/sulfamethoxazole.*

† Fee paid to the physician's office for processing samples that are sent to an outside laboratory.

The most common ICD-9 codes for uncomplicated UTI visits were used to estimate costs (ICD-9 595.000-595.910, 599.000-599.030, 753.100-753.190).

uncomplicated UTI visits (ICD-9 595.000-595.910, 599.000-599.030, 753.100-753.190). To be conservative, the lowest value of each range was selected and rounded to the nearest dollar. The insurer also reported the most common copayment amounts of the health plans it offers. These are typical copayments, not the copayments reported by the insurer. The assumed reimbursement costs as paid by this insurer are reported in Table 3. These estimated costs were based upon those most typically paid by the insurer since the ranges were wide.

As shown in Table 3, the model also incorporated a copayment of $20 for office visits, $5 for a generic TMP-SMX prescription, and $15 for a brand-name prescription. Prescription reimbursements were entered as reported by the HBPP and not rounded. The second drug, used after a failure of either ciprofloxacin or TMP-SMX, was assumed to be a branded product at equal per-dose cost as ciprofloxacin XR and prescribed once daily for 7 days.

This model compares the economic impact of prescribing extended release ciprofloxacin versus generic TMP-SMX. Generic ciprofloxacin (250 mg given twice per day) was not considered because the payer's cost per treated patient was calculated to be $27.45, which is considerably higher than both the brand-name ciprofloxacin XR ($3.23) and generic TMP-SMX ($0.21).

Clinical Data

Clinical success and failure probabilities incorporated in the model were derived from literature sources. The failure rate among TMP-SMX-resistant patients treated with TMP-SMX was estimated to be 50%.[27] Because a similar failure rate for ciprofloxacin resistance could not be identified in the literature, a rate of 50% was assumed, as has been used in previous models.[23] Consistent with a similar model developed by Le and Miller (2001), it was assumed that all TMP-SMX-susceptible infections treated with TMP-SMX and all ciprofloxacin-susceptible infections treated with ciprofloxacin XR were cured.

Among those who fail first-line therapy, it was assumed that 8% would seek further care in an ER and the remaining 92% of patients would return to their physician's office. This is based on data from a study published by the Centers for Disease Control and Prevention that stratified the number of ambulatory care visits in 1997 by diagnosis and setting of care.[28] During that year, there were 2.675 million visits due to cystitis; 261,000 (9.8%) were treated in an ER. Given that a portion of these episodes were likely to be initial visits, an estimate of 8% was used in the model for the second visit. No ER visits were assumed for initial therapy in a conservative estimate of initial costs.

Resistance Rates

Data on TMP-SMX and ciprofloxacin *E. coli* resistance rates were obtained from TSN (Tables 1 and 2). In Table 1, the average resistance rates from the 38 states reporting for uUTI isolates were 15.31% and 1.03% for TMP-SMX and ciprofloxacin, respectively. In Table 2, the average rates for UTI, more broadly defined, were 16.1% and 2.5%, respectively.

Outcomes of Interest

Costs from each of the 3 possible treatment paths (initial success, failure requiring second office visit, and failure requiring ER visit) were summed to calculate an average treatment cost for both TMP-SMX and ciprofloxacin XR treatment groups. The formula below is used to compare average costs based on resistance rates and also to determine the threshold TMP-SMX-*E. coli* resistance rate at which total average costs become equal for both treatment groups:

Average treatment cost per group =

$$[(1 - (R * F)) * CS] + [(R * F * (1 - F_{ER})) * CF_{No\ ER}] + [(R * F * F_{ER}) * CF_{ER}]$$

where,

R = rate of local antibiotic resistance

F = rate of clinical failure due to resistance

F_{ER} = percentage of failures that result in ER visit for treatment

CS = cost of treatment success

$CF_{No\ ER}$ = cost of treatment failure without an ER visit

CF_{ER} = cost of treatment failure with an ER visit

TABLE 4 Case Scenarios Demonstrating Use of the Model—Calculation of Threshold TMP-SMX-*E. coli* Resistance Rate and Resulting Treatment Costs

	TMP-SMX*			Ciprofloxacin XR		
	Success	Failure		Success	Failure	
		Without ER†	With ER†		Without ER†	With ER†
Case 1a: Base case that uses resistance rates from Table 1 (2001 data from 38 states reporting to The Surveillance Network, Focus Technologies; 15.3% for TMP-SMX and 1.0% for ciprofloxacin)						
Treatment cost	$45.21	$219.08	$364.08	$48.23	$222.10	$367.10
Average total treatment cost	$59.40			$49.19		
Resistance rate	15.3%			1.0%		
Case 1b: Base case that uses resistance rates from Table 2 (regional 2001 data from Karlowsky et al. 2002; 16.1% for TMP-SMX and 2.5% for ciprofloxacin)						
Treatment cost	$45.21	$219.08	$364.08	$48.23	$222.10	$367.10
Average total treatment cost	$60.14			$50.55		
Resistance rate	16.1%			2.5%		
Case 2: Break-even analysis: If ciprofloxacin resistance is held constant at 1%, at what TMP-SMX resistance rate does the average total cost reach equality for both treatments?						
Treatment cost	$45.21	$219.08	$364.08	$48.23	$222.10	$367.10
Average total treatment cost	$49.19			$49.19		
Resistance rate	4.3%			1.0%		
Case 3: Effect of a telephone-based empirical prescribing protocol for uUTI on average total treatment costs						
Treatment cost	$0.21	$174.08	$319.08	$3.23	$177.10	$322.10
Average total treatment cost	$4.19			$4.19		
Resistance rate	4.3%			1.0%		
Case 4: Cost based on reported average duration of use data from Versipan (11.6 days for TMP-SMX and 4.1 days for ciprofloxacin)						
Treatment cost	$52.26	$226.13	$371.13	$53.91	$227.78	$372.78
Average total treatment cost	$54.87			$54.87		
Resistance rate	2.8%			1.0%		
Case 5: The TMP-SMX resistance rate that needs to be exceeded before ciprofloxacin becomes more cost effective in a "worst-case scenario," whereby ciprofloxacin XR resistance reaches 10%						
Treatment cost	$45.21	$219.08	$364.08	$48.23	$222.10	$367.10
Average total treatment cost	$57.50			$57.50		
Resistance rate	13.3%			10.0%		

** TMP-SMX = trimethoprim/sulfamethoxazole. †ER = emergency room.*

Case Scenarios

Case 1a is considered the base case and incorporated national average resistance rates for uUTI for both TMP-SMX (15.31%) and ciprofloxacin (1.03%) (Table 1).[22] Case 1b incorporated the national average resistance rates for UTI (Table 2).[21] Case 2 is considered the "break-even" case. The threshold local TMP-SMX-*E. coli* resistance rate was identified by holding constant the resistance rate for ciprofloxacin XR cited in Case 1a while adjusting the local TMP-SMX-*E. coli* resistance rate until the average total treatment cost for each group was equal.

Since many MCOs may encourage minimal laboratory testing and empiric antibiotic prescribing by telephone,[7,29] Case 3 is a modification of Case 1a to reflect telephone prescribing for all (100%) cases, which obviates the need for an initial office visit and initial urinalysis. Case 4 uses data reported on the average duration of therapy for each antibiotic for treating uUTI.[30] The average durations of 11.6 days for TMP-SMX and 4.1 days for ciprofloxacin XR were applied to Case 1a. Finally, Case 5 uses a 10% rate of ciprofloxacin resistance as a worst-case scenario—10 times the best estimate available for the nationwide average resistance to ciprofloxacin in uUTI shown in Table 1. Again, the 10% rate was applied to Case 1a.

Results

The results are presented in Table 4. In Case 1a, the base case, using national averages for resistance given in Table 1, the aver-

age treatment cost for TMP-SMX ($59.40) exceeded that of ciprofloxacin XR ($49.19) by $10.21. Using 2002 resistance data from Karlowsky et al.,[21] Case 1b shows that the average treatment cost for TMP-SMX ($60.14) exceeded that of ciprofloxacin ($50.55) by $9.59 (19%).

For Case 2, the break-even point, an average cost of $49.19 for both therapies is reached when the threshold resistance rate of TMP-SMX is 4.3% and the ciprofloxacin resistance rate is 1.0%. Case 3 included no costs for initial office visits or urinalysis, assuming that empirical prescribing was done by telephone. Here, the resistance threshold is also 4.3%, and the average cost per patient at the break-even point drops dramatically to $4.19 for both treatments. Case 4 utilized real-world data reported on average actual duration of these specific therapies in uUTI. In this scenario, the threshold rate of TMP-SMX resistance was 2.8% to achieve equal average costs at $54.87. To test the influence of a "worst-case" scenario for fluoroquinolone resistance, Case 1a was modified in Case 5 to include a 10% local ciprofloxacin-*E. coli* resistance rate. This change increased the TMP-SMX resistance threshold rate to 13.3% to reach an average cost of $57.50 for both groups.

Discussion

This study utilized straightforward clinical assumptions for uUTI. (e.g., cystitis) to demonstrate the treatment and cost implications of increased resistance by *E. coli* to TMP-SMX. It compares typical empirical treatment with double-strength TMP-SMX to ciprofloxacin XR, a new extended-release formulation of ciprofloxacin. The results demonstrate that, while the per-dose cost of the ciprofloxacin XR exceeds the per-dose cost of the TMP-SMX, the net plan costs per *course of therapy*, after accounting for copays, network discounts, and dispensing fees are similar for the 2 drugs (TMP-SMX $0.21 versus ciprofloxacin XR $3.23). Furthermore, at the expected local levels of *E.coli* resistance to TMP-SMX and current levels of ciprofloxacin resistance, the average total treatment costs are actually lower for ciprofloxacin XR.

Results for cases 1a and 1b (Table 4) demonstrate that, at the average rate of *E. coli*-TMP-SMX resistance in the United States, cost savings are achieved using ciprofloxacin XR. Even when using the more conservative national estimates presented by Karlowsky et al. (2002), which may include various types of UTI and not just uUTI, a considerable per-patient cost saving ($9.59) is achieved on average. In Case 2, the TMP-SMX-*E. coli* resistance rate was adjusted until the average total cost for each treatment group was equal. When local *E. coli* resistance rates are below this threshold, the "break-even" point, total cost of therapy for TMP-SMX is less than that of ciprofloxacin XR. When resistance rates reach or exceed the threshold, use of fluoroquinolones becomes cost effective. Case 2 demonstrates that, at *E. coli*-TMP-SMX resistance rates as low as 4.3%, the total average costs would be equal between TMP-SMX and ciprofloxacin XR. At resistance rates higher than 4.3%, the total cost of care for the ciprofloxacin XR group is lower than for TMP-SMX. This case provides reassurance to MCO decision makers that use of the product with higher per-dose costs can be less costly and more effective when resistance rates are considered.

Even if Case 2 assumptions are modified so that one half of all return visits involved urine culture and sensitivity testing and one half of the second courses of antibiotics were handled by telephone prescribing without a second visit and additional medical costs, an average cost of $38.77 for both therapies is reached when the resistance rate of TMP-SMX is 6.8% and the ciprofloxacin resistance rate is 1.0%. Similarly, lowering the office copay in the model to $10 serves only to increase the average total cost for treatment to the MCO by $10. The total average treatment cost increases from $49.19 to $59.23, a difference of $10.04. In this scenario, the threshold TMP-SMX resistance rate drops from 4.3% to 4.1%—a negligible change.

Very low per-patient treatment costs can be achieved by MCOs that have adopted treatment protocols allowing for empiric prescribing by telephone for cystitis. Case 3 suggests that these costs can be as low as $4.19 on average. The threshold *E. coli* resistance rate remains at 4.3% in this case. Even with a substantial reduction in health care service use, this case again demonstrates that the product with higher per-dose costs can be less costly and more effective when resistance rates are considered. When the national average TMP-SMX resistance rate of 15.3% is used in this case, the cost per case for TMP-SMX increases to an average of $14.40 (data not shown) as compared with $4.19 for ciprofloxacin XR.

The recommended duration of empirical therapy—3 days—was used in the base case (Cases 1a and 1b). However, some clinicians may suspect that these recommendations are not always followed. For Case 4, drug costs were adjusted to account for the average number of days of therapy identified in a claims database that included recent information for the new extended-release formulation of ciprofloxacin.[30] When the real-world, average durations of use in uUTI are used (11.6 days for TMP-SMX and 4.1 days for ciprofloxacin XR), the TMP-SMX resistance threshold drops to 2.8% to achieve equal cost for both groups. The per-patient cost for ciprofloxacin XR treatment increased from $3.23 to $8.91, a difference of $5.68. However, the per-patient cost of TMP-SMX increased from $0.21 to $7.26, a difference of $7.05.

Case 5 presents the worst-case scenario for ciprofloxacin resistance, using a rate of 10% in comparison with its current national average of 1% in uUTI patients. Le and Miller also used 10% as an extreme estimate of ciprofloxacin resistance.[23] It is unlikely that any geographic region in the United States will observe such an increase any time soon. This model demonstrates that treatment costs would be the same for both groups if the TMP-SMX resistance rate was 13.3%. A TMP-SMX resistance higher than 13.3% would therefore result in cost savings with use

of ciprofloxacin XR, even at a 10% ciprofloxacin resistance rate.

The model reflects the perspective of the MCO or insurer, after subtraction of copayment (out-of-pocket) costs paid by MCO members. Patients will have to pay a higher copayment in most plans for brand versus generic drugs. This may mean an out-of-pocket cost difference of $10 or more. Some patients may resist paying the higher copayment and request the generic alternative. The health care provider must consider the risk that a patient may not have a prescription filled if the differences are considerable. The MCO or insurer may want to consider waiving the brand-level copayment in this type of clinical scenario. For example, in Case 1a, when the copayment for the patient is reduced to $5.00 for the brand-name ciprofloxacin XR and the second drug, increasing their costs by $10 each, the ciprofloxacin XR group still maintains a $0.93 per-patient average cost advantage over TMP-SMX, with the TMP-SMX resistance rate at 15.3% and the ciprofloxacin resistance rate at 1.0%.

Comparisons With Similar Models

The model presented here has both similarities and differences with past models. This model is simplified to exclude consideration of yeast infections and hospitalization for pyelonephritis. However, the results of Le and Miller (2001) demonstrate that these very low probability events have little impact on total average costs. The models by Le and Miller (2001) and by Perfetto and Gondek (2002) reported a 19% to 22% TMP-SMX *E. coli* resistance threshold range for ciprofloxacin cost-effectiveness to be achieved.[23,24] The thresholds reported in this study are much lower. However, the findings here are consistent with those in previous models in that both reported that the most significant cost drivers were the costs for the fluoroquinolone and for the follow-up physician office visits. Both of these cost drivers are lower in the current model than in past models. The daily cost of ciprofloxacin XR is less than that of ciprofloxacin immediate-release tablets. The cost for the office visit is lower since it is actual reimbursement data from an HBPP and not derived from the literature as was done in previous models.[23,24] Also, past models assumed that a small percentage of failures would go on to hospitalization for pyelonephritis. However, this would account for only a small amount of the differences found. It is important to note that when the health care costs from this study are applied to the Perfetto and Gondek (2002) model, the 19% threshold reported in that study drops to 5.8%, closer to the findings reported here and demonstrating the significant impact of the cost assumptions.

Another previously reported model used prospective data from a randomized clinical trial of elderly women with acute UTI in which ciprofloxacin (250 mg twice daily) was compared with TMP-SMX (160 mg/800 mg twice per day). Of the 261 patients enrolled in the study, 172 (66%) met the criteria to be included in the efficacy analysis (e.g., no protocol violations, no missing data, not lost to follow-up, etc.). For these patients, clinical resolution was achieved in 97% versus 85% of the ciprofloxacin and TMP-SMX groups, respectively. While cost per cure was higher ($98.68 for ciprofloxacin versus $86.17 for TMP-SMX), the differential in the incidence of antimicrobial resistance between groups (1.2% versus 11.2%) rendered ciprofloxacin more cost effective ($64 versus $87, respectively) in terms of average total treatment costs.[26] It should be noted that 1996 Medicare MEDPAR data and 1996 average wholesale drug price data were used to calculate cost in their model, which would not reflect the costs for most managed care providers for younger, more typical cystitis patients today.

Implications for Managed Care Organizations

These cases demonstrate how MCOs can utilize resistance data when making decisions related to formulary management and antibiotic treatment policies. An important point to be stressed is that these data should not be used to suggest that fluoroquinolones be used as the first-line empiric choice at lower rates of TMP-SMX-*E. coli* resistance. This could result in an entirely new spectrum of resistance issues as resistance to fluoroquinolones would begin to increase. Instead, the data should be used to provide assurance to decision makers that switching to a more expensive per-dose alternative at the IDSA-recommended levels of TMP-SMX resistance (greater than 10% to 20%) will not increase costs and may lower the total cost of care. The data offer assurance that a provider can achieve better outcomes at lower costs using local resistance-rate data and clinical guidelines. Responsible use of antibiotics for uUTI requires the selection and administration of the most suitable antibiotic at the right dosage for an appropriate period of time in order to eliminate pathogens quickly and successfully. Therefore, the decision to use an alternative first-line therapy for uUTI should be driven by local resistance and susceptibility data—not drug acquisition costs alone.

Implications for Clinicians

Use of these models implies that local resistance rates are known by clinicians and are being weighed in clinical decision making. Some providers may not give appropriate consideration to resistance rates. They may question: "How large a problem is this?" Given that concentrations of TMP-SMX, as well as most antimicrobials, reach high levels in the urine, many may believe that clinical resolution will be likely despite isolate resistance. Some may not know what percentage of TMP-SMX-treated cases go on to clinical failure when the *E. coli* is resistant. Many clinicians do know that TMP-SMX is an inexpensive alternative and may always try it first, using a fluoroquinolone second-line, only if needed for failures.

Clearly, the data provided through TSN demonstrate the magnitude of the TMP-SMX-*E. coli* resistance problem. Of the 38 states reporting isolates (Table 1), one quarter report TMP-SMX resistance rates of 20% or greater. Approximately half

report rates higher than 15%. The model demonstrated through the case scenarios in this study can help a provider understand the implications of failing to respond to increasing *E. coli* resistance rates and the costs involved.

This means that health care providers, especially primary care physicians, nurse practitioners, physician assistants, and pharmacists must be educated and knowledgeable with regard to pathogen resistance and susceptibility in their geographic area of practice. They must understand the implications of resistance in clinical decision making, formulary selections, and treatment protocol applications. However, it has become difficult for some organizations to have a clear understanding of what their own resistance rates are due to the rise in empiric treatment and a decline in the acquisition of urine cultures and sensitivities in uncomplicated cases. Managed care cost-containment efforts, which may result in a reduction in urine culture laboratory orders for uncomplicated cases, may be contributing to an increasing scarcity of outpatient resistance rate data.[29] This may impact the monitoring of resistance and failure rates in the future. MCOs may need to conduct more internal surveillance in order to better understand resistance and its implications in their own, eligible populations. In the absence of specific internal data on resistance, inpatient *E. coli* susceptibility data for uUTI is a reasonable basis for decision making.[9]

Practitioners must also be concerned about rising fluoroquinolone resistance. As indicated in Tables 1 and 2, national rates for ciprofloxacin-*E. coli* resistance range from 1.03% to 2.5% on average. Other authors have indicated rates as low as .5%, and isolated areas of the country have reported rates as high as 6%.[21,23] While these rates remain low, practitioners must be mindful of the implications of increasing bacterial resistance. Following guidelines and monitoring local resistance rates must become a routine part of clinical practice to keep resistance in check.

Patients may prefer once-per-day dosing. Convenient and short-course dosing can enhance patient compliance, which can result in increased effectiveness.[19,31] It must also be considered that the model does not account for any of these kinds of differences between therapies (e.g., increased effectiveness due to better compliance, therapeutic effectiveness).

Limitations

It is important to note the limitations of any modeling exercise. The clinical assumptions and costs used in this model were derived from various sources and may not reflect the actual situation for any specific MCO. It is important that each organization use its own local resistance rates, clinical parameters, cost data, and copayments to derive meaningful information that can guide clinical decision making in a given health system.

Also, two primary objections have been noted regarding the use of publicly available resistance data to determine whether TMP-SMX is the most appropriate first-line therapy for uUTIs. First, some argue that the resistance data in these databases historically pertain to isolates from hospitalized patients instead of community pathogens. However, several studies have found no differences between pathogens isolated from these 2 patient populations.[9] Second, there is a concern that microbiological resistance may not translate to adverse clinical outcomes.[15,32] However, a growing body of literature indicates that this objection to the use of surveillance data may also be unfounded. Specifically, resistant *E. coli* has been shown to have a greater likelihood of treatment failure.[10,11,16,27,33] That is, a 50% clinical failure rate is expected for UTI patients with TMP-SMX-resistant uropathogens who are treated with TMP-SMX.

It should be noted that the model described in this study compares ciprofloxacin XR with 1 therapeutic alternative. Other common first-line therapies such as nitrofurantoin or second-line agents such as cephalexin were not considered.

Conclusions

A straightforward economic model was used to compare empiric antibiotic therapies for uncomplicated urinary tract infections. Standard empiric therapy, double-strength TMP-SMX administered twice daily for 3 days, was compared with a new option, ciprofloxacin XR administered once daily for 3 days. The model demonstrated that, when using costs typical of an MCO and national estimates of resistance, the total average cost for ciprofloxacin XR-treated patients is less than that of TMP-SMX-treated patients. It can be concluded that ciprofloxacin XR is an appropriate alternative to standard empiric treatment in areas where local *E. coli* resistance to TMP-SMX exceeds guideline-recommended levels.

Local resistance-rate data can provide assurance to MCO decision makers that switching to a more expensive per-dose alternative at the IDSA-recommended levels of resistance (greater than 10% to 20%) will not increase costs and may lower the total cost of care. The data offer assurance that a provider can achieve better outcomes at lower costs using local resistance rates and clinical guidelines.

The decision to use an alternative first-line therapy for uUTI should not be made based on drug acquisition costs alone. Local resistance and susceptibility data should be factored into this decision making. Accordingly, efforts should be focused on improving the availability of local susceptibility data to clinicians to help guide patient care.

DISCLOSURES

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REFERENCES

1. Warren JW. Practice guidelines for the treatment of uncomplicated cystitis. *Curr Urol Rep.* 2001;2:326-29.

2. Jancel T, Dudas V. Management of uncomplicated urinary tract infections. *West J Med.* 2002;176:51-55.

3. Garrison J, Hooton TH. Fluoroquinolones in the treatment of acute uncomplicated urinary tract infections in adult women. *Expert Opin Pharmacother.* 2001;2(8):1227-37.

4. Foxman B, Barlow R, H D'Arcy, et al. Urinary tract infections: self-reported incidence and associated costs. *Ann Epidemiol.* 2000;10:509-15.

5. Wallach FR. Update on treatment of pneumonia, influenza, and urinary tract infections. *Geriatrics.* 2001;56(Sept):43-47.

6. Centers for Disease Control, Division of Bacterial and Mycotic Diseases. Urinary tract infections, technical information. Available at: http://www.cdc.gov/ncidod/dbmd/diseaseinfo/urinarytractinfections_t.htm. Accessed May 13, 2003.

7. Barry HC, Hickner J, Ebell MH, Ettenhofer T. A randomized controlled trial of telephone management of suspected urinary tract infections in women. *J Fam Pract.* 2001;50:589-94.

8. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Dis Mon.* 2003;49:71-82.

9. Gupta KA, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA.* 1999;281:736-38.

10. Gupta K. Addressing antibiotic resistance. *Am J Med.* 2002;113:29S-34S.

11. Noskin GA, Zembower T, Chmielewski J, Tang P, La Rosa M, Peterson LR. Disappearance of the 'uncomplicated' urinary tract infection. *Clin Drug Invest.* 2001;21(suppl):13-20.

12. Zhanel GG, Karlowski JA, Harding GKM, et al. A Canadian national surveillance study of urinary tract isolates from outpatients: comparison of activities of trimethoprim-sulfamethoxazole, ampicillin, mecillinam, nitrofurantoin, and ciprofloxacin. *Antimicrob Agents Chemother.* 2000;44(4):1089-92.

13. Dyer IE, Sankary TM, Dawson J. Antibiotic resistance in bacterial urinary tract infections, 1991 to 1997. *West J Med.* 1998;169:265-68.

14. Brown PD, Freeman A, Foxman B. Prevalence and predictors of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* isolates in Michigan. *Clin Infect Dis.* 2002;34:1061-66.

15. Davey P, Steinke D, MacDonald T, Phillips G, Sullivan F. Not so simple cystitis: how should prescribers be supported to make informed decisions about the increasing prevalence of infections caused by drug-resistant bacteria? *Br J Gen Pract.* 2000;50:143-46.

16. Stamm WE. An epidemic of urinary tract infections? *N Engl J Med.* 2001;345(14):1055-57.

17. Seifert R, Weinstein DM, Li-McLeod J. National prevalence of *E. coli* resistance to trimethoprim-sulfamethoxazole: managed care implications in the treatment of urinary tract infections. *J Manag Care Pharm.* 2001;7(2):132.

18. Seifert R, DeRouin D. An economic assessment of the impact of *E. coli* resistance to trimethoprim-sulfamethoxazole in the treatment of urinary tract infection. Poster presented at: ISPOR 7th Annual International Meeting; May 2002; Arlington, VA.

19. Naber KG. Treatment option for acute uncomplicated cystitis in adults. *J Antimicrob Chemother.* 2000;46(suppl. S1):23-27.

20. Gilbert DN, Moellering RC, Sande MA, eds. *The Sanford Guide to Antimicrobial Therapy* 2003. 33rd edition. Hyde Park, VT: Antimicrobial Therapy Inc; 2003.

21. Karlowsky JA, Kelly LJ, Thornsberry C, Jones ME, Sahm DF. Trends in antimicrobial resistance among urinary tract infection isolates of Escherichia coli from female outpatients in the United States. *Antimicrob Agents Chemother.* 2002;46:2540-45.

22. Bayer Corporation. The Surveillance Network, Focus Technologies. USA UTI Study. Data on file, 2001.

23. Le TP, Miller LG. Empirical therapy for uncomplicated urinary tract infections in an era if increasing antimicrobial resistance: A decision and cost analysis. *Clin Infect Dis.* 2001;33:615-21.

24. Perfetto EM, Gondek K. Escherichia coli resistance in uncompli-cated urinary tract infection: a model for determining when to change first-line empirical antibiotic choice. *Manag Care Interface.* 2002;15:35-42.

25. Seifert R, Keating K, Merchant S, Choudhri S, Karlowsky J, Sahm D. An economic model to calculate the cost of treating uncomplicated urinary tract infection—a regional analysis. Poster presented at: Infectious Diseases Society of America (IDSA); October 24-27, 2002; Chicago, IL.

26. Li-McLeod J, Cislo P, Gomolin IH. 2000. Cost analysis of ciprofloxacin oral suspension vs. trimethoprim/ sulfamethoxazole oral suspension for treatment of acute urinary tract infections in elderly women. Poster presented at: Conference of American Society of Consultant Pharmacists; November 1-4, 2000; Boston, MA.

27. Raz R, Chazan B, Kennes Y, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clin Infect Dis.* 2002;34:1165-69.

28. Centers for Disease Control. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1997. *Vital Health Stat.* 1999;143:19.

29. Gross PA, Pujat D. Implementing practice guidelines for appropriate antimicrobial usage. *Med Care.* 2001;39(8)(suppl 2):II-55-69.

30. Verispan Physician Drug & Diagnosis Audit (PDDA). Chart 1: Based on Mean Days Therapy for Uncomplicated UTI/Cystitis (ICD-9 Diagnoses—595.000-595.910, 599.000-599.030, 753.100-753.190) MAT ending February 2003. Yardley, PA: Scott-Levin, Inc.

31. Richter A, Anton SF, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. *Clin Ther.* 2003;25(8):2307-35.

32. Baerheim A, Digranes A, Hunskaar S. Are resistance patterns in uropathogens published by microbiological laboratories valid for general practice? *Acta Pathol Microbiol Immunol Scand.* 1999;107:676-80.

33. Gomolin IH, Siami P, Haverstock D, et al. Efficacy and safety of ciprofloxacin oral suspension vs. TMP/SMX for treatment of community- and nursing home-residing elderly women with acute urinary tract infections. *J Am Ger Soc.* 1999;47:S39. Abstract P111.

ORIGINAL RESEARCH

Markov Modeling Analysis of Health and Economic Outcomes of Therapy With Valsartan Versus Amlodipine in Patients With Type 2 Diabetes and Microalbuminuria

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ABSTRACT

OBJECTIVE: To estimate 8-year health and economic outcomes of the angiotensin II receptor blocker valsartan versus the calcium channel blocker amlodipine in therapy of patients with type 2 diabetes and microalbuminuria based on clinical endpoints from a 6-month randomized controlled clinical trial, the MicroAlbuminuria Reduction With VALsartan (MARVAL) study.

METHODS: We developed a Markov model that utilized urinary albumin excretion rate data to project patient distributions to 7 possible health states over 8 years. For each health state, we identified quality-adjustment weights (health utilities) and medical care costs from public sources. The model then calculated mean quality-adjusted survival, medical care costs, and cost-effectiveness ratios for each treatment arm. Treatment arms were compared with the incremental cost-effectiveness ratio.

RESULTS: Patients treated with valsartan gained 7 months (mean) per patient of quality-adjusted survival relative to patients treated with amlodipine (77 versus 70 months; $P<0.01$); valsartan patients also incurred $32,412 (mean) per patient lower medical costs than amlodipine patients ($92,058 versus $124,470; $P<0.01$). Model results were consistent for each year of analysis and robust to changes in key model parameters.

CONCLUSION: This research (1) extends 6-month clinical trial outcomes to an 8-year period, (2) translates health outcomes from technical clinical endpoints to quality-adjusted survival, and (3) estimates economic consequences of therapeutic outcomes. The results quantify the favorable long-term health (i.e., quality-adjusted survival) and economic benefits (i.e., lower total medical costs) of therapy with valsartan, an angiotensin II receptor blocker, versus amlodipine, a calcium channel blocker, in the treatment of patients with type 2 diabetes and microalbuminuria based on an extension of the results of a short-term clinical (MARVAL) trial. These research findings are important to the extent patients with type 2 diabetes and microalbuminuria do not receive the recommended antihypertensive agents that block the renin-angiotensin system (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers).

KEYWORDS: Amlodipine, Diabetes, End-stage renal disease, Markov model, Microalbuminuria, Outcomes research, Quality-adjusted survival, Valsartan

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Diabetic nephropathy is the leading cause of renal failure and end-stage renal disease.[1] Microalbuminuria as measured by overnight urinary albuminuria excretion rate (UAER) is the first sign of diabetic renal disease[2] and the best predictor of progressive failure.[3] In addition to risk of renal failure, patients with diabetes are also at increased risk for hypertension and cardiovascular diseases.[4,5] Blood pressure reduction alone is well known to play a major role in reducing the risk of cardiovascular events and delaying onset and progression of renal disease.[6-8] Newer antihypertensive agents that block the renin-angiotensin system have been shown to confer additional benefits from UAER reduction.[6,9] Clinical evidence of renal protective effects of angiotensin-converting enzyme inhibitors (ACEIs) is well established,[10-12] and similar effects have more recently been demonstrated with angiotensin II receptor blockers (ARBs).[6,13-16]

Expert guidelines endorse ACEIs as first-line therapy for persons with type 1 or type 2 diabetes and mild or severe hypertension; ARBs are also recommended as first-line therapy for patients with type 2 diabetes and microalbuminuria or clinical nephropathy.[17] Yet, empirical research suggests that many patients who could benefit from these recommendations may also remain untreated with them.[18,19] To highlight the benefits of appropriate treatment, we modeled long-term health and economic outcomes of therapy with valsartan (Diovan), an angiotensin II antagonist, versus amlodipine (Norvasc), a calcium channel blocker.

A recently published 6-month clinical trial of 332 of patients with type 2 diabetes and microalbuminuria reported therapeu-

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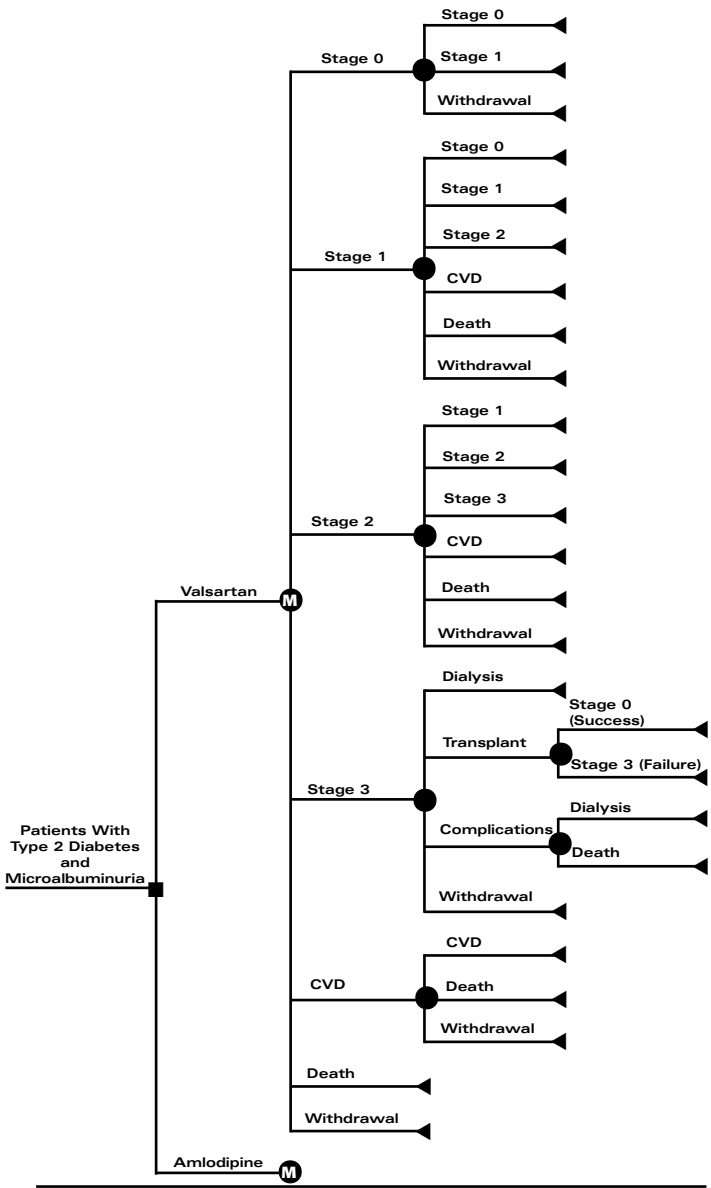
tic results achieved with valsartan (N=169) compared with amlodipine (N=163), a widely prescribed calcium channel blocker, in terms of blood pressure and UAER clinical endpoints.[15] Trial findings showed a large and statistically significant reduction in UAER from baseline in patients treated with valsartan (absolute reduction = 25.6 mcg/min) compared with amlodipine (absolute reduction = 4.7 mcg/min), 56% of baseline versus 92% of baseline, respectively ($P<0.001$), despite similar reductions in blood pressure (absolute reduction of 6.6 mm diastolic with valsartan versus 6.5 mm with amlodipine) achieved by each treatment.[15] Notably, twice as many patients on valsartan therapy returned to normoalbuminuria than amlodipine patients (29.9% versus 14.5%; $P = 0.001$).[15] Consistently favorable results were observed in subgroups of study patients with type 2 diabetes and microalbuminuria with or without hypertension.[15]

The objective of our modeling analysis was to extend the results of the above-described trial of valsartan versus amlodipine in type 2 diabetes with microalbuminuria by quantifying long-term health consequences of treatment in terms of quality-adjusted survival (QAS) and estimating the economic consequences of treatment outcomes. These data highlight the potential health and economic benefits that could be gained by timely adherence to expert prescribing guidelines for patients with type 2 diabetes and microalbuminuria. These data are relevant, as research suggests many patients who are prime candidates for agents that block the renin-angiotensin system may not be receiving them.[18,19]

Our study employed a modeling approach. A well-designed model can potentially enhance the value of clinical trials by extending the time period studied, expressing outcomes not directly assessed in the trial, allowing cost estimation, and permitting sensitivity analysis.[20] Our model extends a 6-month clinical trial to 8 years, expresses clinical outcomes in terms of QAS (rather than intermediate clinical endpoints such as UAER), quantifies associated economic costs of therapy, and enables sensitivity analysis to be conducted on all key model parameters. By presenting our model results, decision makers may perhaps more clearly see the long-term impact of important prescribing decisions.

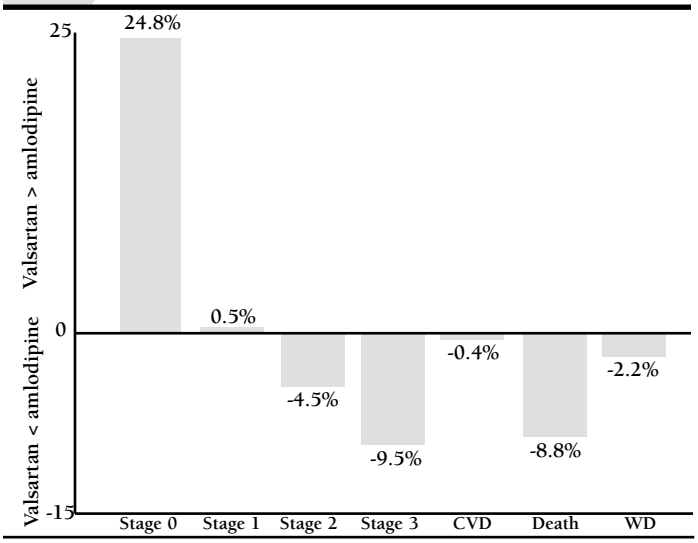
Our investigation adds to the body of modeling research of interventions that mediate renal disease progression. Wu et al. developed a 10-year population simulation model to evaluate the impact of type 1 diabetes on quality-adjusted life-years (QALYs) and economic costs and found intensive therapy was associated with additional QALYs as well as cost savings.[21] Rodby et al. developed a model to compare lifetime health outcomes and associated economic costs for patients with type 1 and type 2 diabetes and overt nephropathy treated with either captopril or placebo, based on clinical results of a randomized placebo-controlled trial, and concluded that treatment with captopril would result in substantial cost savings.[22] Hogan et al. estimated the economic impact of health outcomes observed in a 3-year randomized trial plus its 3.6-year (median) extension study of adjunct benazepril versus placebo in patients with chronic renal insufficiency of any etiology (of which 10% was attributed to diabetes) who were managed for hypertension with agents excluding ACEIs and found that patients treated with adjunct benazepril enjoyed more QAS and lower medical costs than adjunct placebo-treated patients.[23] The U.S. Centers for Disease Control and Prevention (CDC) Diabetes Cost-Effectiveness Group developed a model to evaluate the cost-effectiveness (CE) of various interventions (intensive glycemic control,

FIGURE 1 Schematic Representation of the Markov Model



M = Markov node. CVD = cardiovascular disease.
The amlodipine subtree is identical in structure to the valsartan arm; only transition probabilities differ.

FIGURE 2 Treatment Arm Comparison of Projected Health State Outcomes at 8 Years



Details of the Figure

Proportions by treatment group:							
Valsartan	*49.1%*	*3.7%*	*6.2%*	*9.1%*	*1.9%*	*8.5%*	*21.4%*
Amlodipine	*24.3%*	*3.2%*	*10.7%*	*18.6%*	*2.3%*	*17.3%*	*23.6%*
*Difference**	*24.8%*	*0.5%*	*<4.5%>*	*<9.5%>*	*<0.4%>*	*<8.8%>*	*<2.2%>*

** Valsartan proportion greater than <less than> amlodipine.*
CVD = cardiovascular disease. WD = withdrawal.

TABLE 1 Health State Transition Probabilities Employed in the Model

Transition from:	Transition to:	Valsartan Arm	Amlodipine Arm
Stage 0* (normal)	Healthy	1	1
	Relapse	0	0
	Stops treatment	0	0
Stage 1† (microalbuminuria)	Recover	0.0482	0.0220
	Routine care	0.9024	0.8970
	Progress to Stage 2	0.0239	0.0503
	Cardiovascular disease	0.0025	0.0025
	Death	0.0013	0.0022
	Stops treatment	0.0218	0.0249
Stage 2‡ (nephropathy)	Improve	0	0
	Routine care	0.9386	0.9314
	Progress to Stage 3	0.0460	0.0506
	Cardiovascular disease	0.0025	0.0025
	Death	0.0129	0.0155
Stage 3‡ (kidney failure: ESRD)	Dialysis	0.9307	0.9280
	Transplant	0.0400	0.0400
	ESRD complications	0.0293	0.0320
Transplant‡	Success	0.25	0.25
	Failure	0.75	0.75
ESRD complications	Dialysis	0.5	0.5
	Death	0.5	0.5
Cardiovascular disease†	Cardiovascular disease	0.975	0.975
	Death	0.025	0.025

** Relapse to State 1 from State 0 and withdrawal from the study from states other than State 1 are possible in theory; however, there are no probability data for these events in this study.*
† 6-month data per Viberti (2002);[15] extended data per Brenner (2001),[13] Lewis (2001),[10] and Parving (2001).[14]
‡ Per United States Renal System (2003).[25]
ESRD = end-stage renal disease.

intensified hypertension control, and reduction in serum cholesterol level) for the treatment of type 2 diabetes using clinical outcomes data from the United Kingdom Prospective Diabetes Study over a median period of 10 years and found that intensified hypertension control was most cost effective.[8]

Methods

Model Description

We developed a 7-state Markov model, which is summarized in Figure 1. Health states included the stages of renal disease, specifically (1) Stage 0 disease indicated by normal albumin levels, (2) Stage 1 disease characterized by microalbuminuria, (3) Stage 2 disease characterized by nephropathy, and (4) Stage 3 disease: kidney failure, also known as end-stage renal disease.[7] Three additional health states completed the model structure: (5) cardiovascular disease, (6) death, and (7) withdrawal from the study for any reason.

The probabilities of patients transitioning to different health states over 8 years (Table 1) were extrapolated linearly based on data from the 24-week MicroAlbuminuria Reduction With VALsartan (MARVAL) study,[15,24] recently published longer-term studies,[10,13,14] and government documents.[25] For each health state, quality weights (health utilities) were obtained from the medical literature and costs were obtained from publicly available sources. A third-party payer perspective was taken. Future costs were assumed to increase at a rate of 2.8% per year, equal to the average net increase in medical prices above the general price level from 1991 to 2001 based on the consumer price index.[27] A 3% annual rate was used to discount future period costs and effectiveness units to present value equivalents. The model calculated outcomes on a quarterly (3-month) basis, but results are presented on an annual basis. Key model parameters were varied in sensitivity analysis.

Effectiveness (Quality-Adjusted Survival)

The effectiveness unit employed in the model was years (or equivalent months) of QAS. QAS was calculated by multiplying the time patients spent in each health state by the health state's associated quality weight (health utility). Health utilities assigned to each health state were obtained from the medical literature (Table 2).

Costs

Costs were obtained from public sources and expressed in 2001 dollar values (Table 3). Medical care costs included the costs of study drugs, routine health care services, and aggregate estimates of medical care associated with the various health states. Aggregate costs were calculated by multiplying the time patients spent in different health states by the medical costs associated with those health states.

Cost-Effectiveness Ratios

Ratios of costs to effectiveness units were calculated for each treatment arm by dividing costs by years of QAS. The CE ratio describes

the relative cost to purchase the equivalent of 1 full year of QAS.

Incremental Cost-Effectiveness Ratio

The ratio of incremental costs to incremental effectiveness for 2 treatments is calculated as the difference in costs divided by the difference in effectiveness: $(C_a - C_b)/(E_a - E_b)$. The incremental CE ratio is a measure of economic efficiency. It describes the relative economic cost to purchase extra effectiveness yielded by a more effective agent, expressed in terms of 1 whole unit of effectiveness. If the incremental CE ratio has a negative value, it is important to note whether the negative arises in the numerator or denominator, because a negative in the numerator is favorable to valsartan (it would mean valsartan therapy results in lower medical care costs than amlodipine), but a negative value in the numerator is favorable to amlodipine (i.e., it would mean valsartan is less effective than amlodipine).

Analyses

Costs, years of QAS, and CE ratios were calculated for each treatment arm. The 2 treatment groups were compared with the incremental CE ratio. Bootstrap methods were employed to determine statistical significance of differences in QAS, costs, and the incremental CE ratio. Sensitivity analysis was performed on key model parameters to ascertain the stability of the results to changes in baseline values. Key parameters were health state transition probabilities, costs, and utilities; medical cost inflation; and the discount rate.

Results

Health State Outcomes

The model's distribution of patients to health states over 8 years favored the valsartan group (Figure 2). More than twice as many patients in the valsartan arm returned to normal albuminuria—the best possible model outcome—as did patients in the amlodipine arm. Half as many valsartan patients were projected to reach end-stage renal disease as patients taking amlodipine (9.1% versus 18.6%), and mortality outcomes were similarly favorable to valsartan, at 8.5% versus 17.3% for amlodipine patients. Fewer valsartan patients progressed to cardiovascular disease than did their amlodipine patients (1.9% versus 2.3%, respectively). Rates of withdrawal were similar between the 2 arms (21.5% valsartan versus 23.7% amlodipine).

Effectiveness (Quality-Adjusted Survival)

Mean discounted years of QAS for each treatment arm are shown in Table 4. The advantage for the valsartan arm versus amlodipine was small in year 1 (0.011 years) but increased to 0.555 years per patient by the end of year 8. This is equivalent to 7 months per patient of additional survival in full health.

Medical Care Costs

Cumulative discounted mean per-patient medical care costs increased in both treatment arms over the model period, indicating that all patients required increasing medical care over time. Costs increased less for patients in the valsartan arm than in the amlodipine arm (Table 5). After the first year of analysis,

TABLE 2 Quality Weights (Health "Utilities") Used in the Model

Renal disease states	
Stage 0: Normal albuminuria*	1.00
Stage 1: Elevated microalbuminuria†	0.99
Stage 2: Advanced nephropathy‡	0.90
Stage 3: End stage renal disease§	0.53
Other states	
Cardiovascular disease‖	0.88
Death	0.00
Withdrawal¶	0.85

* *Assumed to be 1.*
† *As this condition is asymptomatic, only a slight decrement from normal albuminuria is assumed.*
‡ *Per Hogan (2002),[23] chronic renal insufficiency.*
§ *Per Hogan (2002),[23] dialysis.*
‖ *Per Tsevat (1993),[26] cardiac arrest/myocardial infarction.*
¶ *Utility associated with "withdrawal" is assumed to be the average of Stages 0 to 3.*

TABLE 3 Estimated Annual Medical Care Costs (2001 Dollar Values)*

Drug therapy costs†	**Valsartan**	**Amlodipine**
Medication‡	$724.88	$722.76
Services§	$1,105.76	$1,158.08
Health state costs		
Renal disease		
Stage 0: Normal albuminuria‖	$5,244	
Stage 1: Elevated microalbuminuria‖	$9,584	
Stage 2: Advanced nephropathy‖	$17,208	
Stage 3: End-stage renal disease‖	$40,632	
Other		
Cardiovascular disease‖	$24,364	
Death¶	$31,910	
Withdrawal#	$18,164	

* *Future medical care costs are assumed to increase at an annual rate of 2.8%, representing the average increase in the medical component of the CPI over general inflation from 1991 to 2001.[28]*
† *Data represent average costs for each treatment arm.*
‡ *Average wholesale prices: valsartan: $1.37 per 80 mg and $2.74 per 160 mg; amlodipine: $1.35 per 5 mg and $2.70 per 10 mg; supplemental bendroflumethiazide: $0.28 per 2.5 mg; and supplemental doxazosin: $0.92 per 2.5 mg. Patients were treated as necessary to achieve target blood pressure of 135/85 mm Hg. Drug prices per Drug Topics Red Book (2001).[28] Generic product prices used when available (i.e., for bendroflumethiazide and doxazosin).*
§ *Services based on the number of office visits required to achieve blood pressure control. Clinician visit prices per average insurance company payments (APD Context, Inc. Physician Fees–2001, Roseland, NJ; 2001[29]) for routine visits (CPT-4 99212, $38.68).*
‖ *1992 values per Brown (1999)[30] inflated to reflect 2001 dollar values using the medical component of the consumer price index (U.S. Department of Labor, Bureau of Labor Statistics, www.bls.gov, MCPI-All Urban Consumers[27]), excluding study medication and visit costs.*
¶ *1999 dollar values per Hogan (2002)[23] inflated to reflect 2001 values using the medical component of the CPI.[2]*
\# *Withdrawal costs calculated as the average for Stages 0 to 3 renal disease costs.*

TABLE 4 Cumulative Discounted Mean per-Patient Quality-Adjusted Survival*

Year of Model Analysis	Valsartan Arm	Amlodipine Arm	Difference Favoring Valsartan
1	0.957	0.946	0.011
2	1.861	1.819	0.042
3	2.715	2.622	0.093
4	3.525	3.363	0.162
5	4.294	4.048	0.246
6	5.025	4.684	0.341
7	5.723	5.278	0.445
8	6.390	5.835	0.555

** QAS expressed in years; discounted to 2001 values.*

TABLE 5 Cumulative Discounted Mean per-Patient Medical Care Costs by Treatment and Savings for Valsartan Relative to Amlodipine (2001 Dollar Values)

Year of Model Analysis	Valsartan Arm ($)	Amlodipine Arm ($)	Difference Favoring Valsartan ($)
1	11,909	12,915	1,006
2	23,082	26,440	3,358
3	34,324	41,224	6,899
4	45,744	57,083	11,339
5	57,317	73,684	16,367
6	68,960	90,662	21,701
7	80,574	107,683	27,109
8	92,058	124,470	32,412

per-patient medical care costs were $1,006 lower for valsartan than amlodipine, which increased to $11,339 after 4 years, and $32,412 ($P< 0.01$) at the end of 8 years of analysis.

Cost-Effectiveness Ratios

In year 1, the CE ratio per year of QAS for valsartan was $12,444 compared with $13,653 for amlodipine. In year 8, the CE ratio for valsartan rose to $14,407 per year of QAS, and for amlodipine, to $21,332. (A lower CE ratio is better.)

Incremental Cost-Effectiveness Ratio

Both dimensions of outcome—costs and effectiveness—favored valsartan relative to amlodipine. Valsartan was *less* costly and *more* effective in terms of QAS than amlodipine. This scenario gives the incremental CE ratio a negative value (i.e., –$58,400 per QALY gained; $P<0.01$), and indicates here that there is no trade-off between cost and effectiveness in this analysis because the same treatment option yields both lower costs and more effectiveness.

Sensitivity Analysis

Sensitivity analysis on key baseline model parameters (Table 6) shows model conclusions are stable given wide variation in key assumptions. The parameters with the greatest impact on model results are the costs and utility weights assigned to health states, but changes in these parameters modify the magnitude of the QAS and economic outcomes without changing the overall rank ordering of the treatment arms. Health state transition probabilities were analyzed by revising them to the lower and upper 95% confidence limits reported in the core clinical trial from which they were identified[15]; these changes had relatively little impact on the relative outcomes of each treatment arm. Model outcomes were also analyzed with the direct drug price of amlodipine set equal to $0.30 per 5 mg tablet, a price considered to be equal to that of generically available ACEIs. This change reduced mean per-patient drug costs for the amlodipine arm from $773 to $161 and the difference in costs between valsartan and amlodipine treatment arms from $32,412 in the base-case analysis to $28,611, but the rank ordering of the treatments remained stable even at this low price. Direct drug costs represent a relatively small portion of total medical care costs for these patients, and this result highlights the importance of clinical effectiveness as the key driver of health and economic outcomes for these patients. Changes in the discount rate applied to future costs and QAS, as well as the time period of analysis, have little net effect on results.

Discussion

Our 8-year modeling analysis of the health and economic outcomes of valsartan versus amlodipine in the management of type 2 diabetes with microalbuminuria is the first to be performed in the United States. Results extend data from a 6-month clinical trial to 8 years, interpret health outcomes in terms of quality-adjusted patient survival, and estimate associated costs of medical care. Results highlight the potential long-term health and economic benefits of treating relevant patients with appropriate classes of pharmaceutical agents and the penalty of suboptimal prescribing practices.

These findings for amlodipine versus valsartan remain relevant today even in the presence of expert guidelines that recommend the use of agents that block the renin-angiotensin system (ACEIs or ARBs) for patients with type 2 diabetes and microalbuminuria because research suggests that more patients could benefit from these agents who are not yet receiving them. One managed care study showed that 51% of persons with chronic renal insufficiency—and 35% of persons with chronic renal insufficiency and *diabetes*—were not treated with either an ACEI or ARB.[18] Another managed care study revealed that fewer than 50% of diabetic hypertensives were receiving an ACEI.[19] These findings suggest ample opportunity to improve patient

health while avoiding substantial medical care costs by treating high-risk patients with diabetes, microalbuminuria, and/or poorly managed hypertension with appropriate therapy.

Our findings of the economic benefits of valsartan relative to amlodipine are consistent with, though perhaps greater in magnitude than, findings of other models. The CDC diabetes CE group modeled 3 interventions for type 2 diabetes over a 10-year period and found intensified hypertension control yielded greater QAS and lower cost than either intensive glycemic control or cholesterol reduction, a finding that highlighted the CE of intensified antihypertensive therapy, in general, for patients with type 2 diabetes.[8] Hogan et al.[23] conducted an economic evaluation in the U.S. setting of results of the European Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency study[11] in which persons with chronic renal insufficiency of any etiology treated for hypertension with various agents (excluding ACEIs) were randomized to either an ACEI (benazepril) or placebo and followed for a median period of 6.6 years. Results of that analysis revealed more QAS enjoyed by the ACEI group than the placebo arm and lower cumulative mean medical care costs of $12,991 per patient (1999 values) in the U.S. setting; medical care costs were estimated to increase to $16,794 per patient when dialysis and transplantation rates were increased to reflect U.S. patterns rather than the European experience observed in the trial.[23] The greater magnitude of cost savings reported in our study may be explained, at least in part, by a longer period of analysis, selection of a higher-risk group of patients for analysis, a greater difference in effectiveness of therapeutic agents, and/or use of more favorable model parameters.

Limitations

There are several potential limitations to our model analysis. The model is based on health state transition probabilities obtained from a 6-month clinical (MARVAL) study of valsartan versus amlodipine in the United Kingdom. These data were used to formulate the probabilities with which patients transitioned to various health states over an 8-year period. However, these data were compared with other longer-term trial results, and we believe the potential variation between the data we used in the model and other clinical evidence is minor.

A limitation common to modeling evaluations is the use of aggregate costs for each health state. The use of actual costs for different practice settings may be more representative of local conditions, and caution is recommended when evaluating aggregate model results with respect to a particular setting. For a range of proportional changes in input prices, analytical results of the model also changed roughly proportionately (Table 6). But altering input costs that do not reflect proportional changes across health states (e.g., higher prices associated with end-stage renal disease and lower prices associated with cardiovascular disease) could result in different CE ratios and incremental CE ratios than those shown.

TABLE 6 Results of Sensitivity Analysis

Value	Cost (US $) Amount Valsartan Below Amlodipine	QAS (Years) Amount Valsartan Above Amlodipine	ICER: Valsartan Versus Amlodipine
Baseline assumptions 3% discount rate; costs, utilities, and transition probabilities as described in the text; analysis over 8 years	32,412	0.555	(58,400)
Discount rate			
Low: 1%	34,795	0.615	(56,577)
High: 5%	28,749	0.502	(57,269)
State costs			
Two-thirds base case	21,716	0.555	(39,128)
Per Wu (1998)[21] and USRDS (2001)[25]	44,404	0.555	(80,007)
Medication costs			
Amlodipine priced at $0.30	28,611	0.555	(51,551)
State utilities			
Low: reduced 0.05	32,412	0.485	(66,829)
High: increased 0.05	32,412	0.648	(50,019)
Transition probabilities			
Low: reduce gap 36%*	11,668	0.200	(58,340)
High: increase gap 168%†	54,452	0.932	(58,425)
Time period			
2 years	3,358	0.042	(79,792)
4 years	11,339	0.162	(69,994)

** This is the lower 95% confidence limit of return to normoalbuminuria from MARVAL trial.*

† This is the upper 95% confidence limit of return to normoalbuminuria from the MARVAL trial.

QAS = quality-adjusted survival.

ICER = incremental cost-effectiveness ratio.

Utilities associated with health states were obtained from the literature. While it would be unusual to have utility measures available at the local level, preferences for health states may vary over time and between people and should be carefully considered.

To the extent that readers would like to see a comparison of valsartan, an ARB, to an ACEI, particularly a generic ACEI, our model will be seen as limited by its derivation from a published clinical trial comparing valsartan and amlodipine, a calcium channel blocker. Further research comparing ARBs and ACEIs would be informative. However, our research objective was to highlight health and economic consequences of treatment with either valsartan or amlodipine. Given the evidence suggesting that many appropriate patients may still be receiving agents other than ARBs or ACEIs, this research is relevant.

Conclusion

Extending the results of a clinical trial using our model suggests

that substantial health gains and cost savings can be realized by treating patients with type 2 diabetes and microalbuminuria with valsartan, an angiotensin II receptor blocker, rather than with amlodipine, a calcium channel blocker. Our study also demonstrated the value of using pharmacoeconomic modeling for purposes of extending the results available from clinical trials. By applying the data obtained from a clinical trial of central importance to data from related clinical trials and information on costs and utilities, a broader and richer set of results can be obtained by decision makers.

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DISCLOSURES

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REFERENCES

1. MEDLINE plus Medical Encyclopedia. Diabetic nephropathy/sclerosis. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/0000494.htm@contentDescription. Accessed December 1, 2002.

2. National Kidney Foundation. Microalbuminuria in diabetic kidney disease. Available at: http://www.kidney.org/general/news/diabkid.cfm. Accessed February 2, 2003.

3. NIDDK National Kidney and Urologic Diseases Information Clearing House. High blood pressure and kidney disease. Available at: http://www.niddk.nih.gov/health/kidney/pubs/highblood/highblood.htm. Accessed February 2, 2003.

4. Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB. The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. *J Am Cardiol.* 2002;40(5):954-60.

5. Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ.* 2002;324(7343):939-42.

6. Toto R. Angiotensin II subtype 1 receptor blockers and renal function. *Arch Intern Med.* 2001;161(12):1492-99.

7. Unger T. The role of the renin-angiotensin system in the development of cardiovascular disease. *Am J Cardiol.* 2002;89(2A):3A-9A.

8. The CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *JAMA.* 2002;287:2542-51.

9. Tabibiazar R, Jamali AH, Rockson SG. Formulating clinical strategies for angiotensin antagonism: a review of preclinical and clinical studies. *Am J Med.* 2001;110(6):471-80.

10. Lewis EJ, Hunsicker LG, Bain RP, et al. Collaborative Study Group. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Eng J Med.* 1993;329:1456-62.

11. Maschio G. Alberti D. Janin, G, et al. Effect of the angiotensin-converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med.* 1996;334:939-45.

12. Giatras I, Lau J, Levey AS, et al. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. *Ann Intern Med.* 1997;127(5):337-45.

13. Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345;12:861-69.

14. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2001;345:870-78.

15. Viberti G, Wheeldon NM, for the MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation.* 2002;106:672-78.

16. Nakao N, Yoshimura A, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomized controlled trial. *Lancet.* 2003;361:117-24.

17. American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care.* 2003;26 (suppl 1):S80-S82.

18. Kausz AT, Khan SS, Abichandani R, et al. Management of patients with chronic renal insufficiency in the Northeastern United States. *J Am Soc Nephrol.* 2001;12(7):1501-07.

19. Maue SK, Farrelly EW, Frech F, Godley P, and Sabrasula S. The need for improved blood pressure control within the diabetic hypertensive population. Poster presented at: America Diabetes Association's 61st Scientific Sessions; June 22-26, 2001; Philadelphia, PA.

20. Soto J. Health economic evaluations using decision analytic modeling. *Int J Technol Assess Health Care.* 2002;18(1):94-111.

21. Wu SY, Sainfort F, Tomar RH, et al. Development and application of a model to estimate the impact of type 1 diabetes on health-related quality of life. *Diabetes Care.* 1998;21(5):725-31.

22. Rodby RA, Firth LM, Lewis EJ. An economic analysis of captopril in the treatment of diabetic nephropathy. *Diabetes Care.* 1996;19(10):1051-61.

23. Hogan TJ, Elliott WJ, Seto AH, Bakris GL. Antihypertensive treatment with and without benazepril in patients with chronic renal insufficiency: a US economic evaluation. *Pharmacoeconomics.* 2002;20(1):37-47.

24. Syne qua non Ltd. *A Multicentre, Randomized, Double Blind, Amlodipine Controlled, Parallel Group Study of Valsartan in Patients With Type 2 Diabetes Mellitus and Microalbuminuria.* Frimley/Camberley, Surrey, UK: Novartis Pharmaceuticals UK, Ltd. Clinical Study Report Val D 902; May 16, 2001.

25. United States Renal Data System. Available at: http://www.usrds.org. Accessed January 20, 2003.

26. Tsevat J. Goldman L. Soukup JR, et al. Stability of time trade-off utilities in survivors of myocardial infarction. *Med Dec Making.* 1993;12:161-65.

27. Bureau of Labor Statistics. Available at: http://www.bls.gov. Accessed November 12, 2002.

28. *2001 Drug Topics Red Book.* Montvale, NJ: Thomson Medical Economics; 2001.

29. Physician Fees—2001. APD Context, Inc.; Roseland, NJ; 2001.

30. Brown JB, Pedula KL, Bakst AW. The progressive cost of complications in type 2 diabetes mellitus. *Arch Intern Med.* 1999;159(16):1873-80.

Clinical Monograph: Hormone Replacement Therapy

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ABSTRACT

BACKGROUND: For decades, hormone replacement therapy (HRT), which includes both estrogen and progestin, has been administered to postmenopausal women to mainly treat the symptoms of menopause and help prevent osteoporosis, with the added benefit of preventing coronary heart disease (CHD). Recently released study results have left clinicians wondering if HRT should be used at all, and, if so, with whom and under what circumstances.

OBJECTIVE: To provide readers with an example of the real-world operation of a pharmacy and therapeutics (P&T) committee in its use of a concise clinical monograph to guide its formulary decisions.

METHODS: The most relevant information for this committee, interested in evidence, was an analysis of the most current pivotal trials and observational studies that help define the place in therapy of HRT and provide information on product efficacy and safety. These included the Heart and Estrogen/progestin Replacement Study (HERS) and its extension trial, HERS II, in postmenopausal women with CHD and an average age of 67 years. The Women's Health Initiative (WHI) study, where the mean age of postmenopausal women was 63 years was also reviewed. The U.S. Food and Drug Administration (FDA) statements through January 8, 2003, on the appropriate use of these agents were also included in this clinical monograph for P&T committee review.

RESULTS: HERS and HERS II provided evidence that HRT does not provide secondary prevention in women with CHD. Data from the WHI study concluded that HRT promotes CHD and breast cancer in this age group. The Women's Health, Osteoporosis, Progestin, Estrogen study concluded that lower doses of conjugated estrogens (0.3 mg) are just as effective in treating postmenopausal symptoms as higher doses (0.625 mg) and result in fewer side effects.

CONCLUSION: The risk of breast cancer outweighs the benefits of osteoporosis prevention from HRT. According to labeling changes recommended by the FDA, HRT (or estrogen replacement therapy) should be limited to the shortest possible duration. Alternatives to HRT should be considered for the prevention of postmenopausal osteoporosis.

KEYWORDS: Hormone replacement therapy, Estrogen replacement therapy, HERS trial, Women's Health Initiative trial, Osteoporosis, Menopause, Coronary heart disease

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This study discusses an excerpt from a clinical monograph on hormone replacement therapy (HRT) that was used by the pharmacy and therapeutics (P&T) committee of an integrated health network (IHN); the committee has a total membership of 28 physicians and pharmacists who represent both hospitals and medical groups. Information in this monograph was used as the basis for decision making by the P&T committee in February 2003 about HRT products.

Because of the recent release and availability of new data from clinical trials and observational studies, the committee was asked to decide whether various HRT products should be on the IHN formulary, and, if so, which ones. This HRT clinical monograph had been used by one medical group as a resource for developing clinical use guidelines. Two weeks prior to the P&T committee meeting, a binder that included this monograph was mailed to all P&T committee members. The clinical information was also presented at the P&T meeting in a brief (5 to 10 minute) verbal summary. After the committee meeting, more information was released from the Women's Health Initiative (WHI) study that HRT does not guard against Alzheimer's disease, and, in fact, may increase the risk of developing it.[1,2]

Clinical safety and efficacy were considered first by the P&T committee. Health plan formulary coverage, placement (copayment tier), and relative cost were also considerations in the decision-making process. The cost of HRT is mostly an outpatient (health plan) concern since patients are in the hospital for only a few days but may take HRT for years as an outpatient.

The IHN provides hospital and medical services to the commercial membership of 5 health plans, which retain the financial risk for outpatient drugs except injectables. Therefore, the IHN P&T Committee is concerned primarily with the practical effects on continuity of care and coordination between inpatient and outpatient care. Placement of the specific products in the generic tier or in the preferred-brand tier is considered for the 5 major health plans that insure the patients in this IHN. If a drug is not covered or not preferred, the patients cannot readily receive the drug at pharmacies due to processes put in place by the 5 health plans. For example, physicians have to request permission to use the drug, usually in the form of a prior authorization, if the drug is not covered or, in some cases, if the drug is simply not preferred. The extra time consumed in paperwork and phone calls is sufficient to deter most prescribers from using nonformulary drugs.

For the IHN P&T Committee, an attempt was made to obtain drug product dossiers in the AMCP format[3] from the manufacturers of the key products in the current WHI clinical trial, the combination estrogen and progestin products. These

products were selected from all the products in this class because the medical literature is largely focused on conjugated equine estrogens (CEEs) and medroxyprogesterone acetate (MPA), the hormones used in the WHI and HERS studies.[4] Given the desire by the audience for concise presentation of selected relevant data, other product dossiers were not obtained. The dossiers of the selected products were not available at the time this monograph was written. MEDLINE searches provided primary research articles. Some information, including analyses of the WHI data, was obtained through continuing education program presentations for pharmacists. General information was taken from review articles, textbooks, and product prescribing information.

Monograph Format

The clinical monograph followed the drug monograph format used by the University Health-System Consortium (UHC),[5] and includes sections for Indications, Pharmacology, Pharmacokinetics, Clinical Efficacy, Adverse Events, Drug Interactions, Dosing and Administration, Availability, and Conclusions. UHC sells its monographs to many hospitals and pharmacy benefit managers (PBMs) that have formularies and use the P&T process to add and delete drugs from their drug formularies. For the P& T committee of this IHN, the most important section is Clinical Efficacy, followed by the Adverse Events section, then Pharmacology and Pharmacokinetics, Drug Interactions, and, lastly, Indications, Dosing and Administration, and Availability.

The Indications section is important for organizations such as PBMs and health maintenance organizations that select formulary drugs based on their U.S. Food and Drug Administration (FDA)-approved indications. Pharmacokinetic and pharmacologic properties can be unique among products in the same therapeutic class and can be deciding factors in drug choices. For example, if a drug has a unique mechanism of action, it might be included because it offers an alternate approach to therapy. A drug that bypasses first-pass metabolism, through dermal or vaginal administration, for example, can be given in a lower dose and perhaps result in fewer adverse effects. If a drug in the class has a serious safety threat—for example, it causes hepatic failure in some patients—it would be unlikely that the drug would be added to the formulary. If a drug in the class has more drug interactions than the others, it is not likely to be added to the formulary, due to possible deleterious effects from unnoticed drug interactions when prescribed and dispensed. Dosing and Administration and Availability address the concerns of patient compliance and convenience, among others. For example, patients are more likely to be compliant with a drug taken once daily than a drug that has to be taken 3 times daily.

Indications

The indications approved by the FDA for use of the estrogens were summarized in table form for this monograph (Table 1). It was noted that progestins, which are not available except as combination products with estrogen, do not have FDA approval as adjunctive therapy or sole therapy to treat menopausal vasomotor symptoms or to prevent or treat osteoporosis.[6]

TABLE LEGENDS

B = blinded
CABG = coronary artery bypass graft
CEE = conjugated equine estrogen
CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
DVT = deep venous thrombosis
ERT = estrogen replacement therapy
HDL = high-density lipoprotein
HRT = hormone replacement therapy
IHN = integrated health network
ITT = intention-to-treat
LDL = low-density lipoprotein
MC = multicenter
MI = myocardial infarction
MPA = medroxyprogesterone acetate
NS = not significant
OL = open label
PC = placebo controlled
PE = pulmonary embolism
PTCA = percutaneous transluminal coronary angioplasty
R = randomized
RH = relative hazard
RR = relative risk
SD = standard deviation
VTE = venous thromboembolism

Pharmacology

Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principal human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 mcg to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle.

The underlying cause of the onset of menopause is an age-related loss of ovarian function that results in a decline in estrogen secretion by the ovarian follicular unit. Most follicles are lost due to follicular atresia, a normal physiologic process of degeneration of the oocyte and its surrounding stroma.[7] Although some follicles remain in postmenopausal women, they are less sensitive to gonadotropin stimulation, implying that the more hormonally sensitive or functionally normal follicles are depleted earlier in life.[7]

After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. In postmenopausal women, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens. Postmenopausal decline in ovarian estradiol production causes diminished negative-feedback effects on the anterior pituitary glands, which results in a compensatory increase in secretion of the gonadotropins, follicle-stimulating hormone, and luteinizing hormone (LH).[8]

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. Two estrogen receptors (ER) have been identified—alpha and beta. ER alpha is present on endothelial

TABLE 1 FDA-Approved Indications for Estrogens[6]

	Vasomotor Symptoms of Menopause	Osteoporosis Prevention	Abnormal Uterine Bleeding	Atropic Vaginitis	Kraurosis Vulvae	Female Hypogonadism	Female Castration	Primary Ovarian Failure	Metastatic Breast Cancer (Palliative)	Prostate Cancer (Palliative in Advanced Disease)
Estradiol oral										
Estradiol oral	x	x		x	x	x	x	x	x	x
Ethinyl estradiol	x					x			x	x
Estradiol transdermal										
Estradiol patch	x	x	x	x	x	x	x	x		
Estradiol injectable										
Estradiol valerate	x			x	x	x	x	x		x
Estradiol hemihydrate				x						
Estradiol cypionate in oil	x					x				
Other estrogens										
CEE (conjugated equine estrogens)	x	x	x*	x		x	x	x	x	x
Synthetic conjugated estrogens A	x									
Esterified estrogens	x			x	x	x	x	x	x	x
Estrone	x			x	x	x	x	x	x	x
Estropipate	x	x		x	x	x	x	x		
Vaginal estrogens										
Miscellaneous vaginal creams†				x	x					
Combination estrogens and progestins										
Estrogens and progestins, combined in women with intact uterus	x	x‡		x§	x	x‖	x‖	x‖		

* *Injectable formulation only.*
† *Contains either estradiol, conjugated estrogens, or estropipate.*
‡ *Combipatch excluded.*
§ *Femhrt excluded.*
‖ *Combipatch only.*

and smooth muscle cells. ER beta is present in human arteries, veins, and myocardial cells.[9] Women with ER-alpha receptor polymorphism, called IVSI-401 c/c, have high-density lipoprotein (HDL) increases 2 times the extent seen in other women.[10]

Symptom complexes related to estrogen deprivation include genitourinary atrophy and vasomotor instability. Vasomotor symptoms or hot flushes most often prompt postmenopausal women to seek medical care. The cause of these symptoms is estrogen deficiency, possibly leading to aberrant surges of LH or gonadotropin-releasing hormone,[11] which affect the hypothalmic neurons that control central thermoregulation centers. They are most common within 12 to 24 months after the last menstrual period, gradually subsiding thereafter. The hot flush is an acute, episodic event that initially occurs several times a day, often during sleep. Peripheral blood flow increases, causing increased skin temperature. Perspiration occurs as a homeostatic response designed to dissipate heat. An increase in heart rate probably reflects a sympathetic response to change in skin temperature.[12] Estrogen has traditionally been the drug of choice for relieving hot flushes, but MPA in relatively high doses, some ergot alkaloids, clonidine,[12] venlafaxine,[13] and paroxetine[14] are also effective.

Treatment with intravaginal or systemic estrogen reverses the thinning of the vaginal mucosa through epithelial proliferation and decreases vaginal pH to its more normal acidic state. The higher pH that occurs during menopause creates a favorable environment for bacterial colonization by various pathogens. Estrogen therapy often relieves symptoms of vaginitis and frictional dyspareunia.[7,15]

Progesterone is a secretory product of the corpus luteum. Progestins act on the endometrium to change proliferative endometrial tissue into secretory tissue. Progestins alone are as effective as estrogens for relief of vasomotor symptoms. They are useful in the treatment and prevention of osteoporosis and appear to stimulate bone formation via androgenic and anabolic effects.[16] The addition of progestin for 12 days each month with estrogen replacement therapy serves 3 major purposes: to decrease the risk for estrogen-induced irregular bleeding, endometrial hyperplasia, and carcinoma; to protect against breast carcinoma; and to enhance estrogen prophylaxis of osteoporosis.[17]

TABLE 2 Heart and Estrogen/Progestin Replacement Study (HERS) Trials

HERS *(JAMA. 1998.)*[18]

Objective: To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease.
Methods: R, B, MC, PC secondary prevention trial in U.S.
n = 2,763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.
Interventions: n = 1,380 conjugated equine estrogen (CEE) 0.625 mg plus 2.5 mg of medroxyprogesterone acetate (MPA) in 1 tablet daily
n= 1,385 placebo
Follow-up averaged 4.1 years.
Outcomes: The primary outcome was the occurrence of nonfatal MI or CHD death. Secondary cardiovascular outcome included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also evaluated.

Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes.

	HRT	Placebo	RH (95% CI)
MI or CHD death	n=172	n=176	0.99 (0.80-1.22)
VTE	n=34	n=12	2.89 (1.50-5.58)
Gall bladder disease	n=84	n=62	1.38 (1.00-1.92)

Lipid Profiles	HRT Compared With Placebo	*P* value
LDL	HRT 11% lower	P<0.001
HDL	HRT 10% higher	P<0.001

There was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. There were no significant differences in other endpoints for which power was limited, including fracture, cancer, and total mortality.

HERS II Cardiovascular Outcomes *(JAMA. 2002.)*[19]

Objective: To determine if the risk reduction of CHD noted in years 3 to 5 in the HERS trial persisted and resulted in an overall reduced risk of CHD events with additional years of follow-up.
Methods: R, B, PC trial of 4.1 years duration (HERS) and subsequent unblinded follow-up for 2.7 years (HERS II) conducted at 20 outpatient U.S. centers.
n = 2,321 of the original 2,763 women in HERS who were part of unblinded follow-up for 2.7 years. In other words, this is data from the HERS group of women, extended for an additional 2.7 years.
Interventions: Open-label hormone therapy was prescribed at personal physician's discretion during HERS II. The proportions with at least 80% adherence to hormones declined from 81% (year 1) to 45% (year 6) in the hormone group and increased from 0% (year 1) to 8% (year 6) in the placebo group.
Outcomes: The primary outcome was nonfatal myocardial infarction and CHD death. Secondary cardiovascular outcomes were coronary revascularization, hospitalization from unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease.

There were no significant decreases in rates of primary CHD events or secondary cardiovascular events among women assigned to the hormone group compared with the placebo group in HERS, HERS II, or overall.

	CHD Events RH (95% CI)
HERS unadjusted	0.99 (0.81-1.22)
HERS II unadjusted	1.00 (0.77-1.29)
HERS + HERS II combined, unadjusted	0.99 (0.84-1.17)
HERS + HERS II combined, adjusted*	0.97 (0.82-1.14)
Women adherent to randomized treatment	0.96 (0.77-1.19)

*Data adjusted for potential confounders and differential use of statins between treatment groups.

The authors concluded that 6.8 years of hormone therapy did not reduce the risk of cardiovascular events in women with CHD.

HERS II Noncardiovascular Outcomes *(JAMA. 2002.)*[20]

Objective: To evaluate the long-term effect of postmenopausal hormone therapy on common noncardiovascular disease outcomes.
Design: R, B, PC trial of 4.1 years duration (HERS) and subsequent OL observational follow-up for 2.7 years (HERS II) between 1993 and 2000 at 20 U.S. outpatient settings.
Intervention: See HERS II above.
Outcomes: Thromboembolic events, biliary tract surgery, cancer, fracture, and total mortality.

Comparing ITT women given HRT with placebo in combined data from HERS and HERS II. RH (95% CI) data presented.

	HERS + HERS II	*P* Value
DVT/PE	2.08 (1.28-3.4)	0.003
Biliary tract surgery	1.48 (1.12-1.95)	0.005
Any fracture	1.04 (0.87-1.25)	0.66
Breast cancer	1.27 (0.84-1.94)	0.26
CVD death	1.11 (0.89-1.39)	0.36
Any death	1.10 (0.92-1.31)	0.29

Adjusted and as-treated analyses did not alter the investigators' conclusions.

Pharmacokinetics

The products in this class differ by administration route, which affects dose and adverse effects, and by the potency of the type of estrogen in the product. In an effort to be concise, only these pharmacokinetic issues are addressed.

Oral administration may utilize estradiol, conjugated estrogens, esters of estrone, or ethinyl estradiol. Estradiol is not used frequently by mouth because of extensive first-pass hepatic metabolism. A micronized version of estradiol yields a large surface area for rapid absorption, yet high doses must be used because absolute bioavailability remains low.

The ethinyl substitution in the C-17 position inhibits first-

TABLE 3 *Women's Health Initiative (WHI) Study*[21]

METHODS		RESULTS
Objective: An NIH/NHLBI*-sponsored study to determine the risk vs. benefit of ERT vs. continuous HRT (conjugated estrogens with medroxyprogesterone) in postmenopausal women		The benefits of therapy were decreased risk of colorectal cancer and fractures. The study showed a statistically significant increase in risk of CHD, strokes, VTE/PE. After 4 years of therapy, an increase of invasive breast cancer was noted.
Methods:		
n = 27,000 women aged 50-79 years, between 1993 and 1998; scheduled to conclude in 2005.		
Mean age~63 years. Most women were ≥10 years postmenopausal. Only one third were between the ages of 50 and 60 years.		
N~16,000 stopped therapy and included in current publications.		
Interventions:		
3 arms to study:		
1. placebo	3. ERT arm for patients without a uterus	
2. Continuous HRT-CEE 0.625 mg/MPA 2.5 mg once daily	n ~10,000 in ERT arm, which is still ongoing	
Outcomes:		
Global Index (not an index that has been studied and proven valid)		
1. CHD events (nonfatal MI, CHD death)	5. Endometrial cancer	
2. Breast cancer	6. Colorectal cancer	
3. Stroke	7. Hip fracture	
4. Pulmonary embolism	8. Deaths due to other causes	

Note: These were postmenopausal women, and symptoms common during menopause such as vaginal atrophy were not included.
**National Institutes of Health /National Heart, Lung, and Blood Institute.*

pass metabolism of ethinyl estradiol. CEEs are primarily the sulfate esters of estrone, equilin, and other naturally occurring compounds. Esterified esters are mixtures of conjugated estrogens prepared from plant-derived sources. The esters are hydrolyzed by enzymes in the lower gut, removing the charged sulfate group and allowing the absorption of estrogen. Estropipate is estrone solubilized by sulfate and stabilized with piperazine.[22]

During first-pass metabolism of orally administered estrogen, about 60% to 90% of the dose of estrogen is metabolized to estrone or inactive metabolites. High doses of exogenous estrogens must be administered to compensate for this effect.[23]

Estrogen in vaginal creams is readily absorbed through the vaginal epithelium. Estradiol is metabolized very little as it is absorbed from the vagina, and this route of administration results primarily in increased estradiol serum concentrations. But these concentrations return to baseline in approximately 6 hours. Because of the short duration of increased serum concentrations and because vaginal creams are messy, they are not widely used.[24]

The transdermal patch, containing estradiol, offers therapy with no first-pass metabolism of estradiol, convenient administration, and precise dosing.[24] Administration of estradiol via transdermal patches provides slow, sustained release of the hormone and more constant blood levels. Oral administration exposes the liver to high concentrations of estrogens via the portal circulation and causes a more rapid conversion of estradiol or conjugated estrone to estrone. Both of these effects are lessened with transdermal estradiol.[22] Transdermal administration results in estradiol levels equivalent to those in the early-to-mid-follicular phase and an estrone-to-estradiol ratio of approximately 1 to 1, which closely resembles the premenopausal state.[25] Oral administration can achieve similar estradiol levels, but only at the expense of a higher estrone-to-estradiol ratio.[26]

Progesterone is poorly absorbed when administered orally, and thus synthetic forms of 17-hydroxyprogesterone and 19-nortestosterone are used clinically. MPA is the progestin used in treating menopausal symptoms because it is relatively well absorbed orally and has a more acceptable side-effect profile than 17-hydroxyprogesterone or 19-nortestosterone.[27]

Clinical Efficacy

The Heart and Estrogen/progestin Replacement Study (HERS, HERS II) (Tables 2 and 8) and WHI (Tables 3 to 7) studies are the pivotal studies with regard to defining the risks of HRT (Table 2). The findings of HERS and HERS II about the lack of benefit of HRT in cardiovascular high-risk women are supported by findings of 2 randomized trials that assessed the effect of HRT on progression of atherosclerosis.[28,29]

The Estrogen Replacement Atherosclerosis trial[30] randomized 309 postmenopausal women with angiographically verified coronary disease to receive placebo, estrogen replacement therapy (ERT) as 0.625 mg/d of conjugated equine estrogen, or HRT as daily estrogen plus progestin, as in HERS. After 3.2 years of follow-up, the mean minimal coronary artery diameter on repeat coronary angiograms was not significantly different among women assigned to placebo, ERT, and HRT. The findings were unchanged in an analysis limited to patients who complied with treatment.

In the Postmenopausal Hormone Replacement Against Atherosclerosis trial, 321 postmenopausal women with

TABLE 4 WHI Baseline Characteristics[33]

Characteristic	HRT (n = 8,506)	Placebo (n = 8,102)
Age at screening, years in mean (SD)	63.2 (7.1)	63.3 (7.1)
Prior hormone use (%)	26.1	25.6
Body mass index, kg/m^2 in mean (SD)	28.5 (5.8)	28.5 (5.9)
Never smokers (%)	49.6	50.0
Diabetes (%)	4.4	4.4
Hypertension (%)	35.7	36.4
Statin use at baseline (%)	6.9	6.8
Family history breast cancer (%)	16.0	15.3
History of MI (%)	1.6	1.9
History of CABG/PTCA	1.1	1.5, *P* = .04

Note: These patients had some risks for cardiovascular disease: 36% had hypertension, 4.4% had diabetes, 50% had a history of smoking. At baseline, this could be interpreted as asymptomatic early heart disease in many of these patients.

TABLE 5 WHI Results: Summary of Main Outcomes[33]

Outcome	Relative Risk vs. Placebo* Nominal 95% CI)†	Increased Absolute Risk per 10,000 Women/Year	Increased Absolute Benefit per 10,000 Women/Year
CHD	1.29 (1.02-1.63)	+7	
Invasive breast cancer	1.26 (1.00-0.59) NS	+8	
Stroke	1.41 (1.07-1.85)	+8	
VTE	2.11 (1.58-2.82)	+18	
Colorectal cancer	0.63 (0.43–0.92)		-6
Hip fracture	0.66 (0.45-0.98)		-5
Global index	1.15 (1.03-1.28)		
Death due to other causes	0.92 (0.74-1.14) NS		
Total death	0.98 (0.82-1.18) NS		

**The relative risk or hazard ratio is not generally important unless >2. If it is 1, there is no relative risk; if <1, it is protective.*

†If the 95% CI hits 1, it is not significant. Nominal 95% CI is variability based on a single outcome measured at one point in time. In contrast, the adjusted 95% CI corrects variability for multiple analyses over time.

increased carotid intima-media thickness based on B mode ultrasound were randomly assigned to receive placebo or 1 of 2 HRT regimens (1 mg/day of 17 beta-estradiol continuously along with 0.025 mg of gestodene given from day 17 to day 28 once a month or every third month).[28,29] After 48 weeks, there was no difference between the placebo and active treatment groups in progression of atherosclerosis measured as a change in carotid[28] or femoral[29] intima-media thickness.

The HERS findings for ischemic stroke among high-risk women[31] are consistent with the results of the Women's Estrogen for Stroke Trial.[32] In this trial, 664 postmenopausal women who had recently had an ischemic stroke or transient ischemic attack were randomized to receive placebo or ERT as 1 mg/day of 17 beta estradiol. After 2.8 years of follow-up, the relative risk of nonfatal stroke in women assigned to ERT was 1.0 (95% CI, 0.7-1.4). In the HERS trial, HRT, according to 95% CIs, was not significantly associated with the risk of nonfatal stroke, fatal stroke, or transient ischemic attack.

In the WHI study, the HRT arm, but not the ERT arm, was stopped early, after 5.2 years of follow-up. The safety monitoring board determined that the risks of continuous HRT outweighed the benefits. The increased risks were cardiovascular disease (CVD), strokes, thromboembolic disorders, and invasive breast cancer. The increased risk did not include mortality.

In the fifth year, in the WHI study, there were 2,000 fewer patients in each group, making the placebo event rate of 9 in year 5 lower than expected for this age group, increasing the hazard ratio. The data >5 years was not powered to detect any significant differences. The hazard ratio that is significant, however, is the one in the first year, which shows that the risk does go up (see Table 7).

One hypothesis for why the risk is greater in the first year is that prevention of coronary heart disease (CHD) requires therapy soon after menopause. These were not all healthy patients at baseline: 36% had hypertension, 4.4% had diabetes, 50% had a history of smoking (see Table 4). They could be regarded as asymptomatic women with atherosclerosis. These were also older women, who are less likely to have reversible atherosclerosis. The authors concluded that HRT leads to an increased risk of myocardial infarction (MI), deep venous thrombosis (DVT), and venous thromboembolism (VTE). Here MIs were silent; MIs were identified by EKG changes.

If a Kaplan-Meier estimate is drawn from the WHI data with the cumulative hazard for CHD on the y axis and time in years on the x axis, then plotting the HRT group versus the placebo shows that the largest divergence between the 2 lines occurs within the first 2 years, then the 2 lines run parallel to each other thereafter. The same higher risk for CHD in the first 2 years was also seen in the HERS data.

As shown in Table 8 for the HERS trial, the number of placebo events in the first year (38) is less than expected, increasing the hazard ratio. The first-year hazard ratio could have been due to chance alone because when the study was extended out 2.8 more years, the outcome of a hazard ratio <1 continued.

Finally, there is a hypothesis that there is some subset of women who have an increased risk of CHD due to some genetic predilection (see "Pharmacology," estrogen receptors). When considering the Framingham study results, the anticipated benefit is 26% to 39% reduction in risk of coronary events in the subset of women with IVSI-401 c/c polymorphism.[10] There are

also prothrombotic mutations. The risk of MI increased 11-fold in women with a prothrombin mutation 20210GA who took HRT and had hypertension.[34]

As a result of the WHI findings, new language has been inserted into the CEE,[11] combination CEE with MPA (CEE/MPA),[35] and conjugated estrogens A, synthetic,[36] prescribing information. The new language essentially states that the WHI study reported increased risks of MI, stroke, invasive breast cancer, pulmonary edema, and DVT in postmenopausal women during 5 years of treatment with CEE 0.625 mg combined with MPA 2.5 mg relative to placebo.

Other doses of conjugated estrogens and MPA and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Therefore estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration.[11,35,36] In other words, these are class effects and not product specific. (Note: this point differs from the actual monograph presentation to the P&T committee in February 2003 and is updated for this article.)

The FDA announced on January 8, 2003, that all labels on estrogen and estrogen-progestin replacement therapy will be revised to carry a boxed warning that identifies the increased risks of heart disease, heart attacks, strokes, and breast cancer and that these products are not approved for heart disease prevention. Estrogen is still recommended for hot flushes and night sweats but should be used at the lowest doses and for the shortest possible time. For vaginal and vulvar atrophy, vaginal estrogen products are suggested. New labels will state that before using estrogen to prevent osteoporosis, alternative nonestrogen therapies should be considered.[37] In the June 2003 prescribing information for the CEE/MPA combination product, the labeling states, "When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. . . . When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and nonestrogen medications should be carefully considered."[35] (Note: this point differs from the actual monograph presentation to the P&T committee in February 2003 and is updated for this article.)

TABLE 6 WHI Results: Summary of CVD Outcomes[33]

Outcome	HRT n (%)	Placebo n (%)	Hazard Ratio	Nominal 95% CI
CHD	164 (0.37)	122 (0.30)	1.29	1.02-1.63
CABG/PTCA	183 (0.42)	171 (0.41)	1.04	0.84-1.28
Stroke	127 (0.20)	85 (0.21)	1.41	1.07-1.85
VTE	151 (0.34)	67 (0.16)	2.11	1.58-2.82
Total CVD	394 (1.57)	546 (1.32)	1.22	1.09-1.36

TABLE 7 WHI Results: CHD by Year[33]

Year	HRT n (%)	Placebo n (%)	Hazard Ratio*
1	43 (0.51)	23 (0.29)	1.78
2	36 (0.43)	30 (0.38)	1.15
3	20 (0.24)	18 (0.23)	1.06
4	25 (0.32)	24 (0.32)	0.99
5	23 (0.39)	9 (0.16)	2.38
6+	17 (0.33)	18 (0.42)	0.78

**z score for trend across all years = -1.19; test for trend based on Cox proportional hazard model with time-dependent treatment effects.*

TABLE 8 HERS CHD Events by Year[18]

Year in Trial	Treated Cases	Placebo Cases	Hazard Ratio (95% CI)
1	57	38	1.52 (1.01-2.29)
2	47	48	1.00 (0.67-1.49)
3	35	41	0.87 (0.55-1.37)
4	33	49	0.67 (0.43-1.04)

Adverse Events

Serum Lipids

Clinical trials have shown that HRT has favorable effects on serum lipids, increasing HDL cholesterol and decreasing low-density lipoprotein (LDL) cholesterol. In one comparative trial of the effects on lipids of oral versus transdermal HRT, the authors reported that transdermal estrogen appears to cause smaller beneficial changes in lipoprotein profiles (about 50% of those brought about by oral administration), possibly because the liver is not exposed to the high estrogen levels obtained right after dosing.[38]

Progestins, both the C-19 nortestosterone derivatives and the C-21 derivatives, cause a dose-related decrease in HDL cholesterol and an increase in LDL cholesterol. The combination of medroxyprogesterone with estrogens tends to attenuate the positive effects that estrogens have on serum lipids. The recent Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study,[39] which looked at data from cycle 6 (6 months of treatment) and cycle 13 (13 months of treatment), showed that the addition of MPA to CEE still elevated HDL, but to a lesser extent than CEE alone. The addition of MPA to CEE also resulted in a slightly smaller decrease in LDL compared with CEE alone, but still significantly greater than placebo. What is troubling is that both CEE alone and a combination of CEE/MPA resulted in an elevation of triglycerides, with the greater increase seen in the CEE-alone group.

Venous Thromboembolism/Thromboembolism

Unlike oral estrogens, transdermal estrogen delivery has no significant effect on production of certain hepatic proteins, renin

TABLE 9 WHI Results: Invasive Breast Cancer Summary by Year[33]

Year	HRT No. of Patients (%)	Placebo No. of Patients (%)	Hazard Ratio*
1	11 (0.13)	17 (0.21)	0.62
2	26 (0.31)	30 (0.38)	0.83
3	28 (0.34)	23 (0.29)	1.16
4	40 (0.50)	22 (0.29)	1.73
5	34 (0.57)	12 (0.22)	2.64
6+	27 (0.53)	20 (0.47)	1.12

**z score for trend across all years = 2.56; test for trend based on Cox proportional hazard model with time-dependent treatment effects.*

TABLE 10 ERT, HRT, and Breast Cancer

Study	RR (95% CI) ERT Alone	RR (95% CI) Estrogen With Sequential Progestin	RR (95% CI) Continuous Combined
Schairer C. *JAMA.* 2000.[44]	1.1 (1.0-1.3)	1.5 (1.0-2.4)	too few cases
Ross RK. *JNCI.* 2000.[45]	1.06 (0.97-1.15)	1.38 (1.18-1.68)	1.38 (0.88-1.35)

substrate, sex-hormone-binding globulin, thyroxine-binding globulin, and cortisol-binding globulin. Elevations in these proteins may be associated with some of the adverse effects of oral estrogen therapy, including hypertension, gallbladder disease, and thrombosis, although the clinical significance is not known.[40,41]

Estrogens and progestins produce a complex variety of effects on coagulation. A history of thromboembolism is a relative contraindication to estrogen therapy.[42] Progestins may increase or reduce prostacyclin production, but synthetic estrogens increase prostacyclin production. Platelet aggregation is generally unchanged by estrogens, although there is some data to the contrary. Virtually all clotting factors, particularly factors II, VII, IX, X, XII, and fibrinogen, are elevated by synthetic estrogens. The effects on clotting factors are primarily related to estrogen potency. Elevations are relatively marked with ethinyl estradiol but are either not observed or are not clinically significant after use of estrogen patches and ointment or natural estrogens.[43]

Hypertension

The concern that hypertension may be caused or exacerbated by estrogens has contributed to the belief that hypertension is a contraindication to estrogen therapy. Most clinical evidence shows no causal relationship between ERT and hypertension. Oral estrogen therapy, particularly potent synthetic products, but not transdermal estrogen, causes increased renin substrate and may increase angiotensin II and aldosterone, although the clinical significance is unknown.[43] Progestins produce a dose-related elevation in blood pressure by causing sodium and water retention.[12]

Premenstrual Syndrome

Progestins, when used alone or during the progestin phase of a combination regimen, cause an iatrogenic premenstrual tension-like syndrome. Breast tenderness or mastalgia, bloating, edema, and abdominal cramping, as well as anxiety, irritability, and depression, are frequent complaints. Weight gain, headache, and drowsiness can occur. Approximately 5% of patients are intolerant to all types of progestins, but others may benefit from a dosage reduction or change to another type of progestin.

The 17-hydroxyprogesterone derivatives are used primarily in HRT and are less androgenic but are associated with depression and anxiety symptoms.[17,41]

Monthly Bleeding

Progestins alone, or given with estrogen in a biphasic manner in a monthly cycle, bring on monthly bleeding in 80% to 90% of women. In contrast, unopposed estrogen causes monthly withdrawal bleeding in 25% of patients. Continuous therapy with a monophasic estrogen-progestin combination is an option for women who wish to avoid monthly bleeding.[27]

Endometrial Cancer

The increased frequency of uterine cancer from estrogens is related to endometrial hyperplasia, caused by unopposed estrogen therapy.[43] Overall, estrogen users have a 4-fold to 8-fold increase (range: 1.7-fold to 20-fold) in risk of developing endometrial cancer relative to the risk in the normal female population of 1 case per 1,000. The addition of progestin to estrogen therapy confers protection against hyperplasia and is generally recommended, either cyclically for at least 10 days per month or continuously in patients with an intact uterus.[43,46]

Breast Cancer

At year 5, in the WHI trial, notice that the number in the placebo group is 12, which is lower than expected and contributed to the increase in the hazard ratio (Table 9). These data are not stratified by age, which may have been the driver of the breast cancer incidence. If increasing length of time on HRT increased the risk, why does the hazard ratio decline for those who had HRT for 6+ years? There is the thought that the group that had 6+ years of HRT was not powered to see differences. Also at 5 years, there were 2,000 fewer people in the study. There is the possibility that there were preexisting lesions that did not show up until year 4.

One might conclude that the increased risk for breast cancer is from the progestin component. Recall that the patients who received ERT in WHI have not been withdrawn from the study

TABLE 11 Drug Interactions of Estrogens[6]

Precipitant Drug	Object Drug		Description
Estrogens	Anticoagulants, oral	↓	Estrogens may theoretically reduce the hypoprothrombinemic effect of anticoagulants.
Estrogens	Tricyclic antidepressants	↔	Pharmacologic effects of these agents may be altered by estrogens; the effects of this interaction may depend on the dose of the estrogen. An increased incidence of toxic reactions may also occur.
P450 inducers – barbiturates, rifampin	Estrogens	↓	Coadministration of barbiturates, rifampin, and other agents that induce hepatic microsomal enzymes may produce lower estrogen levels than expected.
Estrogens	Corticosteroids	↑	An increase in the pharmacologic and toxicologic effects of corticosteroids may occur via inactivation of hepatic P450 enzyme.
Hydantoins	Estrogens	↓	Breakthrough bleeding, spotting, and pregnancy have resulted when these medications were used concurrently. A loss of seizure control has also been suggested and may be due to fluid retention.
Estrogens	Hydantoins		

TABLE 12 Drug Interactions of Progestins[6]

Precipitant Drug	Object Drug		Description
Aminoglutethimide	Medroxyprogesterone	↓	Aminoglutethimide may increase the hepatic metabolism of medroxyprogesterone, possibly decreasing its therapeutic effects.
Rifampin	Norethinedrone	↓	Rifampin may reduce the plasma levels of norethinedrone via hepatic microsomal enzyme induction, possibly decreasing its pharmacologic effects.

because they have not shown an increased risk of breast cancer. Two recently published trials concluded that ERT alone did not increase breast cancer risk (Table 10).

HRT is probably not a carcinogen per se, and does not initiate the turning of a normal cell into a cancer cell, but it might promote cell proliferation of the cancer cell.[39]

Drug Interactions

See Table 11 for drug interactions of estrogens and Table 12 for drug interactions of progestins.

Dosing and Administration (for Menopausal Symptoms and Osteoporosis Prevention)

Conjugated Estrogens Oral

For the management of moderate to severe vasomotor symptoms associated with menopause, the usual dose is 0.625 mg daily. For atrophic vagina and vulva associated with menopause, the dose is 0.3 mg to 1.25 mg or more daily. It may be administered continuously or cyclically (25 days on drug, 5 days off). If conjugated estrogens are used in the treatment of vasomotor symptoms and the woman is menstruating, administration of the drug is started on the fifth day of the menstrual cycle. If the woman has not menstruated for 2 or more months prior to the initiation of therapy, administration can be started at any time. For the prevention of osteoporosis, the usual oral dose is 0.625 mg daily, administered in continuous fashion or cyclically (25 days, 5 days off).[47]

Conjugated Estrogens Vaginal Cream

For the management of atrophic vaginitis or kraurosis vulvae, 0.5 g to 2 g of conjugated estrogens can be administered once daily in a cyclical fashion.[47]

Conjugated Estrogens A, Synthetic Oral

For the management of vasomotor symptoms associated with menopause, the initial dose is 0.625 mg daily, with titration up to 1.25 mg daily. For the management of vulvar and vaginal atrophy, the usual oral dose is 0.3 mg daily.[6,47]

Esterified Estrogens Oral

For the management of vasomotor symptoms associated with menopause, the usual dose is 0.3 mg to 1.25 mg daily in a cyclic regimen. Dosage may be increased to 2.5 mg or 3.75 mg daily if neces-

sary. For kraurosis vulvae, the usual dosage is 0.3 mg to 3.75 mg daily in a cyclic regimen. The cyclic regimen refers to 21 days of drug therapy, followed by 7 days off the drug, and then the cycle is repeated: 1.25 mg daily administered 3 weeks on and 1 week off. If the woman has not menstruated for 2 months prior to initiation of therapy, administration can begin at any time. If the woman has been menstruating, start therapy on the fifth day of the menstrual cycle.[47]

Estradiol Oral

For vasomotor menopausal symptoms and vulval/vaginal atrophy associated with menopause, the dose is 1 mg to 2 mg/day initially in a cyclic regimen. Adjust to control symptoms. Attempt to taper or discontinue medication at 3- to 6-month intervals.[6] For the prevention of osteoporosis, the usual oral dose is 0.5 mg daily in a cyclic regimen. The drug usually is administered once daily for 21 consecutive days, followed by 7 days without the drug, and then the regimen is repeated.[47]

Estradiol Transdermal

Transdermal estradiol is available in formulations that are applied to the skin once or twice weekly, depending on the individual product. For women with an intact uterus, the transdermal system can be applied cyclically, e.g., 3 weeks on drug followed by 1 week without drug, and then the regimen is repeated. In women who do not have a uterus, the patches should be applied in a continuous fashion.[47] When used to manage severe vasomotor symptoms associated with menopause or for the management of atrophic vaginitis or krausosis vulvae or the prevention of osteoporosis, apply patches that deliver an initial dose of 0.025 mg to 0.05 mg/24 hours. For the management of menopausal symptoms, increase dose as necessary and attempt to taper to discontinue every 3 to 6 months.[6]

Estradiol Vaginal Tablet

For the management of atrophic vaginitis, the initial dose is one 25 mcg tablet, intravaginally, once daily for 2 weeks. The maintenance dose is 25 mcg tablet, intravaginally, twice weekly.[6]

Estradiol Vaginal Cream

For the short-term management of atrophic vaginitis or kraurosis vulvae, administer 2 g to 4 g daily for 1 to 2 weeks. Gradually reduce to one half initial dosage for a similar period. A maintenance dose of 1 g given 1 to 3 times a week in a cyclic regimen may be used after restoration of the vaginal mucosa has been achieved.[47]

Estradiol Vaginal Ring

For the management of postmenopausal urogenital symptoms, 1 ring (delivering estradiol 0.0075 mg/24 hours) is inserted into the upper one third of the vaginal vault and remains in place for 3 months. After 3 months, it should be removed and, if needed, replaced.[47]

Estradiol Valerate Injectable

For the management of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with menopause, the usual dose is 10 mg to 20 mg every 4 weeks.[6,47]

Estradiol Cypionate Injection

Vasomotor symptoms: intramuscular (IM) injection of 1 mg to 5 mg weekly for 3 to 4 weeks.[47]

Estrone Injectable

For the management of moderate to severe vasomotor symptoms associated with menopause or for the management of atrophic vaginitis or kraurosis vulvae, the usual dose is 0.1 mg to 0.5 mg 2 or 3 times weekly.[47]

Estropipate Oral

For the management of moderate to severe vasomotor symptoms associated with menopause or the management of atrophic vaginitis or kraurosis vulvae, the usual dose is 0.75 mg to 6 mg daily in a cyclic regimen (21 consecutive days on the drug, 7 days off). For the prevention of osteoporosis, the usual dose is 0.625 mg daily in a cyclic regimen (25 days on, 6 days off).[47]

Estropipate Vaginal Cream

For the management of atrophic vaginitis or kraurosis vulvae, the usual dose is 2 g to 4 g of 0.15% estropipate vaginal cream intravaginally once daily.[47] Administer cyclically, 3 weeks on, 1 week off. For short-term use only.[6]

Ethinyl Estradiol Oral

For the management of vasomotor symptoms associated with menopause, the usual dose range is 0.02 mg to 0.05 mg/day. The dose may be as low as 0.02 mg once every other day. Administer cyclically, 21 days on and 7 days off.[6,47]

Estrogens and Progestins, Combined

Oral

For the management of moderate to severe vasomotor symptoms associated with the menopause, the management of atrophic vaginitis, or the prevention of osteoporosis, a dose of 0.625 mg conjugated estrogens is given in conjunction with 2.5 mg to 5 mg of MPA once daily in a continuous daily regimen. When a dose of conjugated estrogens is administered in a continuous daily regimen and MPA is administered cyclically, conjugated estrogens are given as a daily dose of 0.625 continuously, while MPA are given as a daily dose of 5 mg on days 15 to 28 of the cycle.[47]

When ethinyl estradiol is used in combination with norethinedrone acetate for HRT in the management of moderate to severe vasomotor symptoms associated with menopause or for the prevention of osteoporosis, the usual dose is 5 mcg of ethinyl estradiol combined with 1 mg of norethinedrone acetate daily.[47]

Transdermal

For the management of moderate to severe vasomotor symptoms associated with menopause and vulvar or vaginal atrophy, the transdermal patch may be administered as a continuous combined regimen or as a continuous sequential regimen. In the continuous combined regimen, 1 patch delivering 0.05 mg/24 hours of estradiol and 0.14 mg/24 hours of norethinedrone (Combipatch) is applied twice weekly. The dosage of norethinedrone acetate may be increased by using the dosage system that delivers 0.25 mg/24 hours of norethinedrone. In the continuous sequential regimen, a patch delivering 0.05 mg/24 hours of estradiol (Vivelle) is applied twice weekly for the first 14 days of a 28 day cycle, then 1 patch delivering 0.05 mg/24 hour of estradiol and 0.14 mg/24 hour of norethinedrone acetate (Combipatch) is applied twice weekly for the remaining 14 days of the cycle.[47]

Two published studies from the Women's HOPE study showed that lower doses of HRT may be as efficacious as the higher dose in treating vasomotor symptoms[48] and cause less bleeding.[49]

Progestins

There are no convincing data to support the premise that continuous combined HRT reduces progesterone-induced adverse effects relative to sequential HRT.[17] One common regimen is the addition of oral MPA 5 mg to 10 mg daily during the last 10 to 12 days of the cycle.[6,47] Other progestins used in cyclic therapy include norethinedrone 2.5 mg, norgestrol 150 mcg, or micronized oral progesterone 300 mg.[17] This cyclic regimen results in the return of regular menstrual bleeding, which some women find objectionable. An alternative regimen for women for whom bleeding is unacceptable is the continuous administration of estrogens and lower-dose progestins (2.5 mg to 5 mg daily MPA) with the benefit of avoidance of withdrawal bleeding.[50,51]

Studies of the addition of a progestin for >7 days of a cycle of estrogen use showed a lowered incidence of endometrial hyperplasia. Studies of endometrium suggest that 10 to 14 days of progestin are needed to provide maximal maturation of endometrium and to eliminate any hyperplastic changes. It has not been clearly established that the addition of progestin will provide protection from endometrial cancer. Additional risks, such as adverse effects on lipids, impairment of glucose tolerance, and possible enhancement of mitotic activity in breast epithelial tissue, may be associated with progestin use.[27] The results of the WHI trial suggest that progestins increase the risk of CVD, VTE, and breast cancer. (Note: Some injectable formulations are not FDA-approved for menopausal symptoms or osteoporosis prevention so their dosing regimens were not included above.)

Availability

See Table 13 for drug availability, dosing, and costs.

Summary

The HERS,[18] HERS II,[19,20] and WHI[33] results have changed the way many clinicians view HRT in menopausal women. The WHI study results have shown that HRT does not protect against CHD. This lack of protection occurs early in treatment, within the first 1 to 2 years. The WHI results in Table 7 show that the hazard ratios for CHD were highest in year 1, at 1.78, and in year 5, at 2.38. However, the high hazard ratio in year 5 may be falsely elevated due to a relatively lower incidence in the placebo arm for that year only.

The HERS trial, which was a secondary prevention trial in postmenopausal women, reported that, after an average of 4.1 years of follow-up, there was no overall difference in CHD endpoints between women randomized to receive placebo or HRT. HRT was given as a continuous combined regimen of 0.625 mg/d of CEE plus 2.5 mg of MPA. Based on a trend of decreasing risk of CHD events with increasing duration of HRT use, the HERS authors speculated that the HERS results were a consequence of domination of the antiatherogenic effects of HRT by early thrombotic effects. The implication was that a net benefit for CHD would have been observed with longer duration of HRT use. However, in HERS II, a study of women recruited to HERS for an additional 2.7 years of follow-up, the anticipated overall net benefit of HRT use for coronary events did not materialize. The lower rates of coronary disease in long-term users of HRT were not sustained. In HERS II, HRT provided no benefit for prevention of ischemic stroke, confirming an earlier report from the randomized portion of HERS.[31]

In the report of the noncardiovascular endpoints of HERS II[20] by Hulley, there was an overall increase in the risk of VTE and biliary tract surgery in HRT users. Also, the risk of fracture was not decreased in HRT users in HERS II. This is inconsistent with randomized trials that have established the effectiveness of ERT and HRT in preventing postmenopausal bone loss.[52,53] The lack of information about use of bisphosphonates and raloxifene after unblinding makes the HERS II findings on fracture somewhat difficult to interpret. In randomized trials, these drugs have been shown to prevent fracture.[54,55] If more women initially assigned to placebo initiated use of bisphosphonates or raloxifene after unblinding, any benefit of HRT use for fracture prevention would be obscured.

It is possible that ERT might prevent CHD in women free of coronary disease. There is a possibility that many women enrolled in the WHI trial had asymptomatic atherosclerosis. The Estrogen Prevention of Atherosclerosis Trial[56] provides only limited evidence. This trial assessed the effect of ERT on carotid intima-media thickness in 222 postmenopausal women without preexisting cardiovascular disease. The women had LDL cholesterol levels of at least 130 mg/dL. They were randomized to receive placebo or 1 mg/day of 17 beta-estradiol. After 2 years of follow-up, the rate of atherosclerosis progression measured as change in intima-media thickness was less in the ERT-treated group than in the placebo group, but the benefit of ERT was limited to women who did not also take lipid-lowering medication.

TABLE 13 Drug Availability, Dosing, and Cost[6,47]

Brand Name	Generic Name	Dosage Forms	Dosing Regimen	Cost/30 days ($)
Premarin oral (Wyeth)	Conjugated equine estrogens (CEE)	oral: 0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.50 mg	1 tablet once daily orally	 22.76 28.85 34.50 39.90 53.70
Premarin injectable (Wyeth)	CEE	injection: 25 mg	1 injection of 25 mg that may be repeated in 6-12 hours for emergency treatment of abnormal uterine bleeding	64.75 for 1 injection
Premarin vaginal (Wyeth)	CEE	oral: 0.625 mg/g x 42.5 g	0.5-2 g daily intravaginally	63.38 - 190.14
Cenestin (Barr)	Conjugated estrogens A, synthetic	oral: 0.3 mg 0.625 mg 0.9 mg 1.25 mg	1 tablet once daily orally	 20.49 25.97 31.20 36.00
Prempro (Wyeth)	CEE/medroxyprogesterone acetate (MPA)	oral: 0.625 mg/2.5 mg 0.625 mg/5.0 mg	1 tablet once daily orally	 39.00 39.00
Premphase (Wyeth)	CEE/MPA	oral: 0.625 mg/5.0 mg	Days 1-14 CEE Days 15-28 CEE/MPA in 1 tablet; 1 tablet once daily orally	39.00
Menest (Monarch)	Esterified estrogens	oral: 0. 3 mg 0.625 mg 1.25 mg 2.5 mg	1 tablet once daily orally	 9.94 14.13 19.71 18.36
Estratest (Solvay)	Esterified estrogens/ methyltestosterone	oral: 1.25 mg/2.5 mg	1 tablet once daily orally	 54.90
Estratest HS (Solvay)	Esterified estrogens/ methyltestosterone	oral: 0.625 mg/1.25 mg	1 tablet once daily orally	 44.40
Estradiol (generics)	Estradiol	oral: 0.5 mg 1 mg	 0.5 mg qd for osteoporosis prevention; 1-2 mg/d for menopausal symptoms, orally	 7.62 10.27 - 20.55
Activella (Novo Nordisk)	Estradiol/norethinedrone	oral: 1 mg/0.5 mg	1 tablet once daily	30.69
Ortho-Prefest (Monarch	Estradiol/norgestimate	oral: 1 mg/0.9 mg	1 tablet once daily	31.47
Estradiol Cream (generic)	Estradiol	intravaginal: 0.1 mg/g x 42.5 g	2-4 grams once daily intravaginally for 1-2 weeks; maintenance doses 1 g 1-3 times a week for 3 weeks	57.34-172.02
Estring (Pfizer)	Estradiol	dermal: 0.0075 mg/24 hrs	1 ring intravaginally for 3 weeks, out for 1 week	104.26
Vagifem (Novo Nordisk)	Estradiol	intravaginal: 25 mcg	1 tablet daily intravaginally for 2 weeks, then 2 times/week maintenance	49.32 for first month, then 21.92 thereafter
Alora (Watson)	Estradiol	dermal: 0.025 mg/24 hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	2 patches/week	 31.92 32.61 33.30 34.00
Climara (Berlex)	Estradiol	dermal: 0.025 mg/24 hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	1 patch/week	 33.63 33.63 33.63 33.63
Esclim (Women's First Health)	Estradiol	dermal: 0.025 mg/24hr 0.0375 mg/24 hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	2 patches/week	 30.80 31.13 31.13 32.30 32.30

(Continued on next page)

TABLE 13 Availability, Dosing, and Cost[6,47] *(continued)*

Brand Name	Generic Name	Dosage Forms	Dosing Regimen	Cost/30 days ($)
Estraderm (Novartis)	Estradiol	dermal: .05 mg/24 hr 0.1 mg/24 hr	2 patches/week	 32.78 35.14
Vivelle (Novartis)	Estradiol	dermal: 0.025 mg/hr 0.0375 mg/hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	2 patches/week	 33.34 33.47 34.12 34.84 35.58
Vivelle-Dot (Novartis)	Estradiol	dermal: 0.025 mg/24hr 0.0375 mg/24 hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	2 patches/week	 33.48 33.48 34.12 34.84 35.58
Combipatch (Novartis)	Estradiol/norethinedrone	dermal: 0.05 mg/0.14 mg/24 hr 0.05 mg/0.25 mg/24 hr	2 patches/week	 37.02 38.14
Estradiol valerate (generics)	Estradiol	injection: 20 mg/ml x 10 ml 40 mg/ml x 10 ml	10 mg-20 mg injection once every 4 weeks	 13.95
Estrogen cypionate (generics)	Estradiol	injection: 5 mg/ml in 10 ml	1 mg-5 mg injection once every 3-4 weeks	 19.98
Estrone (generics)	Estrone	injection: 2 mg/ml x 10 ml 5 mg/ml x 10 ml	0.1 mg-0.5 mg injection 2 or 3 times weekly	 14.95
Ortho-Est (Women's First Healthcare)	Estrone	oral: 0.75 mg 1.5 mg	1 tablet once daily orally	 42.86 56.15
Estropipate (generic)	Estrone	oral: 0.75 mg 1.5 mg 3 mg	1 tablet once daily orally	 12.94 18.60 30.12
Femhrt (Galen)	Ethinyl estradiol/ norethinedrone	oral: 5 mcg/1 mg	1 tablet once daily	 29.34
Medroxyprogesterone acetate (generic)	Medroxyprogesterone	oral: 2.5 mg 5.0 mg	1 tablet once daily for 14 continuous days in a 28-30-day cycle	 4.17 6.30
Aygestin (Wyeth)	Norethinedrone	oral: 5.0 mg	1 tablet once daily for 14 continuous days in a 28-30-day cycle	 50.40

Costs are based on the average wholesale price per unit in 2003.[57] The cost per 30 days was calculated by multiplying the unit cost by the number of doses per month, based on the dosing regimen. For the sake of a fair comparison, costs of continuous dosing regimens only, not cyclic, were used. Dosing regimens for indications other then the treatment of menopausal symptoms and the prevention of osteoporosis were not included, in an effort to make fair comparisons. This table was added in peer review and was not used in the actual monograph. For the P&T Committee, the author calculated the cost from the pharmacy claims data for the actual patients treated by the IHN. The pharmacy claims data are proprietary and confidential information and could not be used here.

The HOPE study results in 2001 showed that using lower doses of combination therapy such as CEE 0.3 mg/MPA 1.5 mg was just as effective in treating vasomotor symptoms as 0.625 CEE mg alone. The HERS and HERS II trials concluded that HRT did not protect postmenopausal women with CHD from further cardiovascular events. The WHI trial concluded that HRT increased women's risk for breast cancer, VTE, and CHD by 7 to 8 women per 10,000 treated per year.

Delivery of HRT via the transdermal patch delivers more of the drug into the blood stream than oral administration because ethinyl estradiol is not metabolized by first-pass metabolism when given via this route. Ethinyl estradiol is a much more potent estrogen than its metabolite, estrone. The vaginally administered estrogens also are not subject to first-pass metabolism and deliver the product locally to help treat vaginal atrophy. The estradiol ring and estradiol vaginal tablet are not absorbed systemically and can be used safely in almost any patient if vaginal atrophy symptoms are present.

Most of the medical literature has focused on the combination of CEEs and MPA as standard HRT. This was the HRT ther-

apy used in the HERS and WHI trials. Whether different estrogens or progestins exert different cardiovascular effects remains to be seen. However, the FDA has asked that the prescribing information for all estrogen and estrogen/progestin combination products carry the warnings now found in the conjugated estrogens/medroxyprogesterone products.

As it stands today, the evidence suggests that HRT increases the risks of breast cancer and CHD events in women who already have CHD. It can be presumed that many women in the WHI trial already had undiagnosed CHD, since they were mostly in their sixties at the time of the study and many had cardiovascular risk factors. The FDA is urging that nonestrogen alternatives be considered in the prevention of osteoporosis. HRT is still used for symptoms of menopause but should be used only for the shortest duration at the lowest effective dose. If menopausal symptoms of vaginal atrophy are being treated, vaginally delivered products, which are not systemically absorbed, should be considered first-line therapy.

P&T Committee Recommendations

It had been established some years ago that there is little difference in efficacy or side-effect profiles of the various HRT products. The latest findings suggest that HRT use is associated with an increased risk of breast cancer and cardiovascular disease. Because of this, use should be restricted to the lowest effective dose and shortest duration possible. The FDA has mandated that all HRT products carry warnings in their labels regarding these risks, and these risks are essentially a therapeutic class effect.

Therefore, the choice of products can be made based on economics. At our IHN, the outpatient pharmacy risk is retained by the 5 major health plans in the region. For our P&T committee, the drug coverage status and product placement in each of the formularies of the health plans is a principal focus. In the interest of continuity of care, it is desirable for patients to be able to receive the same medication as inpatients as they would as outpatients. Most women are started on HRT as outpatients. The final P&T decision was to add all of the generic products and the branded products that were available at the second-tier copay (preferred brand) on most of the outpatient drug formularies of the 5 major health plans that insure the patients served by this IHN.

Conclusion

This is an example of a clinical monograph that was used in real-world clinical decision support at an administrative level with input from clinicians (i.e., P&T committee members). This is not an exhaustive review of HRT. There is a much larger body of literature available that evaluates the efficacy of HRT in osteoporosis prevention, for example. This monograph author assumed that P&T committee members, who were practicing pharmacists and physicians, had sufficient knowledge of the older published trials, and, therefore, only the latest pivotal trials were presented. As a result of this monograph, P&T committee members were informed about the current evidence of the risks of HRT and the need to limit therapy to the shortest duration of time.

DISCLOSURES

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REFERENCES

1. Shumaker SA, Legault C, Rapp SR, et al. for the WHIMS Investigators. Estrogen plus progestin and incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative: a randomized controlled trial. *JAMA.* 2003;289(20):2651-62.

2. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA.* 2003;289(20):2663-72.

3. Academy of Managed Care Pharmacy. *Format for Formulary Submissions* Version 2.0. available at: www.fmcpnet.org. Accessed June 9, 2003.

4. Nolan TE, Johnson S, Dore R, et al. The faculty speaks: a roundtable discussion on postmenopausal Health Care. Medscape CME activity. HRT and SERMs: new guidelines for patient management–part 2. Available at: http:www.medscape.com/viewarticle/448858. Accessed June 9, 2003.

5. Novation Drug Monographs. University Health System Consortium, Oak Brook, IL. Available at: www.uhc.edu. Accessed June 9, 2003.

6. Wickersham RM, ed. *Drug Facts and Comparisons.* St Louis, MO: Facts and Comparisons, Inc.; 2002:217-33.

7. London SN, Hammond CB. The climacteric. In: Danforth DN, Scott JR, eds. *Obstetrics and Gynecology.* 5th ed. Philadelphia, PA: Lippincott; 1986:905.

8. Utian WH. Biosynthesis and physiologic effects of estrogen and pathophysiologic effects of estrogen deficiency: a review. *Am J Obstet Gynecol.* 1989;161: 1828-31.

9. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med.* 1999;340(23):1801-11.

10. Herrington DM, Howard TD, Hawkins GA, et al. Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. *N Engl J Med.* 2002;346:967-74.

11. Premarin (conjugated estrogen tablets) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; July 2003.

12. Ravnikar V. Physiology and treatment of hot flushes. *Obstet Gynecol.* 1990;75(suppl 4):3S-8S.

13. LoPrinzi CL, Pisansky TM, Fonseca R, et al. Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. *J Clin Oncol.* 1998;16:2377-81.

14. Stearns V. Isaacs C, Rosland J, et al. A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors. *Ann Oncol.* 2000;11:17-22.

15. Mishell DR. Estrogen replacement therapy: an overview. *Am J Obstet Gynecol.* 1989;161:1825-27.

16. Young RL, Kumar NS, Goldzieher JW. Management of menopause when estrogen cannot be used. *Drugs.* 1990;40:220-30.

17. Whitehead MI, Hillard TC, Crook D. The role and use of progestogens. *Obstet Gynecol.* 1990;75(4 suppl):59S-76S.

18. Hulley S, Grady D, Bush T, et al. for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA.* 1998;280:605-13.

19. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA.* 2002;288(1):49-57.

20. Hulley S, Furberg C, Barret-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone replacement. Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA.* 2002;288:58-66.

21. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials.* 1998;19:61-109.

22. Loose-Mitchell DS, Stancel GM. Estrogens and Progestins. In: Hardman JG, Limbird LE, ed. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* New York: McGraw-Hill; 2001:1597-1634.

23. Lievertz RW. Pharmacology and pharmacokinetics of estrogens. *Am J Obstet Gynecol.* 1987;156:1289-93.

24. Estrogens (systemic and vaginal). In: Johnson KW, ed. *USPDI.* Rockville, MD: U.S. Pharmacopoeial Convention; 1994:1304.

25. Chetkowski RJ, Meldrum Dr, Steingold KA, et al. Biologic effects of transdermal estradiol. *N Engl J Med.* 1986;314:1615-20.

26. Powers MS, Schenkel L, Darley PE, et al. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17 beta-estradiol: comparison with conventional oral estrogens used for hormone replacement. *Am J Obstet Gynecol.*1985;152:1099-1106.

27. Pugh MC, Mullins PM. Hormone replacement therapy. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy*. Stamford, CT: Appleton & Lange; 1999:1355-65.

28. Angerer P, Stork S, Kothny W, et al. Effect of oral postmenopausal hormone replacement on progression of atherosclerosis: a randomized, controlled trial. *Arterioscler Thromb Vasc Biol.* 2001;21:262-68.

29. Angerer P, Stork S, Kothny W, von Schacky C. Effect of postmenopausal hormone replacement on atherosclerosis in femoral arteries. *Maturitas.* 2002;41:51-60.

30. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med.* 2000;343:522-29.

31. Simon JA, Hsia J, Cauley JA, et al. Postmenopausal hormone therapy and risk of stroke: the heart and estrogen-progestin replacement study (HERS). *Circulation.* 2001;103:638-42.

32. Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med.* 2001;345:1243-49.

33. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-33.

34. Psaty BM, Smith NL, Lemaitre RN, et al. Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. *JAMA.* 2001;285(7):906-13.

35. Prempro/Premphase (conjugated estrogens/medroxyprogesterone acetate) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; revised June 2003.

36. Cenestin (conjugated estrogens A, synthetic) [prescribing information]. Cincinnati, OH: Duramed; revised January 2003.

37. Davis J. FDA approves new HRT warning label. Medscape Alert. Available at: http://www.medscape.com/viewarticle/447629. Accessed January 15, 2003.

38. Walsh BW, Li H, Sacks FM. Effects of postmenopausal hormone replacement with oral and transdermal estrogen on high density lipoprotein metabolism. *J Lipid Res.* 1994;35:2083-93.

39. Archer D. HOPE Study 2001. Women's health: an update on hormone replacement therapy. Wyeth Pharmaceuticals, GMR Group. [CD-ROM]. Presented at: AMCP Educational Conference; October 9, 2002; Washington, DC.

40. Mashchak CA, Lobo RA, Dozono-Takano R, et al. Comparison of pharmacodynamic properties of various estrogen formulations. *Am J Obstet Gynecol.* 1982;144:511-18.

41. Lufkin EG, Carpenter PC, Ory SJ, et al. Estrogen replacement therapy: current recommendations. *Mayo Clin Proc.* 1988;63:453-60.

42. Sitruk-Ware R. Estrogen therapy during menopause: practical treatment recommendations. *Drugs.* 1990;39:203-17.

43. Notelovitz M. Estrogen replacement therapy: indications, contraindications, and agent selection. *Am J Obstet Gynecol.* 1989;161:1832-41.

44. Schairer C, Lubin J, Troisi R, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA.* 2000;283(4): 485-91.

45. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst.* 2000;92(4):328-32.

46. Writing group for the PEPI trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Post-menopausal Estrogen/Progestin Interventions (PEPI) trial. *JAMA.* 1996;275:370-75.

47. McEvoy GK, ed. *AHFS Drug Information.* Bethesda, MD: American Society of Health-System Pharmacists; 2003:2936-44.

48. Utian WH, Shoupe D, Bachman G, et al. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril.* 2001;75(6):1065-79.

49. Archer DF, Dorin M, Lewis V, et al. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on endometrial bleeding. *Fertil Steril.* 2001;75(6):1080-87.

50. Jensen J, Riis BJ, Strom V, Christiansen C. Continuous estrogen-progestogen treatment and serum lipoproteins in postmenopausal women. *Br J Obstet Gynaecol.* 1987;94:130-35.

51. Sporrong T, Hellgren M, Samsioe G, et al. Comparison of four continuously administered progestogen plus oestradiol combinations for climacteric complaints. *Br J Obstet Gynaecol.* 1988;95:1042-48.

52. O'Connell D, Robertson J, Henry D, Gillespie W. A systematic review of the skeletal effects of estrogen therapy in postmenopausal women, II: an assessment of treatment effects. *Climacteric.* 1998;1:112-23.

53. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med.* 1992;117:1016-37.

54. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metabol.* 2000;85:4118-24.

55. Ettinger B, Black DM, Mitlak BH, et al. for the MORE Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA.* 1999;282:637-45.

56. Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2001;135:939-53.

57. *2003 Drug Topics Redbook.* Montvale, NJ: Thomson PDR; 2003

Cost-Effectiveness Analysis and the Formulary Decision-Making Process

ZHIXIAO WANG, MS; J. WARREN SALMON, PhD; and SURREY M. WALTON, PhD

ABSTRACT

BACKGROUND: Faced with high drug expenditures in an environment of cost containment, drug formulary systems, particularly in managed care, have become more dependent on pharmacoeconomic evaluations to assess the value of new products. Within pharmacoeconomics (PE), cost-effectiveness analysis (CEA) is the most commonly used method. However, current methodological concerns about CEA have limited its practical contribution to the formulary process. Advances in analysis are likely to improve the relevance of CEA over time.

OBJECTIVE: The purpose of this paper is to review CEA, its limitations, and its applications in formulary decision making in order to promote greater utility of CEA for managed care pharmacists.

SUMMARY: Enhancements to CEA, such as the development of modeling software, rank-order stability analysis, cost-consequence analysis (CCA), and budget impact analysis are discussed. A combined method of CCA-CEA and standardized guidelines are suggested to improve the impact of CEA in the drug formulary process.

CONCLUSION: Along with advances in its methodology and relevant standardized guidelines, CEA will gain increased importance in formulary decision making, helping to assure the goal of cost containment while ensuring quality of care.

KEYWORDS: Cost-effectiveness analysis, Economic evaluation, Formulary decision making, Standardized guidelines

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Formularies have existed in various forms for nearly 100 years.[1] Beginning as a simple list of available drugs, they have evolved into a dynamic guide for the selection and application of preferred drug therapies by pharmacists and physicians in clinical applications. Formularies have been utilized widely at the hospital, community, and national levels with distinct functions in cost containment as well as quality assurance.[2] Traditionally, formularies have been used to promote the rational use of drugs and to set drug use standards.[3] Pharmacy and therapeutics (P&T) committees make formulary decisions and evaluate whether the benefits of therapies outweigh the risks primarily based on the documented safety and efficacy of new drug formulations.

However, with drug expenditures increasing at the rate of 14% to 18% a year in ambulatory care and a national drug bill for 2001 that reached between $160 billion and $170 billion, cost considerations have become paramount.[4] The underlying factors for higher drug expenditures, in addition to price increases, are an aging population, longer life spans, improvements in the diagnosis and treatment of diseases, rising prevalence of chronic diseases, the advent of "lifestyle medications," increases in the number of new drugs into the market, and increases in spending on drug promotion, including direct-to-consumer (DTC) advertising. The May 2002 report from the National Institute for Health Care Management, "Prescription Drug Expenditures in 2001: Another Year of Escalating Costs," attributed 39% of the increase in prescription drug expenditures from 2000 to 2001 to the increase in the number of prescriptions, 37% to "price increases," and 24% to a "shift to higher-cost drugs,"[5] also known as drug mix.

The increase in expenditures and related financial pressures has led to a reassessment of the role of drug formularies.[3] Contemporary formulary selection processes now place greater emphasis on the containment of drug costs and assessment of the economic efficiency of drug treatments. Ideally, according to the Academy of Managed Care Pharmacy (AMCP), "every drug would be selected for value, properly prescribed, competently dispensed, diligently monitored, and continually assessed for effectiveness."[6]

In this regard, government, third-party payers, and health care providers are paying more attention to cost-effectiveness analysis (CEA) because it is the most common economic evaluation method for health care.[7] Cost-effectiveness identifies, measures, and compares the net costs and net benefits of alternative interventions. Comparisons are usually expressed as quality-adjusted life-years (QALYs) gained, life-years saved, or disability days avoided. However, little is known about the real

impact of CEA or how CEA results are implemented in actual settings. For example, a recent article by Carey et al. asserted that pharmacoeconomics (PE) has already slowed down the rise in drug costs for insurers and other payers, but no supporting evidence was provided.[4]

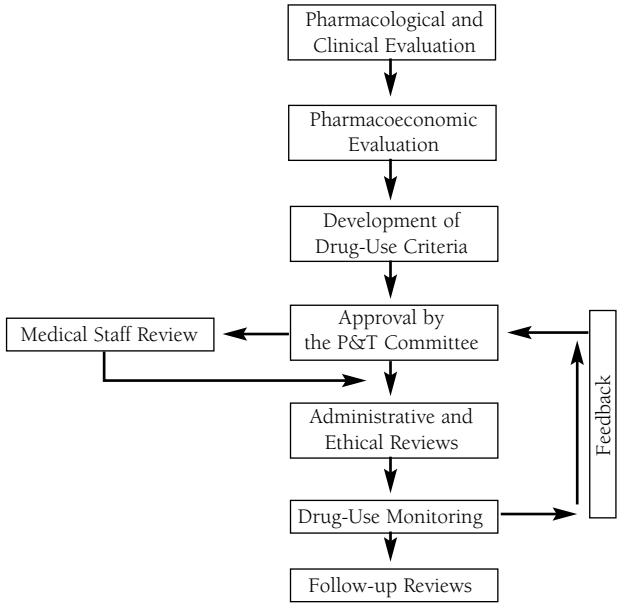
The purpose of this article is to review and evaluate CEA in terms of its application in formulary decision making and to examine available analytic tools that may facilitate formulary decisions.

The Formulary Decision-Making Process[8]

The general procedure of adding a drug to the formulary is described in 7 typical steps by Glennie et al.[8] (Figure 1):

1. ***Pharmacological and clinical evaluation.*** A detailed clinical justification for the new drug is first submitted by the potential prescribers or the manufacturer to the P&T committee, which is composed of pharmacists and physicians and, in some cases, administrators. Subcommittees may be needed to evaluate high-tech or specialty drugs. At this initial stage, only clinical decisions concerning the use of the drug are usually addressed. Drug information (such as new ingredients, efficacy, safety, tolerability, dosage and route of administration, ease of use, patient acceptance, etc.) from clinical trials as well as literature reviews is evaluated at this stage.
2. ***Pharmacoeconomic evaluation.*** After pharmacological and clinical evaluations, the costs and economic benefits of the drug are addressed. This is the step where PE tools may be applied. Optimally, the PE evaluation would draw on published data, noting authorship, funding sources, methodologies, etc., and be assessed by persons with an understanding of PE. The P&T committee may contract with knowledgeable pharmacoeconomists for consultation when necessary to evaluate the data produced by the pharmaceutical companies. Experience with economic modeling is crucial to examine whether assumptions put forth by a drug company in a given model are reasonable and applicable to the specific population served by the provider organization. The fit is never perfect, and pharmacy managers often need to spend time discerning the value of drug company-offered models. Here, various data sources can be employed (e.g., databases of pharmacy, medical, and laboratory claims; PE literature; expert panels; experienced real-world practitioners), where the time spent in acquiring data should be proportional to the magnitude of the decision at hand by the P&T committee.
3. ***Development of drug-use criteria.*** Criteria should be developed with the goal of ensuring appropriate drug use in the covered population over time. The clinical evaluation and PE evaluation mentioned above are useful in helping the P&T committees develop specific criteria. Managed care tools such as prior authorization, quantity limits, prescriber edits, or education interventions with prescribers may be applied, as well as drug benefit design, to promote appropriate use of the adopted new drug.
4. ***Approval by the P&T committee.*** Once the clinical and PE evaluations are completed and the criteria for the use of the drug have been developed, the compiled material should be reviewed and adopted or rejected by the P&T committee. P&T committee recommendations are typically disseminated to the medical and pharmacy staff.
5. ***Administrative and ethical reviews.*** Administrative reviews, though important, tend to be relatively straightforward in terms of what is being examined, such as the terms of rebate contracts with drug manufacturers. As a rule, the health plan is responsible for providing summary information to the manufacturers about the principal drug benefit plan parameters such as copay tiers and the number of health plan members subject to each benefit design. Ethical reviews may include consideration of the type and scope of claim-level data required by the rebate or discount contract with the pharmaceutical manufacturer. Hence, the drug discount-rebate contract process requires careful review that includes coordination of the P&T committee process carried through to the administrative level.
6. ***Drug-use monitoring.*** Structured monitoring of drug use and a plan for follow-up evaluation is an inherent part of the P&T committee's responsibility to optimize drug use. At the time of adoption, plans should be put in place for such continuous quality improvement reviews of drug claims data, including the need for ongoing drug utilization reviews.
7. ***Follow-up review by the P&T committee.*** Following

FIGURE 1 Flowchart of the Formulary Decision-Making Process



Developed by Zhixiao Wang, based on the procedure proposed by Glennie JL et al.[8]

approval, formulary decisions should be subject to a dynamic process of constant oversight. Effective formulary management requires the P&T committee to review the results of retrospective or prospective audits to ensure the appropriate and effective use of drugs.

Cost-Effectiveness Analysis and Its Application in the Formulary Process

CEA has been the most commonly used PE method in drug evaluation.[9] It can help decision makers quantify the value of competing interventions and maximize efficacy of care. However, it also tends to rely on data and assumptions regarding costs and effects that can be manipulated to make a product look better.

Although certain countries have formalized guidelines for CEA, there is not a universally accepted approach to this PE technique in the United States. The U.S. Food and Drug Administration (FDA) does not require CEA in drug approvals, but, increasingly, provider organizations seek such data along more standardized formats, as recommended in the *AMCP Guidance for Submission of Clinical and Economic Evaluation Data to Support Formulary Listing in U.S. Health Plans and Pharmacy Benefits Management Organizations.*[10] Issues about guidelines will be discussed later in this article.

In CEA, costs are measured in dollars and then compared with the effects or improvements of treatments, which are measured in various "natural" or constructed units, such as quality-of-life measures. CEA is most appropriate when the alternative therapies result in different levels of a common effect, such as 2 asthma medications that result in "symptom-free days."[11] The CEA is constructed to identify the most cost-effective therapy when the goal is to provide the highest-quality pharmaceutical care within a fixed budget. To be informative, the drug alternatives in the analysis should include all reasonable options and a baseline comparator (which should reflect the current practice and use a drug on the current formulary).[12] For example, when P&T committees consider new drugs, such as the COX-2 drugs celecoxib, rofecoxib, or valecoxib for formulary inclusion, the COX-1 inhibitors (NSAIDs) should be considered as alternative therapy.

The effect measured should be the primary outcome of the treatment. It is desirable to use final outcomes such as lives saved, life-years saved, cases prevented, rates of a specific side effect, etc. Sometimes, intermediate outcomes can be used if the relationship between the intermediate and final outcome measure can be estimated. For example, the intermediate outcomes of reduced cholesterol levels or reduced blood pressure can be used because they predict future health outcomes, including reduction in cardiac risk.

Measured costs and effects are calculated within realistic clinical pathways, along with probabilities of patients going down each of the clinical paths. The probabilities and paths are used, within some form of model of uncertainty such as a decision tree or a Markov model, to calculate population-expected values. Markov models are different from decision trees in that Markov models can simulate the uncertainty from repeated events, such as complications in the chronic conditions, by putting patients in a finite number of mutually exclusive and exhaustive health states; the probability of transition between health states depends on the current status. Decision trees are only appropriate for simulating uncertainty of nonrecurrent chance events and outcomes. Then, usually, 2 forms of ratios are calculated. The first type of ratio is an average cost-effectiveness ratio, which is defined as the mean value of the costs divided by the mean value of effect for each alternative treatment. Average cost-effectiveness ratios (change in cost divided by change in effect) can be useful in considering the overall affordability of an intervention.

However, average ratios can be misleading when making a decision between 2 exclusive treatments paid for out of the same budget because they do not provide direct information about the costs and effects of making such a decision. For example, in a cost-effectiveness study about interferon beta in multiple sclerosis relative to usual care in the health care setting of the United Kingdom (UK), the average cost per QALY gained with interferon beta was £7,852.3 (pounds sterling) while the average cost per QALY with the usual care was £2,056.8.[13] All that one can tell from this information is that the average cost for interferon beta was higher than that of usual care. Upon closer inspection, discussed in the next paragraph, the average cost-effectiveness ratio is found to be a poor approximation of the actual trade-off relevant to the decision. The reason is that average ratios are a comparison with no treatment, while the relevant and more important decision is between the new treatment and the existing standard of care.

This second type of ratio is called an incremental cost-effectiveness ratio (ICER), which is the change in costs divided by the change in effects in moving from a lower-cost/lower-effect treatment to a higher-cost/higher-effect treatment. Incremental ratios provide an estimate of the cost corresponding to a change in the measured effect through a change in drug therapy and thereby provide information regarding the relative efficiency of alternative options. In the above study involving interferon beta, the ICER was £51,582 per QALY in comparing interferon beta with usual care, which indicated that an additional £51,582 has to be spent to gain 1 additional QALY when switching from usual care to interferon beta.[13] Such a high ICER may not be justified as a cost-effective preventive treatment for multiple sclerosis from the National Health Service perspective in the UK.

Finally, sensitivity analysis should be conducted to test the robustness of the results. CEA studies are inherently based on assumptions, and these assumptions often reflect a certain degree of uncertainty. Moreover, values of some variables in CEA are very difficult to measure with great accuracy, or they change over time and in different settings. By changing the val-

ues of these variables over a certain range or by changing the assumptions of the CEA model, sensitivity analysis provides insight into the robustness of results. Sensitivity analysis also assists in identifying variables that may have a large impact on the results from the CEA model. For example, in a study comparing nefazodone and imipramine (antidepressants), sensitivity analysis indicated that the cost-effectiveness model was most sensitive to assumptions on treatment compliance rates.[14] The ICER ranged from $2,572 to $5,096 per QALY gained when varying compliance rates while the base case ICER was $4,065 per QALY gained. This gives readers a better sense of how to generalize the ICER results and what to expect about the ICER of nefazodone relative to imipramine in situations where compliance rates are different from the base estimate. For example, if the entire range is considered a good value for increased health, then one can be more confident about adopting the new treatment into a patient population with unknown compliance.

Application of Cost-Effectiveness Analysis in the Formulary Process

If used properly, CEA can facilitate formulary decision making for drugs within the same class or with a common effect (e.g., cholesterol reduction) within a relatively homogenous population. It can also be used to evaluate the economic impact of a formulary decision if head-to-head (i.e., comparing a treatment with the next best available treatment) data are available. Some studies have addressed the application of CEA in the formulary decision-making process, though not all of them were positive. For example, a survey of 103 hospitals conducted in 1995 regarding the use of CEA in a hospital formulary decision revealed that CEA was only "a minor tool" in the decision making.[15] The most commonly stated barriers to effective use of CEA included lack of timeliness of studies, lack of generalization on hospitalized patients, biased industry sponsorship, and lack of expertise on economic evaluation.

We examined the potential impact of CEA by researching selected studies. The literature search was performed in July 2001 on MEDLINE and Ovid, 2 large electronic journal databases that provided access to a range of bibliographical or full-text biomedical databases, using different combinations of keywords of "pharmacoeconomics," "cost-effective analysis," "formulary," and "formulary decision." The objective of this literature search was to identify typical studies that reflected the potential benefits of CEA as well as current levels of CEA utilization on formulary decisions. A total of 62 abstracts were identified, and 22 of them were found to be relevant to the application of PE research in formulary decisions. Original articles were obtained and analyzed. Most articles were academic studies rather than examples of how the results of CEAs actually assisted formulary decisions to achieve more cost-effective use of drug therapies.

Cohen studied the application of CEA in the treatment of depression and concluded that the total cost of disease management is similar for generic tricyclics and the more expensive selective serotonin reuptake inhibitors.[16] This result was due to the higher costs of related resource utilization such as outpatient visits and hospitalizations associated with tricyclics that offset their advantage in lower drug acquisition cost. Cohen suggested that CEA in formulary decision making would optimize the use of overall health care resources. This is the key since drug-use costs include more than just the direct acquisition cost of the drug itself.

McCoy et al. did a CEA to assess a 1995 formulary decision that designated cimetidine as the primary histamine-2 receptor antagonist (H2RA) and restricted the use of famotidine.[17] The study used a decision-tree model to estimate the average direct medical costs for the 2 treatments in a 2-month period. The results showed that the average cost of receiving cimetidine was $82.01 and the average cost of famotidine therapy was $92.45, while treatment success rates, the common efficacy measure, were identical for cimetidine and famotidine. The study supported the formulary decision at the health care institution. Therefore, retrospective CEA studies can serve as a measure of evaluation of past formulary decisions.

An important cost category of drugs is antibacterial drugs, which account, generally, for 6% to 21% of a drug budget, or 3% to 25% of the total prescription market in various countries.[18] Hillman discussed the role of CEA in the development and acceptance into formularies of new oral antibiotic products.[18] The author suggested that a comprehensive CEA should be developed by comparing the total stream of costs of an intervention with the total stream of outcomes, with a long-term follow-up. Such analyses would disclose the treatment alternative's hidden costs and real benefits. The author also pointed out that the challenge for the development of new antibiotics is to balance patient needs, such as convenience for administration, safety, and a broad-spectrum of activity, with the economic needs of society within the cost-effectiveness perspective, that is, efficient use of limited resources to achieve maximum benefits.

Finally, in a look to the near future, biotechnology products used for the treatment of cancer patients have already reached the marketplace. Generally, they are very expensive because of the high input of capital and other resources consumed in research and development. For example, imatinib mesylate (Gleevec), a new drug for the treatment of chronic myeloid leukemia, is estimated to cost a patient $25,338 per year if the 400 mg tablets are taken by the patient once daily ($4,222.98 for a supply of 60 tablets [www.drugstore.com; accessed November 7, 2003]). A conservative estimate of the minimum cost of 6 months of maintenance treatment with epoetin alpha (Procrit), a biotech drug for the treatment of anemia in chemotherapy, is $1,867, assuming the patient uses the 2,000 units/ml vial 3 times per week, the lowest dosage available ($414.99 for a supply of 18 vials [www.drugstore.com; accessed

November 7, 2003]).

As new targets emerge, and the rate of new drug introductions increases, institutions and governments will have to decide whether the benefits of these drugs are worth the higher costs. So incorporation of PE evaluations into formulary decision making for biotechnology drugs will definitely become critical.[8] For example, integration of monoclonal antibody (MoAb) products such as gemtuzumab (Mylotarg) or alemtuzumab (Campath) into the existing health care system is a challenge after being approved by the FDA in 2000 and 2001, respectively, because of their high acquisition costs: approximately $12,000 per course of therapy for gemtuzumab and $12,000 to $17,000 per month for alemtuzumab. MoAb products will need both proven clinical and economic profiles to support their place in the health care system.[19]

Although hundreds of studies about CEA have been published, its present contribution in actual formulary decisions is still minor. Researchers have recently shown that CEA is rarely used to inform decisions about health services in the United States.[20] Although 72% of hospital pharmacy departments reported use of some CEA in formulary decision making, only 37% of them had the requisite CEA information available to them when considering a new drug for inclusion in a formulary because PE studies generally appeared in the postmarket phase when the new drug was already in the market.[15] Other surveys showed that, although CEA could have significant influence on formulary decisions made by pharmacy benefit managers (PBMs), health maintenance organizations (HMOs), and other health plans, some barriers impede the extensive application of CEA, such as inappropriate comparators, methodological issues in measuring costs and outcomes (e.g., what costs to be included, which effects to be measured, and how long to follow patients to determine these outcomes), lack of generalizability, concerns regarding study sponsorship, and lack of expertise for economic evaluation.[21,22] Although there is no exact number for what percentage of new drug evaluations for inclusion to formularies utilized CEA, it is obvious that the function of CEA was minor in pharmaceutical decision making in hospitals.[15] For HMOs and PBMs, market dynamics and the rise in drug expenditures demand greater efficiency and evaluation of medical care budgets that extend beyond the pharmacy budget only, increasing the importance and value of CEA for new, expensive drug therapies.

Limitations of Cost-Effectiveness Analysis

At present, there are significant limitations of CEA in formulary decision making. First, CEA is fundamentally limited to comparing a single outcome of a therapy or a single summary measure of related outcomes. Hence, the results hinge on the selection of the effect (outcome). Some diseases may have no distinct and unique measures that reflect the overall benefits/outcomes of drug therapies to serve as the indicator of outcomes. For example, reduction of gastroesophageal reflux disease symptoms may be used as the effect measure for a CEA, but this effect does not necessarily reflect how much patients really benefit. Another example is chemotherapy. Although chemotherapy may extend a patient's life, its side effects may also severely impair the patient's quality of life. Therefore, some PE studies tend to use more than 1 effect measure to capture treatment outcomes. For example, a study comparing the cost-effectiveness of antidepressants provided cost-effectiveness ratios for 2 outcome measures—symptom-free days and treatment success rates, which were defined as a more than 50% decline on scores of depression instruments such as Beck Depression Inventory and Hamilton Rating Scale of Depression, without relapse over a certain duration.[23] Similarly, a general or disease-specific, health-related quality of life (HRQL) instrument score can be used in conjunction with clinical indicators to provide more information to the audiences.

CEA is simply a measure of production efficiency, not a measure of net gains or losses in welfare.[24] CEA can only identify the most efficient treatment, not whether the clinical outcomes gained are worth the cost of implementing the treatment. The most efficient treatment may still not be an acceptable use of resources, or treatments that look expensive in terms of the measured effect may produce unmeasured gains valued very highly by patients. Life-style drugs, such as sildenafil (Viagra) and minoxidil (Rogaine), are very expensive in terms of effect compared with life-saving drugs, but their benefits to the patients are highly valued and significantly impact reported quality of life.

A second limitation of CEA arises from inappropriate application of the tool. Some CEA studies compare only the new drug therapy with older therapies or even a placebo,[25] which can result in favorable incremental ratios simply by construction of the analysis. A close substitute in the same class or the most commonly used treatment would reflect the real value of the new drug and, therefore, be more informative to decision makers.

A third limitation is that timeliness in conducting PE analyses is often problematic in that a time lag for publication of studies makes them unavailable for formulary decisions when new drugs enter the market. Ideally, research should be completed before product launch and be available from the manufacturer if not yet published. The absence of reliable PE evaluations presents a major dilemma for P&T committees. Fortunately, many manufacturers are attempting to integrate PE research early in the drug development process.[26] Specifically, pharmaceutical companies can establish PE teams in Phase I clinical trials to gather relative economic information, conduct "cost-of-illness" studies, and formulate a PE model. In Phase II (small controlled clinical trials for safety and efficacy), preliminary PE research is then conducted, and in Phase III (large controlled or uncontrolled trials for efficacy), more extensive PE analyses are performed. Further, all the PE data gathered

TABLE 1 Description of Analytic Methods

Method	Description	Advantages	Disadvantages
Cost-Effectiveness Analysis (CEA)	Goal: To maximize a specific health-effect measure for a fixed budget. Measures costs in dollars and compares with effects in natural units (e.g., dollar/life-year saved). Results: Average Cost-Effectiveness Ratio, Incremental Cost-Effectiveness Ratio	Quantifies the trade-off between costs and health effects. Measures effect in natural units that are easy for clinicians to understand and interpret. Considers health effects equally across patients.	Results depend on the measure of effect and the comparators selected in the analysis. Primary measure of effect may miss important benefits. Decision makers are left to decide whether the treatment is worth doing. Ratios do not give information about total impact on costs and effects.
Cost-Consequence Analysis (CCA)	Calculates and lists all costs and effects separately. Further economic evaluation such as CEA can be done based on the cost-effect list.	Decision makers have the flexibility to choose the costs and effects of interest to conduct economic evaluation.	Decision makers are left to decide whether the treatment is worth doing.
Budget Impact Analysis (BIA)	Measures the budget impact by the product of net cumulative cost of treatment and number of patients in specific populations.	Ability to measure the financial impact of adding a new drug to the formulary on the provider's budget.	Does not incorporate health effects.
Conventional Sensitivity Analysis (CSA)	Varies one or more probabilities or costs to identify variables that have a big impact on the results of economic evaluation.	One-way analysis is easy and provides some information about the robustness of the result.	Often, sensitivity analyses ignore relationships (e.g., correlations) between variables. Selection of which variables to include can bias results.
Probabilistic Sensitivity Analysis (PSA)	Uses Monte Carlo simulation to model variance in estimates. Model parameters can be randomly selected from inputted distributions, and repeated simulation of patient cohorts illustrates potential variance in the model.	Can incorporate realistic distributional qualities of certain parameters and can incorporate known relationships between parameters in a model.	Results are more difficult to interpret. Involves selection of variables to include in the analysis and selection of the distribution to use. Different random number generators used on the simulations can affect the results.
Rank-Order Stability Analysis (ROSA)	Provides the range for variables over which results are valid. (Similar to a confidence interval approach.)	Provides a framework for how to vary parameters and includes all relevant parameters in the analysis.	Does not solve problems with multivariate sensitivity analysis. Method of how to select ranges of variables is not yet fully validated.

in Phases I, II, and III are analyzed and prepared for supporting the application for managed care organization (MCO) formulary listing. In this way, some valuable information can be gathered for a PE assessment by the P&T committee on a timely basis.

A fourth limitation is that drug company sponsors may make different modeling assumptions or give varying perspectives for the same set of drug therapies. The studies may have very different results and sometimes can be contradictory. Consequently, PBM and health plan decision makers must, at a minimum, perform their own independent assessment of the CEA model and reinterpret the findings. More commonly, the objectivity of manufacturer-sponsored CEA studies is called into question, which tends to result in dismissal of these studies in decision making.[25]

Furthermore, it is sometimes recommended that CEA should take a social perspective rather than the view of segregated parties, such as patients, payers, or clinicians.[9] However, cost categories from a CEA study with a social perspective are broader than those from the perspective of a specific institution or health plan because, for example, providers may not consider patient costs or social costs. From a social perspective, costs would include time and costs that patients spend in the waiting room and transportation and even time and costs their families and friends spend in caring for the patient. However, these cost categories may not be as important from the payer's perspective. For example, evaluation of the cost-effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C from a social perspective showed that the ICER was €11,800 (euros) per QALY.[27] Decision makers from different interests, such as payers, may find information derived from a social perspective important but less so than the business interests associated with delivering the best possible care at an affordable price.

A fifth limitation is disagreement about what costs to include. Components generally included in CEA studies are direct costs (medical and nonmedical direct costs) and indirect costs reflecting productivity losses. However, health economists argue that, in some cases, productivity costs are implicitly included in the denominator of the cost-effectiveness ratio and therefore should not be added to the numerator.[28] For example, work days and leisure time lost from illness are indirect costs and can be included in the total costs. However, if the effect

measure is also adjusted for loss of time from work and leisure, the analysis would involve double counting. Furthermore, there is debate regarding how indirect costs should be calculated. Currently, the Human Capital method and the Friction Cost method are used to estimate indirect costs.[29,30] The Human Capital method quantifies the total loss of productivity in terms of total forgone earnings, while the Friction Cost method measures the cost as lost earnings up to the time it takes for the worker to be replaced. Estimates using these 2 methods can be quite different, particularly for long illnesses and high-mortality illnesses.[29] One study found that the short-term indirect costs of back pain estimated by the Human Capital method were 3 times higher than the indirect costs estimated by the Friction Cost method.[30]

Moreover, as discussed above, CEA typically leads to results presented in terms of ratios, i.e., average and incremental ratios. An inherent limitation of ratios is that they hide the underlying magnitude of the numerator and denominator. Hence, they do not inform decision makers regarding whether the treatment will have a significant overall impact on the budget.

Finally, PE models often rely on many assumptions, which may be incorrect or inappropriate. This has been one of the major concerns for decision makers and other readers. It is important to validate PE models whenever real-world data become available. Unfortunately, this has not been done frequently enough. A recent study reexamined 2 decision-analytic models for cost-effectiveness analysis comparing proton-pump inhibitor (PPI)-clarithromycin, or PPI-amoxicillin with bismuth-metronidazole-tetracycline (BMT) for *Helicobacter pylori* eradication in ulcer patients.[31] The original models heavily relied on assumptions and concluded that expensive PPI-based regimens were more cost effective than the relatively cheap BMT. In their study, Fairman and Motheral reassessed the analysis and found that a few key assumptions were inaccurate and biased the results, including discontinuation of antisecretory medication for all successfully treated patients, recurrent-associated utilization, inpatient care for all hospital care, and the degree of noncompliance. After adjusting the assumptions according to empirical data and expert opinion, the study found that the previous models overestimated the cost-effectiveness of PPI-based regimens and underestimated the cost-effectiveness of BMT. Therefore, reassessing the validity of PE models with empirical evidence is important for assuring the integrity and value of the PE information.

Developments Facilitating the Application of Cost-Effectiveness Analysis

Some developments in various fields related to PEs have helped overcome some of the limitations of CEA and can work to make the method more applicable (Table 1).

Software

As mentioned above, formularies have been developed in many institutions, but local formulary decision makers may find it difficult to establish their own formularies using the published data because effectiveness and costs vary across different practice settings. In addition, some MCOs may find it difficult to utilize CEA studies with a social perspective.

An interactive computer program based on published CEA studies of hypercholesterolemia has been designed to enable users to adapt published data to their particular setting and perspective.[32] This software consists of 5 basic modules: a work sheet, data file, chart, macro program, and user interface. It allows the user to change all baseline data, such as efficacy data, drug costs, costs of side effects, physician and lab treatment protocol for each drug, and costs for physician and laboratory services. This model provides a generalized CEA framework for the specific health care institutions, such as HMOs and hospitals, and, therefore, is flexible and modifiable according to the particular end users and population. In addition, since the program does not require experience with computer-based tools, it is easier to use.

There are also other computer simulation models providing CEA on national or regional scales.[33-35] More such software modules will likely come onto the market in the future; there is surely a need for applicability to the unique settings and demographics of population groups. Modules that allow users to customize assumptions in a model to fit their setting, and thereby correct biases in costs and effects from "baseline" assumptions, are particularly needed.

Sensitivity Analysis

CEA involves many assumptions and variables with uncertain values, such as probabilities, life expectancies, discount rates, disease severity, target populations, etc. Sensitivity analysis can help in understanding the impact of uncertainty on the final results and ensures the validity of findings, such as how the change of one cost category affects the result.[12,36] However, conventional sensitivity analyses can sometimes lead to even greater confusion and misinterpretation.[37] For example, a cost-effectiveness study on rapid diagnostic testing followed by empiric antiviral therapy compared with no antiviral therapy for healthy adults with symptoms of influenza showed that the results were sensitive to influenza infection probability, proportion of type B influenza, the efficacy of antiviral drugs, and the value of a workday.[38] However, the sensitivity analysis was done by 1-way sensitivity analysis, i.e., varying the parameters one by one. The overall uncertainty was underestimated because the result depended on multiple parameters.

If more than 3 parameters, such as influenza infection probability, proportion of type B influenza, and the efficacy of antiviral drugs, are handled simultaneously in a multiple-way sensitivity analysis, the result would become very difficult or even impossible to interpret or illustrate with a graph. On the other hand, varying only a limited number of parameters at one time may not detect interactions between those parameters. Also, the selection of variables and alternative values for the variables to

be included in a sensitivity analysis is subject to debate. Maximum and minimum values are commonly used to reflect the range of the analysis, but these values are very unlikely in real situations. Some explorations in statistics aimed to improve sensitivity analysis of CEA include probabilistic sensitivity analysis and rank-order stability analysis.[36,37]

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis is a method that considers uncertainties in all parameters simultaneously.[39] It assumes that each parameter has a range of possible values that follows a distribution function. The estimate of outcomes (costs or effects) is also a distribution function that depends on those of the individual parameters. The analysis is based on Monte Carlo simulation; it is used to compute point estimates and confidence intervals for the outcomes, such as mean costs, mean effects, and net health benefits. This approach has been discussed in detail by Shaw and Zachry.[37,39] Various software programs assist with conducting Monte Carlo simulation, such as TreeAge Software's DATA 4.0 or DATA Pro. Though more comprehensive in its ability to predict the impact of uncertain parameters and to vary multiple parameters, its results still hinge on structural assumptions in the model. Furthermore, many of the inherent limitations of CEA, such as difficulty in capturing all outcomes and disagreement on cost categories to be included, are not resolvable through any form of sensitivity analysis.

Rank-Order Stability Analysis

Einarson et al. proposed an approach called the rank-order stability analysis (ROSA), which is a comprehensive and readily understandable method for validating results.[36] It is similar to a confidence-interval approach by providing ranges for all of the variables over which the results are valid. Compared with sensitivity analysis, ROSA is more comprehensive in that it provides intervals for all parameters under consideration and therefore improves the problem of incomplete PE analyses. The authors illustrated the steps of ROSA using an example of a PE analysis for drugs (drug A, B, and C) treating major depression and analyzed the impact of all factors to provide a comprehensive sensitivity analysis. ROSA provided upper and lower limits (where the rank order of ICER for the specified drug would change) for all parameters in the PE model, including duration of therapy, annual drug cost, annual medical care cost, and treatment success rate. Within the limits, the results were stable in the sense of what treatment should be chosen. Confidence intervals for parameters with available real-life data were calculated to further validate the robustness of the results. When the confidence intervals for the variables are located within the corresponding limits, the results were deemed stable.

Overall, ROSA reduces the potential for bias from incomplete conventional sensitivity analysis, which only selectively evaluates some, but not all, factors. However, further evaluation with this method may be necessary because this study only varied parameters one at a time while keeping other parameters constant. More meaningful information may be provided by manipulating multiple parameters simultaneously because parameters are often related to each other (i.e., in reality, 2 or more parameters may tend to move together).

Complementary Approaches

Two relatively new approaches—cost-consequence analysis (CCA) and budget impact analysis (BIA)—may help to reduce the barriers to the applicability of CEA in the formulary decision-making process by serving as complementary information to decision makers.

Cost-Consequence Analysis

Some researchers proposed this new approach to be used in the formulary decision-making process and believe it reflects the direction of future PEs.[40] Conceptually, CCA is a method in which costs and effects are calculated and listed as individual components but not aggregated into QALY or cost-effectiveness ratios.[41] Ideally, all relevant costs and health consequences, including direct costs, indirect costs, quality of life, QALYs, and clinical outcomes, are collected.

In addition, variation in the costs and effects across subpopulations are better presented, if available. For example, older patients may experience more side effects and less improvement than younger patients for a drug treatment. These differences in outcomes in age subpopulations should be listed. In effect, CCA includes inputs and outputs of one or more drug therapies as thoroughly as possible and then provides a cost-consequence tabulation created with the information collected for each therapy. These tabulations can be used to compare competing interventions. They can also be used as a basis for CEA.[41]

An obvious advantage of CCA is that formulary decision makers can choose the resources, costs, and outcomes of interest to include in their economic evaluation. Since the cost-consequence list keeps all the information disaggregated, decision makers have to devise their own weight system to determine whether any additional health outcomes associated with the new drug deserves the extra cost incurred. For example, a CCA was developed by Paul et al. for the costs and consequences of an antiviral drug (acyclovir) compared with no treatment for varicella zosta virus infections, using data from a variety of sources.[42] The study provided a comprehensive range of costs and outcomes, including direct medical costs, productivity losses, and quality-of-life impact. The advantage of this analysis is that it allows readers to examine the data from different perspectives, such as from a managed care payer or from the societal standpoint. As an exercise, it would be worthwhile to involve P&T committee members in such greater PE sophistication.

Technically, for CEA to become more useful in formulary decisions, a combination of CEA and the usually disaggregated cost

and outcome data found in CCA seems to be a promising approach. Pharmacoeconomic data submitted for formulary consideration should be presented in a cost-consequence list, which has all the cost categories and possible consequences listed separately. Clear and easy-to-understand summary results from CEA, including ICERs and sensitivity analyses, are provided accordingly. Such analyses may be better initiated by manufacturers alongside drug development to improve the reliability and timeliness of the analysis. It is also suggested that guidance from the FDA would be beneficial to reduce bias from the pharmaceutical teams that control the data; FDA guidance would provide consistency and oversight for providers to further trust the results.

Using this procedure, the limitations of CEA can be expected to be minimized. Decision makers who value CEA but would like more appropriate data may also find this approach useful because they can choose the information of most interest to perform their own CEA to closely reflect their concerns.[41] Nevertheless, such a procedure would still involve decisions being made based on comparing costs with specific measures of effect. Implicitly or explicitly, valuations will be put on the measured effects, and these should be scrutinized.

CCA has been used in various situations, including the evaluation of vaccines to provide estimates of the costs and benefits of different vaccine programs. For example, a cost-consequence analysis provided separate estimates of the direct medical care costs and productivity losses for a routine varicella vaccination program, which allows decision makers to assess their own budget impact and also the impact to society.[43] CCA was also used in the assessment of impacts for HIV infection treatment. A study evaluated the effect of adding lamivudine to treatment regimens containing zidovudine in patients with HIV infection and provided cost estimates for reduced HIV disease progression to AIDS or death, reduced number of hospital stays, unscheduled outpatient visits, and medications for HIV-related illness.[44] It showed that the lamivudine regimen had the potential to reduce the monthly costs associated with HIV-related illness and adverse events. Another study provided a list of costs and consequences associated with 2 drug treatments (zidovudine or zalcitabine) for patients with AIDS.[45] The data included health care utilization, functional status, quality of life, and work status. It showed that zidovudine had substantial advantages over zalcitabine in initial monotherapy of AIDS in terms of quality of life and resource utilization.

Budget Impact Analysis

Most CEA studies often fail to provide budget information with which the decision makers may be most concerned. However, manufacturer budget models could have built-in biases that should be checked. This could be done by examining whether and how the model includes appropriate cost categories and effects according to the model's perspective. Health care decision makers usually have to consider the costs and benefits that fall within their own scope of responsibility, usually in terms of acquisition costs or budget "silos" to evaluate the impact of adding a new drug to the formulary. BIA, also called cost-impact analysis, provides an approach to evaluate the true financial impact of a new drug on the provider's budget, an increasing concern with new drug introductions and rising overall drug costs.[46] BIA typically evaluates the total pharmacy costs incurred by adding 1 new drug into the formulary, from the purchaser's perspective. For example, Meyer et al., using administrative claims data, estimated the incremental budget impact of a new interferon beta-1a product.[47] The per-member-per-month (PMPM) cost change for the addition of interferon beta-1a to a health plan with full injectable coverage and placement on tier 3 with prior authorization was $0.047. The authors concluded that such an incremental PMPM change would have minimal impact on the managed care pharmacy budget and, therefore, health care benefit managers would have flexibility in designing coverage for interferon beta-1a. However, since this study was conducted before the launch of the actual product, it has been criticized for not using complete information and making inappropriate assumptions related to relapse-free rate, costs of treating side effects, and incidence of neutralizing antibodies, etc.[48] As a result, it is necessary to update the BIA results using available empirical data to reflect the true impact of the drug.

CEA and BIA appear to complement each other to provide comprehensive cost and benefit information for formulary decision makers. For example, the decision maker can first rank-order drug alternatives according to the results from the CEA and then evaluate the budget impacts for treating different populations based on the budget constraints. It has been suggested by some national guidelines that BIA could be appropriate as a complementary approach for other PE analyses for the above consideration.[49-52]

Evaluation of Pharmacoeconomic Literature

Despite the improvement in the CEA methodologies, published studies are not equally valid and reliable. Thus, it is important to assess the quality of the PE literature to ensure that the P&T committee can at least differentiate papers with low and high quality and, accordingly, put a greater weight on better papers when making decisions. There are numerous guidelines, checklists, and criteria for the evaluation of PE literatures. Drummond's framework for analysis is a popular checklist for qualitative assessment of literature.[53] This checklist has 19 questions to cover important aspects that a qualified PE study should have. Recently, Ofman et al. developed a new instrument for quantitative assessment of PE analyses, called the Quality of Health Economic Studies instrument.[54] The QHES includes 16 questions that are assigned weighted points according to their relative importance. PE analyses evaluated by the QHES will receive different scores according to their quality.

This instrument gives decision makers an explicit and clear method to assign value to specific PE studies. The QHES has been shown to have good construct validity.[54]

The Role of Guidelines for Cost-Effectiveness Analysis in Formulary Decision Making

CEA guidelines are evidentiary standards for the provision of information to support clinical and economic evaluations of pharmaceuticals. Internationally, governments have driven the development of their own guidelines for PE evaluations, yet the FDA has confined itself to the marketing and promotional uses of such data. Creation of a Medicare drug benefit program could propel standardization of PE analyses and make these a requirement in formulary decision making. At the same time, private health systems in the United States are making a continuous effort to drive PE research based on the results of clinical trials toward naturalistic approaches, which are noncontrolled evaluation approaches that integrate drug assessments into routine or "natural" daily medical practice.[55] AMCP has been a leader in shaping standardization in formulary decision making.

Although CEA is being improved and complemented by various new technologies, the utilization of CEA cannot be guaranteed to be reliable without regulation. The advent of various guidelines provides standardized formats for PE evaluation, which may practically promote the application of CEA in formulary decision processes, as long as these guidelines are well structured and updated with the advance of science in PE, such as better ways of measuring costs, more flexible or accurate economic models, easy-to-use software, etc. Such guidelines, in their evolutionary development, must seek to transcend the interests of various parties and ultimately demonstrate that they are dedicated to public health improvements. For example, does the drug therapy improve outcomes in patients' quality of life, prevention of complications, and relief of the economic burden of disease on society?

Official guidelines have been adopted in countries other than the United States. Australia was the first country that required pharmaceutical companies seeking national formulary listing to provide a detailed economic analysis to support their case.[56] The Australian *Guidelines for the Presentation of Submissions to the Pharmaceutical Benefits Advisory Committee* came into effect on January 1993. Two other countries, Canada and New Zealand, have also made similar efforts. In Canada, the first edition of the *Guidelines for Economic Evaluation of Pharmaceuticals: Canada* was published in November 1994 and has been updated based on experiences and advances in the science.[57,58] The New Zealand guidelines came into effect on July 1, 1993.[54] Although guidelines raise the importance of economic evaluations for formulary approval, they need further refinement as PE improves as a science and as more experience is gained in its application.[56,57] It is important to recognize that advances in the field must be disseminated to the majority of managed care practitioners for proper implementation according to accepted standards in the field of PE outcomes research, such as criteria evolved and accepted in the International Society of Pharmacoeconomics and Outcomes Research.

In the United States, although the FDA has not required PE data as part of new drug applications, results of PE studies have become more likely to be required by P&T committees of provider institutions and MCOs in drug formulary decisions.[59] In 2001, AMCP published its *Format for Formulary Submissions*.[60] Since that time, it has become common practice for pharmaceutical manufacturers to submit clinical and economic dossiers for formulary approval.[10] The AMCP *Format* requires data-driven economic evaluations, including prospective cost efficacy, or cost-effectiveness studies, as well as retrospective economic evaluations, along with literature reviews. PE models are used to examine the impact of uncertainty in the estimates of treatment effectiveness and resources consumed by each treatment process. These models can support the formulary decision by providing information, such as total costs, total effectiveness, and incremental cost-effectiveness ratios of the drug and its appropriate comparator products. A number of drug manufacturers have endorsed this step and are working with MCOs in its speedy implementation; they see the guidelines fostering communication between plans and manufacturers around evidence-based materials.[61]

The AMCP *Format* requests that the manufacturer identify all relevant PE studies for the product and provide a justification of studies for the population being served. Electronic copies of spreadsheets and models are to be submitted so that the P&T committee can rework the data, which is common to determine what areas of uncertainty have major impacts on projected costs and outcomes. Comparisons of studies should reveal limitations and help identify model deficiencies or poor applicability. Such a review will improve competency in PE among firms that have not fully developed their capability. Disease-management strategies that are recommended by the manufacturer are also requested, which gives further opportunities for the MCO to evaluate the degree of integration of clinical and economic factors for the use of the product.

By establishing standardized PE evaluation methods, the AMCP guidelines will spur such PE data for MCOs and may likely spill over for other health care providers, such as hospitals and nursing homes. This delivery system innovation by AMCP should be observed and documented as it evolves through subsequent stages to track its continuing positive influences. The current version 2.0 of the AMCP *Format* was made available in 2002 and included improvements in clarity and ease of use.[60,62,63]

Conclusion

Health care providers, third-party payers, health agencies, and governments are demanding cost-effectiveness data regarding

choices for drug formulary lists. Particularly in consideration of worldwide concern for dramatically rising drug expenditures, it is clearly a very worthwhile advance to have a more firm scientific footing for preferred pharmacotherapeutic choices by providers and governments. Yet, the development and application of PE is still in a nascent phase, which will necessitate continual improvements in designs, methodologies, and applications. As PE matures, a primary concern should be the usefulness of the information that is reported to actual decision makers.

In the short term, when doing a CEA, a BIA can be done from the purchaser's perspective to provide complementary information to decision makers. Including a BIA with CEA will help to increase the applicability and practical usefulness of CEA, thus facilitating the formulary decision-making process. Standard guidelines regarding PE analysis must advance to improve CEA's relevance and reliability and thus provide a more scientific basis for formulary decision processes.

Strengthening PE requirements may exert an additional cost to sponsors and researchers. However, by imposing a standardized approach of reporting cost-effectiveness and CCA, such studies would offer more complete, accurate, reliable, and useful information. In this regard, the AMCP guidelines represent a robust effort to spur the applicability and practicality of CEA. Already, the drug dossiers requested from the manufacturers ask for baseline estimates of resource utilization and costs imposed by new drug therapies, and most U.S. drug manufacturers are complying appropriately to obtain and deliver these data. Scenarios and assumptions specific to a health plan's patient population (e.g., projected for 3 years) allow for a realistic assessment of the aggregate cost impact associated with new treatments. The pharmaceutical industry is increasingly embracing economic modeling techniques, utilizing explicit and recognizable mathematical bases, to incorporate the best available evidence. Standardization demanded by the AMCP *Format* will result in greater trust and respect for the PE analyses presented by pharmaceutical manufacturers in drug product dossiers, increasing the value and use by MCOs in formulary decision making.

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REFERENCES

1. Lipsy RJ. Institutional formularies: the relevance of pharmacoeconomic analysis to formulary decisions. *Pharmacoeconomics.* 1992;1:265-81.

2. Scroccaro G. Formulary management. *Pharmacotherapy.* 2000;20:317S-321S.

3. Pearce MJ, Begg EJ. A review of limited lists and formularies: are they cost-effective? *Pharmacoeconomics.* 1992;1:191-202.

4. Carey J, Barrett A, Arnst C, Arndt M. Drug prices: what's fair? *Bus Week.* 2001:60-70.

5. National Institute for Health Care Management Research and Educational Foundation. *Prescription Drug Expenditures in 2001: Another Year of Escalating Costs.* Washington, DC: National Institute for Health Care Management Research and Educational Foundation; 2002.

6. *Pharmacy's Framework for Drug Therapy Management in the 21st Century*. Alexandria, VA: Academy of Managed Care Pharmacy; 2002.

7. Bakst A. Pharmacoeconomics and the formulary decision-making process. *Hosp Formul.* 1995;30:42-50.

8. Glennie JL, Woloschuk DM, Hall KW. High technology drugs for cancer: the decision process for adding to a formulary. *Pharmacoeconomics.* 1993; 4:405-13.

9. Karlsson G, Johannesson M. The decision rules of cost-effectiveness analysis. *Pharmacoeconomics.* 1996;9:113-20.

10. Sullivan SD, Lyles A, Luce B, Grigar J. AMCP guidance for submission of clinical and economic evaluation data to support formulary listing in U.S. health plans and pharmacy benefits management organizations. *J Manag Care Pharm.* 2001;7(4):272-82.

11. Henry JA, Rivas CA. Constraints on antidepressant prescribing and principles of cost-effective antidepressant use. Part 2: Cost-effectiveness analyses. *Pharmacoeconomics.* 1997;11:515-37.

12. Haddix AC, Shaffer PA. Cost-effective analysis. In: Dunet DO, ed. *Prevention Effectiveness. A Guide to Decision Analysis and Economic Evaluation.* Oxford, UK: Oxford University Press; 1996:103-29.

13. Nuijten MJ, Hutton J. Cost-effectiveness analysis of interferon beta in multiple sclerosis: a Markov process analysis. *Value Health.* 2002;5:44-54.

14. Revicki DA, Brown RE, Keller MB, Gonzales J, Culpepper L, Hales RE. Cost-effectiveness of newer antidepressants compared with tricyclic antidepressants in managed care settings. *J Clin Psychiatry.* 1997;58:47-58.

15. Sloan FA, Whetten-Goldstein K, Wilson A. Hospital pharmacy decisions, cost containment, and the use of cost-effectiveness analysis. *Soc Sci Med.* 1997;45:523-33.

16. Cohen LJ. Pharmacoeconomic issues in the treatment of depression. *Formulary*. 1995;30:S20-S25.

17. McCoy S, Blayney-Chandramouli J, Mutnick A. Using multiple pharmacoeconomic methods to conduct a cost-effectiveness analysis of histamine H2-receptor antagonists. *Am J Health Syst Pharm.* 1998;55:S8-S12.

18. Hillman A. Cost-effectiveness opportunities for new antibiotics. *Pharmacoeconomics.* 1994;5:40-43.

19. Brixner DI, Bull SA. The challenge of integrating monoclonal antibodies into the current healthcare system. *Am J Manag Care.* 1997;3:903-11.

20. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. *JAMA.* 1996;276:1172-77.

21. Grabowski H. The role of cost-effectiveness analysis in managed-care decisions. *Pharmacoeconomics.* 1998;14:15-24.

22. Lyles A, Luce BR, Rentz AM. Managed care pharmacy, socioeconomic assessments and drug adoption decisions. *Soc Sci Med.* 1997;45:511-21.

23. Einarson TR, Addis A, Iskedjian M. Pharmacoeconomic analysis of venlafaxine in the treatment of major depressive disorder. *Pharmacoeconomics.* 1997;12:286-96.

24. Langley PC. Outcomes research and modeling therapeutic interventions for economic evaluations. *Clin Ther.* 1994;16:538-52.

25. Grabowski H, Mullins CD. Pharmacy benefit management, cost-effectiveness analysis and drug formulary decisions. *Soc Sci Med.* 1997;45:535-44.

26. Data JL, Willke RJ, Barnes JR, DiRoma PJ. Re-engineering drug development:integrating pharmacoeconomic research into the drug development process. *Psychopharmacol Bull.* 1995;31:67-73.

27. Siebert U, Sroczynski G, Rossol S, et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut.* 2003;52:425-32.

28. Rothermich EA, Pathak DS. Productivity-cost controversies in cost-effectiveness analysis: review and research agenda. *Clin Ther.* 1999;21:255-67.

29. Hodgson TA. Costs of illness in cost-effectiveness analysis. A review of the methodology. *Pharmacoeconomics.* 1994;6:536-52.

30. Hutubessy RC, van Tulder MW, Vondeling H, Bouter LM. Indirect costs of back pain in the Netherlands: a comparison of the human capital method with the friction cost method. *Pain.* 1999;80:201-07.

31. Fairman KA, Motheral BR. Do decision-analytic models identify cost-effective treatments? A retrospective look at Helicobacter pylori eradication. *J Manag Care Pharm.* 2003;9(5):430-40.

32. Lee JH, Glick HA, Kinosian B, Schulman KA. An interactive computer system for formulary management using cost-effectiveness analysis. *MD Comput.* 1995;12:59-65.

33. Bloom BS. Medical management and managing medical care: the dilemma of evaluating new technology. *Am Heart J.* 1990;119 (3 pt 2):754-61.

34. Glick H, Heyse JF, Thompson D, Epstein RS, Smith ME, Oster G. A model for evaluating the cost-effectiveness of cholesterol-lowering treatment. *Int J Technol Assess Health Care.* 1992;8:719-34.

35. Johannesson M, Hedbrant J, Jonsson B. A computer simulation model for cost-effectiveness analysis of cardiovascular disease prevention. *Med Inform (Lond).* 1991;16:355-62.

36. Einarson TR, Arikian SR, Doyle JJ. Rank-order stability analysis (ROSA): testing PE data. *Med Decis Making.* 1995;15:367-72.

37. Shaw JW, Zachry WM. Application of probabilistic sensitivity analysis in decision analytic modeling. *Formulary.* 2002;37:32-40.

38. Rothberg MB, He S, Rose DN. Management of influenza symptoms in healthy adults. *J Gen Intern Med.* 2003;18:808-15.

39. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Med Decis Making.* 1985;5:157-77.

40. Pettitt D, Goldstein JL, McGuire A, Schwartz JS, Burke T, Maniadakis N. Overview of the Arthritis Cost Consequence Evaluation System (ACCES): a pharmacoeconomic model for celecoxib. *Rheumatology (Oxford).* 2000; 39(suppl 2):33-42.

41. Mauskopf JA, Paul JE, Grant DM, Stergachis A. The role of cost-consequence analysis in healthcare decision-making. *Pharmacoeconomics.* 1998; 13:277-88.

42. Paul JE, Mauskopf JA, Bell L. Cost-consequence models for varicella-zoster virus infections. *Pharmacotherapy.* 1995;15:49S-58S.

43. Lieu TA, Cochi SL, Black SB, et al. Cost-effectiveness of a routine varicella vaccination program for US children. *JAMA.* 1994;271:375-81.

44. Lacey L, Mauskopf J, Lindrooth R, Pham S, Saag M, Sawyer W. A prospective cost-consequence analysis of adding lamivudine to zidovudine-containing antiretroviral treatment regimens for HIV infection in the US. *Pharmacoeconomics.* 1999;15:23-37.

45. Bozzette SA, Kanouse DE, Berry S, Duan N. Health status and function with zidovudine or zalcitabine as initial therapy for AIDS. A randomized controlled trial. Roche 3300/ACTG 114 Study Group. *JAMA.* 1995;273:295-301.

46. Trueman P, Drummond M, Hutton J. Developing guidance for budget impact analysis. *Pharmacoeconomics.* 2001;19:609-21.

47. Meyer CM, Phipps R, Cooper D, Wright A. Pharmacy benefit forecast for a new interferon beta-1a for the treatment of multiple sclerosis: development of a first-line decision tool for pharmacy-budget planning using administrative claims data. *J Manag Care Pharm.* 2003;9(2):168-74.

48. Rich SJ, Meyer C. Shortcomings in pharmacy benefit forecasting—interferon beta products. *J Manag Care Pharm.* 2003;9(4):373; author reply:374.

49. Canadian Coordinating Office for Health Technology Assessment (CCOHTA). *Guidelines for Economic Evaluation of Pharmaceuticals: Canada.* Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); November 1997.

50. Menon D, Schubert F, Torrance GW. Canada's new guidelines for the economic evaluation of pharmaceuticals. *Med Care.* 1996;34:DS77-DS86.

51. Mitchell AS. Current experience in Australia. *Drug Info.* 1996;30:495-502.

52. Torrance G. Current experience with guidelines for economic evaluation in Canada. *Drug Info.* 1996;30:507-11.

53. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes.* Oxford, UK: Oxford University Press; 1997.

54. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examine the value of health economic analyses:implications of utilizing the QHES. *J Manag Care Pharm.* 2003;9(1):53-61.

55. Langley PC. The FDA and pharmacoeconomic research. *Drug Benefit Trends.* 1997;9:17-25.

56. Langley PC. The role of pharmacoeconomic guidelines for formulary approval: the Australian experience. *Clin Ther.* 1993;15:1154-76.

57. Glennie JL, Torrance GW, Baladi JF, et al. The revised Canadian Guidelines for the Economic Evaluation of Pharmaceuticals. *Pharmacoeconomics.* 1999; 15:459-68.

58. Detsky AS. Guidelines for economic analysis of pharmaceutical products: a draft document for Ontario and Canada. *Pharmacoeconomics.* 1993;3:354-61.

59. Johnson JA, Bootman JL. Pharmacoeconomic analysis in formulary decisions: an international perspective. *Am J Hosp Pharm.* 1994;51:2593-98.

60. Academy of Managed Care Pharmacy. *Format for Formulary Submissions,* version 2.0; October 2002. Available at: http://www.fmcpnet.org/data/resource/formatv20.pdf. Accessed November 15, 2003.

61. McCain J. System helps P&T committee get pharmacoeconomics data they need. *Manag Care.* 2001;10:1-5.

62. Fry R. Personal interview from ACMP offices in Alexandria, VA; November 24, 2002.

63. Fry R. Summary of changes to the AMCP *Format for Formulary Submissions*, version 2.0 (mimeograph); September 2002.

CONTEMPORARY SUBJECT

Framework for Pharmacy Services Quality Improvement—A Bridge to Cross the Quality Chasm

Part I. The Opportunity and the Tool

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ABSTRACT

OBJECTIVE: To review the literature on the subject of quality improvement principles and methods applied to pharmacy services and to describe a framework for current and future efforts in pharmacy services quality improvement and effective drug therapy management.

BACKGROUND: The Academy of Managed Care Pharmacy produced the *Catalog of Pharmacy Quality Indicators* in 1997, followed by the *Summary of National Pharmacy Quality Measures* in February 1999. In April 2002, AMCP introduced *Pharmacy's Framework for Drug Therapy Management in the 21st Century. The Framework* documents include a self-assessment tool that details more than 250 specific "components" that describe tasks, behaviors, skills, functions, duties, and responsibilities that contribute to meeting customer expectations for effective drug therapy management.

FINDINGS: There are many opportunities for quality improvement in clinical, service, and cost outcomes related to drug therapy management. These may include patient safety; incidence of medical errors; adverse drug events; patient adherence to therapy; attainment of target goals of blood pressure, glucose, and lipid levels; risk reduction for adverse cardiac events and osteoporotic-related fractures; patient satisfaction; risk of hospitalization or mortality; and cost of care. Health care practitioners can measure improvements in health care quality in several ways including (a) a *better* patient outcome at the same cost, (b) the *same* patient outcome at lower cost, (c) a *better* patient outcome at lower cost, or (d) a *significantly better* patient outcome at moderately higher cost. Measurement makes effective management possible. A framework of component factors (e.g., tasks) is necessary to facilitate changes in the key processes and critical factors that will help individual practitioners and health care systems meet customer expectations in regard to drug therapy, thus improving these outcomes.

CONCLUSIONS: Quality improvement in health care services in the United States will be made in incremental changes that rely on a structure-process-outcome model. The *structure* is provided by evidence created from controlled randomized trials and other studies of care and system outcomes that are based on the scientific method. The *process* portion is created by the application of evidence in the form of clinical practice guidelines, clinical practice models, and self-assessment tools such as *Pharmacy's Framework for Drug Therapy Management.* Incremental changes in structure and process will result in the desirable *outcome* of meeting customer needs for more effective drug therapy and disease management.

KEYWORDS: Drug therapy management, Quality improvement, Pharmacy services

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Certainly, the popular view is that current health care is the best that the world has ever seen. However, despite impressive accomplishments over the last 100 years, current clinical performance still falls far short of its potential.

The Institute of Medicine's (IOM's) Roundtable on Quality catalogued a startlingly broad array of failures in applying extant knowledge to routine care.[1] Other reports extended that list.[2] For example, Schuster et al. found that, across all care delivery settings, only 52% of eligible adults older than 65 years received recommended yearly influenza vaccination, and only 28% received indicated pneumococcal vaccination. Overall, just 50% of Americans receive appropriate preventive care; only 70% of patients suffering from acute disease receive indicated acute care, while 30% receive contraindicated therapies; and only 60% of those treated for chronic conditions received recommended care, and 20% received contraindicated treatments.[3] More recently, the IOM's Committee on Quality of Health Care in America described the wide scope of care-related injuries patients suffer in U.S. hospitals[4] and, in a second report, *Crossing the Quality Chasm: A New Health System for the 21st Century*," called for massive redesign of the health care delivery system to address system-wide failures of execution.[5]

Bridging the gap between the state of the current health care system and the system that patients expect and need is an overwhelming task for all health care disciplines. Pharmacy is no exception. While much attention is devoted to the controversial and sometimes imperfect methods for selecting appropriate drug therapy, administrators, policy makers, and even pharmacists and other health care professionals too often overlook the enormous opportunity to improve drug therapy outcomes through monitoring and managing what happens after the selection of the drug. Pharmacy practice is, or should be, man-

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aging patient care and assuring appropriate drug therapy outcomes. While pharmacists have long possessed the requisite knowledge and skills to take the lead in managing drug therapy, the profession has lacked a long-term vision—a road map—for drug therapy management built on effectively evaluating and meeting customers' needs and expectations. According to Albert Wertheimer, PhD, "Neither pharmaceutical care nor managed care solicits the views of customers/clients as to what they want, and what they are willing to pay for."[6]

Recognizing the need to fill this void, the Academy of Managed Care Pharmacy (AMCP) created a task force early in 1999 to design *Pharmacy's Framework for Drug Therapy Management in the 21st Century*. To fulfill this objective, AMCP developed a strategic plan to create a model for drug therapy management: the *Framework* will support a long-term vision for managing drug therapy that is currently lacking in the profession. The *Framework* started from the building block of customer expectations. It provides health care systems, pharmacists, and other health care practitioners with a tool to systematically analyze whether drug therapy management can be responsive to those expectations, and, if so, to change processes and/or to develop action plans to describe and evaluate how to realistically meet those expectations and then analyze the expected outcome in terms of the customer expectations. The *Framework* has been created to be nonspecific relative to practice setting or disease and with the ability to adapt roles and procedures to meet the needs of various enterprises.

Concerns Regarding the Quality of U.S. Health Care

As the following examples illustrate, providing quality health care and appropriate prescribing, monitoring, and management of drug therapy provide largely unmet opportunities for improvement. The IOM report, *Crossing the Quality Chasm*, published in March 2001, was a milestone in identification of the sources of the "quality gap" in health care in the United States that threatens the health and safety of too many patients.[5] This *Chasm* report followed the flashpoint 1999 IOM report, *To Err Is Human: Building a Safer Health System* that estimated that adverse events occur in 2.9% to 3.7% of hospital admissions, causing 44,000 to 98,000 deaths each year, and that one half of these hospital adverse events are avoidable.[4]

In April 2003, the Midwest Business Group on Health released an updated version of their study, *Reducing the Costs of Poor-Quality Health Care through Responsible Purchasing Leadership*. Based primarily on findings and extrapolations from the published literature and expert analysis, the authors estimate that 30% of all health care outlays today are the result of poor-quality care, consisting of overuse, misuse, and waste (Table 1). Using a 2001 health expenditure figure of $1.4 trillion, the authors estimate that the United States wastes $420 billion each year as a direct result of poor quality. Breaking down the financial costs further, they estimate that poor quality health care costs an individual U.S. employer between $1,900 and $2,250 per employee per year.[7] This cost was specifically attributable to $1,500 in direct costs and another $400 to $750 in indirect costs, such as lost workdays, per covered employee.

TABLE 1 Types of Errors*

Error type	Definition	Example
Misuse	An appropriate medical service is selected, but a preventable complication occurs and the patient does not receive the full benefit of the service	An error in the calculation of a dose of digoxin results in an overdose and subsequent death of the patient
Overuse	The potential for harm exceeds the potential for benefit in the provision of the medical service	An antibiotic is prescribed for an otherwise healthy 30-year-old with a viral upper respiratory tract infection
Underuse	There is a failure to provide a health care service when it would have produced a favorable patient outcome	A patient develops measles at age 26 months because the vaccine dose was missed at age 12 months

** Adapted from Yetman RJ. Preventing misuse errors in health care organizations. J Clin Outcomes Manage. August 2001;29-33; Kohn LT, Corrigan JM, Donaldson MS (eds.). To Err Is Human: Building a Safer Health System. Washington, DC: National Academy Press; 2000; and AHRQ: Medical Errors: The Scope of the Problem—An Epidemic of Errors. Available at: http://www.ahcpr.gov/qual/errback.htm. Accessed August 18, 2002.*

TABLE 2 Medical Errors and Adverse Medical Events Nomenclature*

Term	Definition	Example
Medical error (ME)	A failure to complete a planned action as intended or the use of a wrong plan to achieve an aim	Diagnostic error, such as misdiagnosis leading to an incorrect choice of therapy; or failure to use an indicated diagnostic test; or misinterpretation of test results; or failure to act on abnormal results
Adverse medical event (AME)	An *injury* caused by medical management rather than by the underlying disease or condition of the patient	Postsurgical wound infections or other nosocomial infections caused by exposure to hospital pathogens
Adverse drug event (ADE)	An *injury* that results from the use of a drug	Hip fracture caused by lightheadedness associated with use of an anti-hypertensive drug

**Adapted from Yetman RJ. Preventing misuse errors in health care organizations. J Clin Outcomes Manage. August 2001;29-33.*

FIGURE 1 JCAHO National Patient Safety Goals for 2003

On July 24 2002, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO, Oakbrook Terrace, IL) released its *National Patient Safety Goals for 2003* to focus on the "confusion in identifying patients, miscommunication among caregivers, wrong-site surgery, infusion pumps, medication mix-ups and clinical alarm systems." "For each of the National Patient Safety Goals, there are clear, evidence-based Recommendations to help health care organizations reduce specific types of health care errors. Beginning January 1, 2003, the more than 17,000 JCAHO-accredited health care organizations that provide care relevant to the Goals will be evaluated for compliance with the Recommendations or implementation of acceptable alternatives." Dennis S. O'Leary, MD, president of JCAHO, said, "The know-how to prevent these errors exists. We now need to focus on making sure that health care organizations are actually taking these preventive steps."

The 2003 National Patient Safety Goals and Recommendations are:

Goal 1: Improve the accuracy of patient identification.
Recommendations:
a. Use at least 2 patient identifiers (neither to be the patient's room number) whenever taking blood samples or administering medications or blood products.
b. Prior to the start of any surgical or invasive procedure, conduct a final verification process, such as a "time out," to confirm the correct patient, procedure, and site, using active—not passive—communication techniques.

Goal 2: Improve the effectiveness of communication among caregivers.
Recommendations:
a. Implement a process for taking verbal or telephone orders that requires a verification "read-back" of the complete order by the person receiving the order.
b. Standardize the abbreviations, acronyms, and symbols used throughout the organization, including a list of abbreviations, acronyms, and symbols not to use.

Goal 3: Improve the safety of using high-alert medications.
Recommendations:
a. Remove concentrated electrolytes (including, but not limited to, potassium chloride, potassium phosphate, sodium chloride >0.9%) from patient care units.
b. Standardize and limit the number of drug concentrations available in the organization.

Goal 4: Eliminate wrong-site, wrong-patient, and wrong-procedure surgery.
Recommendations:
a. Create and use a preoperative verification process, such as a checklist, to confirm that appropriate documents, (e.g., medical records, imaging studies) are available.
b. Implement a process to mark the surgical site and involve the patient in the marking process.

Goal 5: Improve the safety of using infusion pumps.
Recommendation:
a. Ensure free-flow protection on all general-use and PCA intravenous infusion pumps used in the organization.

Goal 6: Improve the effectiveness of clinical alarm systems.
Recommendations:
a. Implement regular preventive maintenance and testing of alarm systems.
b. Assure that alarms are activated with appropriate settings and are sufficiently audible with respect to distances and competing noise within the unit.

Note: The 2003 Goals were developed by an expert advisory group composed of physicians, nurses, risk managers, and other professionals. The Goals and related Recommendations were drawn from the 25 issues of JCAHO's patient safety newsletter Sentinel Event Alert. The advisory groups identified a total of 44 expert- and evidence-based recommendations from the publication that include the 11 associated with the 2003 Goals. The remaining Recommendations constitute an initial pool upon which future National Patient Safety Goals may be based. JCAHO expects to issue National Patient Safety Goals and Recommendations each year. Aggregate data on achievement of the Goals will be made public each year, and individual organization compliance information will be disclosed when the reformatting of JCAHO organization performance reports is completed in mid-2004.

The IOM report, *To Err Is Human*, focused public attention on the subjects of medical errors and adverse events. To fully grasp the import of this seminal work, the reader must develop an understanding of the nomenclature of quality improvement (Table 2). It is important to note that some adverse drug events (ADEs) are not preventable, and they reflect the risk associated with treatment, such as a life-threatening allergic reaction to a drug when the patient had no known allergies to the drug.[8] However, a preventable ADE occurs when a patient receives an antibiotic to which he or she is known to be allergic, experiences anaphylactic shock, and dies.

There is considerable controversy regarding the estimated incidence of medical errors (MEs) and adverse medical events (AMEs) versus the true incidence of MEs and AMEs.[9-11] For ADEs specifically, including adverse drug reactions (ADRs), the opportunity for quality improvement may be larger than the available measures would suggest. A study performed in January and February 2001 found that a combination of patient and provider interviews revealed a total of 83 ADEs in 51 patients, or at least 1 ADE in 26% of patients, versus 1 ADE (0.5% rate) determined by a passive ADE reporting system.[12] A report in December 1999 from the Office of the Inspector General, U.S. Department of Health & Human Services, found that "a low percentage of ADR reports is being sent to the U.S. Food and Drug Administration (FDA)" resulting in a situation in which the "FDA does not know the magnitude of the ADR

problem nor whether progress is being made in reducing the number of serious ADRs."[13]

While most drug errors do not result in patient harm, studies have shown that many are preventable.[14] In the institutional environment, a study of 4,031 nonobstetrical adult admissions to 2 Boston tertiary care hospitals found 247 ADEs, a rate of 6.5 ADEs per 100 admissions, of which 43% were either fatal, life-threatening, or "serious"; 28% of all ADEs and 42% of serious ADEs were judged preventable.[15] Higher rates of ADEs have been found in nursing homes. In 18 Massachusetts nursing homes, 546 ADEs were found during 2,403 resident years of observation, a rate of 22.7 ADEs per 100 resident-years; 44% were fatal, life threatening, or serious; 51% of all ADEs and 72% of serious ADEs were judged preventable.[16]

Drug therapy in the elderly has been criticized for being fraught with too many avoidable errors, including headlines such as, "Docs Giving Many Seniors Wrong Drugs."[17] Some recent research findings have suggested that there have been meaningful improvements in the quality of medication use in elderly patients since 1987. Using data from the 1996 Medical Expenditure Panel Survey, Zhan and colleagues[18] reported that the use of some inappropriate medications had declined substantially over the 10-year study period. Nevertheless, this study's authors concluded that, in 1996, almost 1 million community-dwelling elderly individuals received at least 1 of the 11 drugs that an expert panel had determined should always be avoided by elderly patients.

Unfortunately, information related to the incidence of preventable ADEs in the ambulatory geriatric population is limited. However, a 12-month study conducted between July 1999 and June 2000 by Gurwitz and colleagues concluded that the incidence of ADEs in this population was 50 per 1,000 person-years, with a rate of 13.8 preventable ADEs per 1,000 person years. This 5% rate per year appears to be reliable since it was derived from a cohort study of 30,397 person-years of observation using 6 methods of detecting drug-related incidents: (1) reports from health care providers (obtained from mail report cards, an ADE telephone hot line, and an intranet reporting system), (2) review of hospital discharge summaries, (3) review of emergency department notes, (4) computer-generated signals, (5) automated free-text review of electronic clinic notes, and (6) review of administrative incident reports for MEs.[19] This study found that 27.6% of the ADEs were preventable, yielding an incidence of 1.38 preventable ADEs per 100 person-years. Among the 38% of the ADEs that were categorized as serious, life threatening, or fatal, the rate of preventable ADEs was higher, at 42%. Patient adherence was a factor in 21% of the preventable ADEs, prescribing was a factor in 58%, and the monitoring stage of pharmaceutical care was a factor in 61% of the preventable ADEs. Dispensing errors were rare, accounting for fewer than 2% of the preventable ADEs.

Patient safety as a rallying point has helped focus parallel and cooperative efforts among health care organizations and associations. For example, *Pharmacy's Framework for Drug Therapy Management in the 21st Century* melds effectively into the priorities set by the Joint Commission on Accreditation of Healthcare Organizations in its *National Patient Safety Goals for 2003* (Figure 1). The Leapfrog Group, a coalition of more than 135 public and private organizations that provide health care benefits, has developed 3 patient safety standards that reward publicly transparent hospital performance.[20] In May 2003, the National Quality Forum (NQF), a private, nonprofit public benefit corporation created in 1999 to develop and implement a national strategy for health care quality measurement and reporting, released its consensus report, *Safe Practices for Better Healthcare*. The report details 30 health care safe practices that NQF members think should be universally utilized in applicable clinical care settings to reduce the risk of harm to patients. These "voluntary consensus standards" were reviewed and endorsed by the more than 150 NQF member organizations, which include consumer groups, purchasers, payers, health care providers, and government agencies.[21]

There is no dispute that patient safety is paramount, but there is disagreement about (a) the magnitude of the quality chasm in pharmacy services, (b) what constitutes a quality defect, (c) the important quality benchmark measures, and (d) what is necessary to change in the processes in the delivery of pharmacy and other related services to meet customer expectations and to prevent quality defects. However, effective drug therapy management involves more than maximizing patient safety, and some physicians have recognized that "improving the quality of medication use," particularly in the higher-risk elderly, requires "enhanced collaborations between those who prescribe drugs and those who know medications best (clinical pharmacists)."[19]

Evidence of the Effect of Pharmacist Interventions on Outcomes

"Because of the immense variety and complexity of medications now available, it is impossible for nurses or doctors to keep up with all of the information required for safe medication use. The pharmacist has become an essential resource . . . and thus access to his or her expertise must be possible at all times."
Institute of Medicine, To Err Is Human, 2000.[4]

As the 21st century dawned, pharmacy faced new challenges. Rising demand for prescription drugs and prior projections of an over-supply of pharmacists significantly strained the supply of pharmacists—the Pew Health Professions Commission report in 1996 inaccurately predicted "an excess of 40,000 pharmacists by 2005."[22] In this sense, pharmacy had to do more with fewer human resources in the first years of the 21st century. At the same time, public perception in 2003 placed pharmacists above physicians in ratings of honesty and

ethical standards and second only to nurses by these measures.[23]

An update in 2002 on the subject of measuring the value of clinical pharmacist interventions focused on the need for rigorous research designs that include a control group and randomization of patients, whenever possible.[24] In this subject review, Malone cited the design and results of the IMPROVE study that enrolled 1,054 patients from 9 VA medical centers and randomized 523 subjects to ambulatory clinical pharmacy services plus usual medical care and 531 subjects to usual medical care only. There were no differences found in SF-36 scores or patient satisfaction[25] or in the measure of overall resource utilization.[26] By a fourth measure, reduction in total cholesterol (TC) and low-density lipoprotein (LDL), the pharmacy intervention group showed statistically greater reductions compared with the control group. Since both groups showed reductions in LDL and TC, the inclusion of a control group permitted attribution of the LDL and TC reductions to the pharmacist intervention rather than to other factors such as system-wide cholesterol reduction efforts. The IMPROVE study also found that total medical care costs were not greater in the pharmacist intervention group, demonstrating improved *efficiency*; i.e., improved patient outcomes (reduction in TC and LDL) at the same cost.

Outside of the hospital, some have suggested that pharmacists are part of the problem, ignoring electronic drug-interaction messages from drug claims processors and not counseling patients.[27] Conversely, others have shown that clinical pharmacists reduce the incidence of ADEs and improve quality of care. A study of admissions to the intensive care units (ICU) at Brigham and Women's Hospital in Boston found an incidence of 10.4 preventable ADEs per 1,000 ICU patient days. When clinical pharmacists were assigned to work in the ICU, the incidence of ADEs was reduced by 66% to 3.5 per 1,000 ICU patient days.[28] The study design was a before-after, control-group design in which baseline ADE incidence was followed by a pharmacist involved in patient rounds with residents, nurses, and attending staff each morning and on-call consult throughout the day, activities that consumed about one half of the clinical pharmacist's time.

Recent drug product withdrawals highlight opportunities for pharmacists to reduce the incidence of potential ADEs. Physician misprescribing and poor adherence to FDA prescribing guidelines were determined to be factors in the market withdrawal of troglitazone and cisapride early in 2000, alosetron late in 2000, and cerivastatin in mid-2001. For example, 85% of 270 side-effect reports on cisapride were in patients with risks outlined in the drug's label; only 10% of patients on troglitazone received the full monthly regimen of recommended monitoring tests, and liver function tests recommended by the FDA on the label for troglitazone resulted in only 45% of troglitazone patients receiving the baseline test. Full compliance with the liver function monitoring regimen was only 9.3% after 1 month and less than 3% after 3 months.[29] Poor physician adherence to black-box warnings in FDA-approved product labeling has also been documented for isotretinoin and metformin.[30,31] In one large-scale review, almost one quarter of patients with a prescription for metformin had 1 or more absolute contraindications.[32] The authors concluded that physicians might frequently prescribe metformin inappropriately despite black-box contraindications.

Local programs and projects have demonstrated favorable effects of community pharmacist interventions. In one of the longest-running demonstration projects, the city of Asheville, North Carolina, began paying community pharmacists in 1997 to counsel beneficiaries with diabetes in diet, nutrition, exercise, and glycemic control in the hope of reducing complications of the disease.[33] The diabetes management program began as a 6-month pilot project, but initial results, including favorable reactions from beneficiaries, resulted in retention and expansion of the "Asheville Project." Five years later, the Asheville Project had expanded to involve the 3 largest employers in the area: the hospital, city of Asheville, and a paper company. The city of Asheville compensated community pharmacists for clinical interventions involving patients with asthma, hypertension, hypercholesterolemia, and diabetes. Anecdotes from patients attributed behavior change such as regular walking, strict attention to glucose monitoring, daily aspirin use, better asthma control, and use of fewer inhalers to regular pharmacist counseling. As one retired Asheville city employee said, the Asheville Project using community pharmacists "gives you the knowledge, the equipment, and the incentive to control your own destiny."[34]

More thorough analysis of the Asheville Project suggested that pharmaceutical care services (PCS), including patient education, training in the use of self-monitored blood glucose meters, clinical assessment, patient monitoring, follow-up, and referral, had measurable effects on clinical, humanistic, and cost outcomes. In the short term, PCS was associated with improved hemoglobin A1c, improved patient satisfaction with pharmacy services, and an 87% increase in direct medical disease-specific costs ($52 per-patient-per-month [PPPM]). However, these services brought about a 29% decrease in nondiabetes costs ($134 PPPM) and a 16% decrease in all-diagnosis costs ($82 PPPM).[35] The percentage of patients with optimal hemoglobin A1c increased from about 40% at baseline to more than 60% during the first 18 months of follow-up.[36] Cost outcomes showed a reduction of $1,200 (39%) per-patient-per-year in total mean direct medical costs.

Acceptance of these pharmacist-provided services appears to be growing among certain physician groups. Data from national surveys of medical groups performed by the Medical Group Management Association and the American Medical Group Association suggest that physicians are increasingly embracing pharmacist consultant services. Pharmacist services were provided by 49.5% of single specialty medical groups in 2001, up

from 37.4% in 2000, and pharmacist services in multispecialty medical groups increased from 49.1% in 2000 to 56.0% in 2001.[37] The practical implication of this increase in pharmacist consultant services in medical groups in 2001 is perhaps best seen in small medical groups of 5 to 6 physicians and 7 to 9 physicians, where pharmacist consultant services increased by a relative 25% from 2000 to 2001, from 40.8% to 51.3% and from 37.7% to 49.2%, respectively.

Collaboration between physicians and pharmacists not only has the potential to improve drug therapy outcomes but critical evaluation of collaborative practice has also demonstrated such outcomes. The quality of therapeutic determinations made by pharmacists within a collaborative practice was studied by a 12-member panel of physicians and pharmacists. Using randomly selected patient records, the peer-review panel found 5,780 drug therapy problems that were resolved for 2,524 patients receiving pharmaceutical care from this collaborative practice. Achievement of therapeutic goals was found to improve from 74% of patients at the time of the initial pharmaceutical care encounters to 89% at the latest encounters, and the decisions made by the pharmaceutical care practitioners working in collaboration with physicians to provide drug therapy management services were judged by the peer reviewers to be clinically credible.[38]

Creating Pharmacy's *Framework*—Focus on the Customer

For nearly 3 years, more than 100 drug therapy specialists, experts, and pharmacists involved daily in drug therapy management spent more than 3,000 hours creating this resource for others dedicated to improving patient drug therapy. Although the scope of the *Framework* Project originally focused on managed care pharmacy, the authors found the concepts and objectives to be universal for any individual or organization concerned with drug therapy management. For this reason, they broadened the scope of the project to incorporate all practice settings within the profession of pharmacy.

The first steps in the strategic plan involved determining what functions are desired by patients, health care practitioners, payers, insurers, employers, physicians, policymakers, and academicians and then to determine who should have responsibility for that component. What sets the *Framework* Project apart from previous studies of pharmacy is the focus on listening to large numbers of customers/patients in planning drug therapy management services for the future that are setting- or environment-independent.

The *Framework* Project evolved, including thoughtful examination of the work of others who studied pharmacy practice and pharmacy education in the 20th century. The 1927 report *Basic Material for a Pharmaceutical Curriculum* set the standard for the 4-year undergraduate pharmacy curriculum. The American Pharmaceutical Association (APhA) Dichter Report in 1973 focused on effective patient and customer communication, and the 1975 Millis Commission Report highlighted future needs for "clinical scientists" trained in the behavioral sciences and lit the path toward adoption in 1999 of the 6-year PharmD entry-level program of study. Readers are also directed to the excellent, coincident work of other pharmacy professionals, notably the joint efforts of the National Association of Chain Drug Stores, APhA, and the Institute for Safe Medication Practices (ISMP) in the *ISMP Medication Safety Self-Assessment for Community-Ambulatory Pharmacy,* released in September 2001,[39] and the American Society of Health-System Pharmacy in the *ISMP Medication Safety Self Assessment* (for institutional pharmacy). Both are available online at www.ismp.org.

The perspective is a 30,000-foot view of the health care landscape. The *Framework* attempts to achieve universal applicability, with focus placed on fundamental elements of drug therapy management and with a focus on populations, while still maintaining the attention to patients as individuals. Thus, the *Framework* must be applied with the understanding that success in achieving drug therapy goals rests not only on changing attitudes, skills, or behaviors of individual practitioners but also on organizational change. This reflects the understanding that successful drug therapy management is a complex process and requires more than a single person to be carried out. This differs from the popularly held version of pharmacy, which is closely linked to product. The profession has *internally focused* models defining what a pharmacist is responsible for, but the *Framework* projects an *external focus,* with *specific relevance to customer-driven and expressed expectations*. It also addresses how health care systems, pharmacists, and other health care practitioners organize internally and externally to accomplish the mission.

The assumptions employed in building a *Framework* for pharmacy practice in the 21st century included the following:

- Patients want to be healthy.
- Resources to pay for medication and therapy are finite.
- There is a segmented payer system and it will continue.
- Patients are at the center of the pharmacist's point of view.
- Drug therapy demands attention, and pharmacists are uniquely trained and positioned to provide it.
- The health care system is intended to maintain and improve health and to prevent and treat disease.
- Pharmacy should be accountable for the drug therapy process but is dependent on the cooperation of other health care professionals.[40]

One prominent and unique feature of the AMCP *Framework* Project was the very broad definition of pharmacy's *customer*. Specifically, AMCP solicited opinions and perceived needs from employers, academicians, government officials, health plan administrators, pharmaceutical manufacturers, patients, nurses, and physicians. Interviewers found that customer expectations were broad and diverse, reflecting the many types of customers of pharmacy services. So, what do customers want and expect

from pharmacy? The answer is that customers expect much from pharmacists, in part because pharmacy has so many types of customers, often with diverse interests. In many ways, the *Framework* looks at pharmacy from the outside looking in rather than from the pharmacy perspective looking out.

Pharmacy customer expectations appeared to be grouped into some common themes:

- Patients will achieve appropriate drug therapy outcomes.
- Drug-related problems will be identified, resolved, and prevented.
- Care is coordinated and practitioners are competent.
- There is value in the care that patients receive and it is affordable.
- The system is accessible and is looking out for the patient's best interest.
- There is a professional covenant between the patient and practitioner.
- The system will provide adequate and appropriate information and education regarding appropriate drug use.

These pharmacy customer expectations closely parallel the "aims" for health care quality improvement in the 21st century as defined in the IOM report *Crossing the Quality Chasm.*[7] The aims are that health care quality improvement be

- safe,
- effective,
- patient-centered,
- timely,
- efficient, and
- equitable.

Results of Customer Interviews

Customer interviews demonstrated early in the *Framework* Project that customer expectations are often unfulfilled in the present drug therapy process. Shortfalls included (a) insufficient communication between physicians and pharmacists, (b) little structure and insufficient means to continuously monitor patient medication adherence and response to therapy, and (c) fragmentation throughout the drug-use process, all of which are particularly problematic for persons with complex or chronic disease(s). Insufficient communication was seen as a source of (avoidable) MEs.[41]

Interviewees identified these "abc" shortfalls in the present drug-use process as a particular threat to health and safety for patients with multiple prescribers and pharmacies. Effective drug therapy management is necessarily oriented to a continuous, longitudinal care management plan rather than episodic encounters with patients seeking one or more prescription drugs.

The proliferation of direct-to-consumer (DTC) advertising seemed to precipitate a common perception among pharmacy's customers, except for drug company representatives, that prescription drug manufacturers are driving demand for higher-cost drugs. Interviewed customers perceived this demand for higher-cost drugs to be fueled by DTC advertising and by aggressive drug promotion to physicians. Beyond these common areas of agreement among pharmacy customers were many areas of common disagreement. Drug benefit plans and health systems earned criticism for appearing to focus on the drug product rather than quality of pharmacy services. Health plan administrators, for their part, may point their "finger" at drug manufacturers who aggressively promote high-cost drugs to consumers and physicians while at the same time trumpeting their efforts to "partner with us [drug manufacturers] to contain costs." Health plan administrators also may find employer interest in disease management programs, in concept, but greater interest in (premium) cost than in quality of care.

Physicians tended to be opposed or at least cautious about how much pharmacists should know about patient clinical information and how to manage their accessibility to the patient medical record. The implications of this caution are potentially disturbing given the obvious potential for quality improvement and little downside "risk" other than some small cost associated with providing pharmacist access to additional (complete) clinical information in the patient medical record. Interesting in the discussion and concern about medical errors is failure to recognize that the absence of adequate *patient information* at the point of care is one of the most significant contributors to MEs.

Patients believed that computer systems should be developed to link clinical patient data between the pharmacy and the physicians' offices (notwithstanding the efforts by the activists and politicians to "protect" the "privacy" of patient-specific information by making this information less accessible).

Among pharmacy customers, representatives of drug manufacturers were most likely to believe that the benefits of new drugs—reduced hospitalization and improvement in patient adherence through more convenient dosing regimens—outweigh the increase in drug costs for "new" drug therapies. This finding is not dramatic or surprising on its face and underscores the tug-of-war that takes place in justifying the additional costs of new drug therapies. Noteworthy and consistent with the quality improvement paradigm, patients and other pharmacy customers opined that an older drug taken twice per day may be a better choice (quality improvement) than a newer, high-cost drug taken once per day.

More agreement among pharmacy's customers was found in the need for more useful and less-biased drug and health information. Pharmaceutical manufacturer representatives commonly produce readily available drug and health information. Customers noted the Internet as a possible source of useful drug and health information, but there was some skepticism about the accuracy and reliability of information obtained from this source. Although customers can find unbiased drug and health information, it is not common practice for physicians and pharmacies to independently perform the literature research necessary to locate, produce, and periodically update this information.

Coalescence of Quality Criteria and Process Steps Into a Self-Assessment Tool

The professionals who worked on the *Framework* Project had one goal in mind—to use their collective experience and modicum of wisdom to help widen the *perspective* of all persons involved in drug therapy management. None of these professionals would presuppose that this is a "bible" or guideline for individuals or organizations to follow. Rather, each reader may use the *Framework* to help think about best practices and the paths that can lead to best patient outcomes. After all, the ultimate purpose is to *improve* heath care quality, measured in several ways including (a) a *better* patient outcome at the same cost, (b) the *same* patient outcome at lower cost, (c) a *better* patient outcome at lower cost, or (d) a *significantly better* patient outcome at moderately higher cost.

As the *Framework* development process progressed, the scope of pharmacy services to its customers necessary to meet the validated expectations appeared to coalesce in categories or *core focus areas*:

1. Fundamental skills, tasks, and functions are employed for effective drug therapy management.
2. Health management, health promotion, and disease prevention programs and services are offered.
3. The patient is effectively assessed, accurately diagnosed, and appropriate drug therapy is selected.
4. The patient is served by a distribution system that provides accurate drug therapy and understandable health information in a timely manner.
5. Patient response to drug therapy is monitored for effectiveness, adherence, and avoidance of adverse effects, and drug therapy is adjusted to achieve optimal outcomes.
6. Medical benefits are provided through a system that has an appropriate drug-use policy and benefit design.
7. The health system performs ongoing assessment to ensure that the results of drug therapy management lead to healthy individuals and populations.

The hundreds of tasks or components of drug therapy management within the 7 core focus areas are aggregated within *"functional areas."* While these core focus areas and the functional areas within these core focus areas will appear familiar to almost all readers, some of the specific tasks or "components" may be unfamiliar. Some readers may even find themselves challenging the relevance of some components to pharmacy services and delivery systems today. This response is expected for some components. Contributors to the *Framework* Project recognized that pharmacy practice and drug therapy management are not site- or setting-specific, and thus not all of the core focus areas will have relevance to every pharmacy organization. *Framework* contributors encourage all to help set the "bar" ever higher in drug therapy management for all practice sites, environments, and delivery models.

This *Framework* applies to technicians, professionals, clerks, and administrative personnel because effective drug therapy management requires multidisciplinary cooperation and coordination of effort and long-term vision and support from managers and administrators. Accordingly, the term "health care practitioners" used in the *Framework* includes managers, administrative support staff, pharmacists, pharmacy technicians, and other health professionals and support staff. The assessment tool is sufficiently flexible to be used by individual pharmacists, health-system pharmacists, managers, administrators, or organizations.

Effective use of this tool for drug therapy management requires some judgment. Therefore, to determine the role of pharmacy in assuring appropriate medication therapy within the health care delivery system, it is necessary to ascertain the expectations and valued functions performed surrounding the drug-use process from the perspectives of stakeholders. The goal is to determine key competencies brought by the pharmacist, validate a list of functions that need to be performed for appropriate medication therapy, and determine those functions where the pharmacist can be an appropriate and effective provider. The final product will be a bridge and a toolset to assist in moving competencies to the prescribed level from its present place.[6]

The *Framework's* Foundation—Self-Assessment

The Self-Assessment Tool[42] is the foundation of the *Framework* portfolio. Its more than 250 specific "components" describe tasks, skills, and functions that contribute to meeting customer expectations for effective drug therapy management. The purpose of the assessment tool is to provide perspective—a framework—and the means to periodically assess organization and individual performance in key functional areas of drug therapy management. The assessment tool places the patient and the quality of care at the center of pharmacy services. Interestingly, the application of 6 Sigma methods in the Bridges to Excellence program championed by General Electric resulted in the Quality Functional Deployment tool, a quality improvement instrument that resembles the *Framework* Self-Assessment Tool.[43]

As listed previously, there are 7 core focus areas in the Grid and Self-Assessment Tool. The first core focus area addresses components that are applicable whenever a health care practitioner is interacting with patients. Components include key critical and pervasive skills that are fundamental to effective drug therapy management, such as interpersonal communication, leadership, patient education, and quality improvement through feedback. Core focus areas 2 through 7 are organized in a sequence that follows care processes of patients if they progress logically through the health care system. The core focus areas are organized so that they may be used either sequentially or as freestanding units. Therefore, just as some patients or other customers will only require services listed under one or two ore focus areas, so health care practitioners

FIGURE 2 *Framework* Grid and Self-Assessment Tool—User's Instructions

The *Framework* is a collection of tools designed to help individual pharmacists and organizations (i.e., health plans, pharmacy benefit managers, pharmacy chains, hospital pharmacy departments, etc.) improve the management of drug therapy for patients through a system of continuous quality improvement. You might envision a committee that knows it needs to improve the way its organization manages asthma patients but is not quite sure how to do it. You might be an individual pharmacist in a pharmacy and decide you want to do a better job serving your patients. The *Framework* can help you accomplish that. The Grid and Self-Assessment Tool is at the heart of this process.

How does it work?
Organizations and individual practitioners may take different approaches when using the Grid and Self-Assessment Tool to achieve care improvement goal(s) such as:

System or practice assessments
1. The individual or group within an organization reads through the Grid and Self-Assessment Tool, choosing those components (behaviors, skills, functions, duties, responsibilities, etc.) that best describe effective drug therapy management for its particular practice setting.
2. Use the "Does This Apply?" column to indicate whether the component is applicable to you or your organization.
3. After you read a component, rate yourself or your organization according to the degree to which the component skill, function, or task is achieved or performed (i.e., never do it, sometimes do it, usually do it, always do it).
   Suggested evaluation parameters:
   - Never: <25% of the time, not data supported
   - Sometimes: 26%-50% of the time
   - Usually: 51%-75% of the time
   - Always: 76%-100% of the time
4. Next, record the level of importance of the component to you or your organization. If it is important to you and you are not doing very well, develop an action plan that will help you meet the goals that will ultimately help you comply with that specific component.
5. For example:

Core Focus Area #2: Health management, health promotion, and disease prevention programs and services are offered.

Functional Area 2.2 Outreach and Accessibility

	Component	Does This Apply?**	Never	Sometimes	Usually	Always	Level of Importance	Action Plan Reference Number
2.2.5	Health management, health promotion, and disease prevention programs (including support materials) are conducted in languages that are predominant in the target population and are sensitive to cultural differences among ethnic populations.	Yes		XXX			High	#123

6. Enter an action plan reference number into the last column. Then develop an action plan related to this component that would define measurable goals to help improve communications and outreach efforts to members who have English as a second language.
7. The action plan should include the following elements:
   a. defined, measurable goals,
   b. a time frame for accomplishing defined goals,
   c. the amount of resources that will be required,
   d. how goals will be measured, and
   e. who is responsible for the elements of the action plan.
8. Of course, you will need to develop specific action plans to address each area that is targeted for improvement. The *Framework* portfolio includes template examples of action plans.

Targeted Problem Assessment
The first step involves determining what functions regarding drug therapy management are needed by payers, insurers, employers, physicians, and patients, and then to determine who should have responsibility for that component.

For example, using the MCO experience detailed in the accompanying Brent James paper *Making It Easy to Do It Right* as an example, you have determined that inadequate and inappropriate prescribing of discharge medications for patients hospitalized with heart disease is contributing to increased morbidity and mortality among your covered members, resulting in increased hospital and emergency department costs. These steps would be followed in applying the *Framework*:

1. Rate your organization against those components that directly affect the development and implementation of evidence-based prescribing guidelines for discharge medications for patients hospitalized with heart disease and monitoring of their drug therapy outcomes postdischarge.
2. As described above, develop action plans for those components rated as deficient and having a high degree of importance that will help your organization achieve target goals for improving the drug therapy management for this group of patients.
3. Once the components rated as "high" have been improved, begin to focus on those of moderate importance, then those deemed of lower importance.

To conclude, the skills, functions, tasks, responsibilities, etc., necessary to meet customer needs may encompasses one, two, or more core focus areas. Therefore, the *Framework* user will choose to evaluate and develop action plans only for those portions of the Grid and Self-Assessment Tool that address individual or organizational needs.

may only concentrate on one or two core focus areas. The portions of the Grid and Self-Assessment Tool the health care practitioner chooses to use will be those that address the individual customer's needs.

The "component" tasks, skills, and functions in each of the core focus areas are categorized under "functional areas" of drug therapy management. The components under a given functional area are building blocks that interact to permit the health care practitioner or the system to achieve successful patient care. The components are explicitly not limited to site or practice settings but are applicable across a broad array of care environments. Some component skills and behaviors pervade all of the core focus areas. Where this is the case, the Self-Assessment Tool includes each component in the most applicable core focus area with cross-references. Likewise, a few of the functional areas, such as Patient Education and Continuous Quality Improvement, are common to 2 or more core focus areas. A balance between redundancy and readability has been attempted in the core focus areas, functional areas, and components in the assessment tool. Users should view the 7 core focus areas comprehensively, not as individual, stand-alone core focus areas.

The self-assessment scale allows the user to identify whether the component is of importance. If it is, the scale permits the user to rank the incidence of each component from "never" perform this task or function to "sometimes," "usually," or "always." The level of importance of various components and tasks will differ among individuals and organizations. The combination of the "level of importance" and the incidence rate (never, sometimes, usually, always) helps establish priorities for quality improvement for a given organization, pharmacy, or individual health care practitioner. See Figure 2 for a representation of the Grid and Self-Assessment Tool.

The final column of the Self-Assessment Tool allows the user to enter the "action plan reference number." The action plan for improvement will be different for each user. The organization or individual user can outline an action plan and give it an identifiable number.

> *The ultimate objective is not the computation of an overall "score" for the organization. Rather, the purpose of the assessment tool is to provide perspective, a framework, and the means to periodically assess individual and organization performance in meeting customers' needs in key functional areas of effective drug therapy management.*[42]

The components under a given functional area are building blocks that interact to permit the health care practitioner or the system to achieve successful patient care outcomes. Organizations and individuals should evaluate those components in the assessment tool specific to the needs of their customers. Thus, an organization may identify only 3 or 4 components on which to focus quality improvement efforts. The *Framework* portfolio includes an action plan template to further help users put the *Framework* to practical use.

Creating an Action Plan

The real power of the *Framework* tool is in the development and use of an action plan. If an individual or organization reads the *Framework* documents and does a self-assessment but does nothing to institute change, then the process has been of little value. After an assessment has been completed and the individual or organization determines the components that have the highest priority to them, they should develop an action plan that will enable them to make the needed changes. The *Framework* portfolio includes examples of action plans. Of course, the individual users will need to develop specific action plans to address each area they target for improvement.

Action plans usually define the exact goals that are set by individuals or organizations. It is important to remember that goals need to be measurable. This allows the user to rate how well they are doing with their quality improvement process. An example of a ***poor goal*** is: **Our organization will do a better job of educating our patients on the usage of their medication to improve overall health.** Because there is no specific quality measure, this organization will not be able to determine if they are improving or not. An example of a ***measurable goal*** is: **Our organization will improve the overall health of our diabetic patients by implementing an education and monitoring program that allows us to measure their daily fasting blood sugar levels and monthly hemoglobin A1c values.** Once this organization has base-line values for a subpopulation of patients with diabetes, progress to goal can be measured.

There are a number of other important elements of an action plan. These include the time frame desired, the amount of resources that will be required, how goals will be measured, and who is responsible for the action plan. When all of the critical elements are identified in an action plan, the opportunity for success improves dramatically.

The *Framework's* Core Focus Areas—Issues and Opportunities

The following sections summarize some of the key issues and opportunities enumerated in the Self-Assessment Tool related to improving drug therapy for pharmacy's customers. A few examples from the Grid and Self-Assessment Tool are shown in Figure 3.

Core Focus Area 1: Employ Fundamental Skills, Tasks, and Functions for Effective Drug Therapy Management

The components within Core Focus Area 1 are building blocks for drug therapy management. Fundamental communication skills include the text and materials written and produced in multiple languages, at the appropriate reading-comprehension level, the avoidance of jargon, and the use of interpersonal communication techniques to reduce misunderstanding and establish rapport. Behaviors that help reduce misunderstanding in interpersonal communication also promote a sense of caring

FIGURE 3 Examples From the *Framework* Grid and Self-Assessment Tool

Functional Area 3.2 Drug Selection

	Component	Does This Apply?**	Never	Sometimes	Usually	Always	Level of Importance	Action Plan Reference Number
3.2.3	Asymptomatic or otherwise stable patient health status is used as an opportunity to reduce or eliminate drug therapy (e.g., reduction in dose or frequency of acid-suppression therapy).							

Functional Area 3.3 Drug Prescribing

	Component	Does This Apply?**	Never	Sometimes	Usually	Always	Level of Importance	Action Plan Reference Number
3.3.2	Drug therapy is prescribed in accordance with a treatment plan that clearly indicates the goals of therapy and specifies when drug therapy should be reevaluated, changed, adjusted, or discontinued.							

Functional Area 5.1 Patient Monitoring & Documentation

	Component	Does This Apply?**	Never	Sometimes	Usually	Always	Level of Importance	Action Plan Reference Number
5.1.6	On each occasion in which a patient obtains services, the health care practitioner uses the opportunity to assess existing drug therapies. For example, upon a prescription refill, the pharmacist discusses with the patient the response to drug therapy, including untoward effects, and the pharmacist evaluates patient adherence to therapy.							

Functional Area 7.1 Drug Therapy Evaluation

	Component	Does This Apply?**	Never	Sometimes	Usually	Always	Level of Importance	Action Plan Reference Number
7.1.5	Patient feedback is used as a tool to improve drug therapy outcomes for individual patients and as a means to improve care processes and treatment guidelines.							

**Does the component apply to the individual, the practice, or the organization?

and respect. Effective patient education depends on the combination of knowledge and the ability to communicate effectively and caringly. Leadership involves the skills and behaviors that make others *want* to excel in their individual work. Leadership ensures that mission statements and strategic goals are continuously reviewed and revised, providing the framework for operational policies and procedures that deliver the best care, all of the time.

Pharmacy leaders create work environments that continually change and improve based on customer feedback. These work environments use feedback—positive and negative—to teach and inspire workers. Patients are protected by skill documentation and policies and procedures that permit measurement, communication, and follow-through, and, hence, continuous quality improvement.

Satisfaction with care and care providers is an important outcome, and its measure can help define quality along with *clinical* outcomes and cost outcomes. Effective drug therapy management includes quality improvement in patient satisfaction, attained through the use of fundamental provider skills, benefit design, and resource commitment to an infrastructure (e.g., an electronic patient medical record with reliable and efficient access) that supports the immediate transfer of clinical and health information among diverse care settings.

Fundamental communication skills. The first step in more effective communications skills is to understand and embrace a behavioral change model—*attitude, recognition, acceptance, and change*. A person is not likely to improve communication skills while possessing the attitude that "I know everything that I need to know to be effective at interpersonal communication." *Attitude* can be an important barrier to more effective communication since most people believe that they are good (effective) listeners. Second in the change (improvement) process is *recognition* that misunderstanding is the *normal* result of the communication process. *Accepting* the fact that misunderstanding is the normal result of the communication process allows a person to adopt behaviors (*change*) that will help reduce misunderstanding.

Effective interpersonal communication skills such as *repeat* back can be used to protect patient safety as well as improve drug therapy management. The Agency for Healthcare Research and Quality (AHRQ) in its 640-page report, *Making Health Care Safer: A Critical Analysis of Patient Safety Practices,* released in July 2001,[44] stated that 11 of 73 "patient safety practices" are supported by evidence from research, including "asking that patients recall and restate what they have been told during the informed-consent process." Unfortunately, AHRQ found that most hospitals and nursing homes do not routinely perform even the 11 top-ranked safety practices. Among the tools that can be used to improve patient safety, better communication among physicians, nurses, and pharmacists was judged capable of preventing 86% of potentially harmful ADEs compared with 81% potentially preventable with ward-based clinical pharmacists and 76% potentially preventable with computerized physician-order entry.[45]

Privacy of personal health information is another customer expectation that requires fundamental skills that span all dimensions of effective drug therapy management. Privacy expectations pertain to oral communication and protection of personal health information from disclosure to unintended parties for unacceptable purposes such as product marketing.

The IOM *Chasm* report proposed a fundamental change in access to personal health information.[5] The premise is that a better-informed patient is a safer patient. Better-informed patients can participate more actively in their own care, including protection from accidental injury resulting from medical and drug interventions. The IOM *Chasm* report proposed an unprecedented openness of medical record information, electronic or otherwise, in the 21st century, embracing the model that open access to information can inspire trust and better engage patients in their own care.

Leadership is more than management and governance, and according to the American Society for Quality, it is the first of 7 broad topics within the quality management "body of knowledge."[46] Leaders help create a corporate culture that prizes and rewards excellence. Excellent corporate cultures allow failure. In fact, defects can be viewed as treasures, providing information to improve products and services and avoid future defects. The excellent organization continuously searches for defects, researches the defects for causes, and, without assigning blame, changes the procedures and processes to prevent future defects.

Continuous quality improvement includes the premise that elimination of defects will reduce the cost of errors and reduce the cost of health care in the United States. This paradigm of reducing the cost of health care by improving the quality of health care is a difficult concept for many to accept. Don Berwick, in his insightful piece titled *As Good As It Should Get: Making Health Care Better in the New Millennium,*[47] makes the case that we need examples of methods to take us to a higher level of quality and efficiency in health care. "What is needed is a compilation of the very best practices and features, which are embodied in organized delivery systems that

- use safety science techniques to drive error rates continually lower;
- practice and promote prevention seriously;
- create a seamless, timely delivery of care flow for all patients;
- involve patients and families fully in their own care and offer patients increasing control over decisions that affect them;
- break down the walls of intimidation and misunderstanding among professionals, patients, and families;
- perform no scientifically groundless treatments; and
- formally search for effective, proven care practices and assure that patients benefit reliably from such appropriate care."

Core Focus Area 2: Health Management, Health Promotion, and Disease Prevention Programs and Services Are Offered

Evidence suggests that lifestyle changes and health promotion activities have as much influence over health as does pharmacotherapy. Pharmacists are typically more accessible than many other health care practitioners and therefore are in a position to provide counsel, advice, and tools to help individuals adopt lifestyle changes and seek health-risk screening opportunities. Effective health management includes program outreach in which population risk-profiles are developed to identify and notify persons who would be likely to benefit most from health promotion intervention efforts.

Effective drug therapy management includes the perspective that the most effective drug therapy for a given patient may be no drug therapy at all. Within this conceptual framework is the potential value of disease prevention and health promotion in avoidance of the need for pharmacotherapy. Serum cholesterol reduction to target lipid levels through pharmacotherapy reduces the risk of heart attacks. Serum cholesterol reduction to target lipid levels through lifestyle changes (e.g., diet and exercise) results in quality improvement by avoiding pharmacotherapy and its costs; i.e., same outcome at lower cost.

Effective health promotion includes disease prevention through health-risk screening as well as education and methods to affect health behaviors. Effective drug therapy management is more

than getting the right drug to the right patient in the right dose at the right time at an affordable price. Effective drug therapy management includes the prospective identification of persons at risk and those who would benefit from pharmacotherapy as well as health risk reduction and promotion of healthy lifestyles to optimize patient outcomes.

All pharmacists have a responsibility to be aware of or at least to guide customers to valid and reliable sources of health information. Clinical practitioners offer and provide this information through patient encounters. Managed care pharmacists in administrative positions have the responsibility to assist clinicians by supporting the development and availability of tools such as paper and electronic education materials on health promotion and disease prevention, including tools that are independent of drug therapy. The importance of these tools is underscored for persons at risk, including older persons at risk of falls, incontinence, dementia, and hearing loss.[48] The pharmacist can help all persons and, in particular, persons at risk, to locate useful guidelines and patient education materials and make these materials and information readily available at the point of care.

Core Focus Area 3: The Patient Is Effectively Assessed, Accurately Diagnosed, and Appropriate Drug Therapy Is Selected

Effective and safe drug therapy depends on accurate and complete patient diagnosis. This includes assessment of health risk associated with unhealthy lifestyle behaviors, environmental factors, genetic and/or familial predisposition, and susceptibility to future disease and disease complications. Selection of the proper therapeutic agent and dose includes identification and evaluation of unique patient factors, including considerations such as drug therapy in the elderly, pediatric dosing, and patient-specific characteristics such as compromised renal or hepatic function, history of treatment failure, and alternate therapy due to previous ADRs. Drug therapy management includes the efficient and error-free transmission of prescription orders to dispensing pharmacists and the sharing and coordination of patient-specific information among all practitioners involved in the selection and administration of pharmacotherapy to patients.

So-called "collaborative practice" became a mainstream topic in the United States in 2002 and 2003 and part of government recommendations in a Medicare Payment Advisory Commission (MedPAC) report in mid-June 2002. MedPAC recommended that "The Secretary should assess models for collaborative drug therapy management services in outpatient settings."[49] The MedPAC report in June 2002 represented a milestone in public debate about the value of clinical pharmacy services. The following tasks performed by clinical pharmacists engaged in collaborative practice agreements with physicians are not surprising in the context of the realization that persons aged 65 years and older account for 13% of the population but consume 35% of all prescription drugs in the United States each year[49,p.23]:

- assist physicians to improve medication management and continuity of care;
- select, initiate, modify, continue, discontinue, and monitor patients' drug therapy;
- order, perform, and interpret medication-related laboratory tests;
- assess patients' responses to therapy;
- counsel and educate patients on medications; and
- administer medications.

As of June 2003, all but 11 states permitted pharmacists to administer drug therapy pursuant to a collaborative drug therapy management (CDTM) agreement with a prescriber or a physician's order, and, in one state, managed care organization (MCO) pharmacists perform CDTM services under the state medical practice act, which allows physicians to delegate prescribing authority.[50] The primary vehicle for CDTM involves development of patient-specific treatment protocols agreed to by the patient, physician, and pharmacist.

There is nothing in Core Focus Area 3 and its "grid" of components that assumes that pharmacists are routinely involved in patient diagnosis or even in drug prescribing. There is, however, a clear mandate from pharmacy customers that pharmacists have access to sufficient patient-specific information to be able to assess the appropriateness of the prescribed drug therapy, including dose and duration of therapy. Customers expect pharmacists to double-check the "fit" between the prescribed drug therapy and the patient-specific conditions.[41] This check by the pharmacist at the initiation of therapy necessarily involves assessment, and ongoing patient monitoring involves additional clinical assessment of the patient.

Selecting the appropriate drug therapy involves some expectation of effectiveness, which implies that *evidence* exists to support the expectation. As pointed out in the IOM *Chasm* report, many aspects of health care are associated with little or no evidence of either effectiveness or ineffectiveness.[5]

Core Focus Area 4: The Patient Is Served by a Distribution System That Provides Accurate Drug Therapy and Understandable Health Information in a Timely Manner

The drug therapy "product" involves more than drug distribution and dispensing. It includes sufficient useful and accessible information to guide practitioners and the patient to the decisions that are most likely to produce the best drug therapy outcomes. Pharmacy practitioners can improve their effectiveness in patient education and health behaviors by involving and engaging patients, such as in the evaluation of their individual progress in their care management plan. Component tasks in this core focus area also include seemingly mundane but very important functions related to drug distribution, including product storage, product safety, security to prevent tampering or diversion, clean preparation and dispensing areas, and methods to respond quickly and efficiently to product recall notices. Best practice in pharmacy also includes triage and risk management strategies for major environmental events (e.g., earth-

quakes, tornadoes), temporary interruptions in supply (e.g., asthma inhalers, voluntary product recalls, raw material shortages, manufacturing problems), or unexpected spikes in demand (e.g., influenza epidemic, stockpiling, bioterrorism).

Pharmacy customers who use drug therapy have the reasonable expectation that they will receive the correct drug in the correct dose and strength, with 100% accuracy, every time. This zero-defect expectation imposes the highest standards of accuracy and performance at all steps in the medication-use system, yet the evidence suggests that, while remarkably low in frequency, pharmacy dispensing errors that have the potential to cause patient harm or discomfort occur at an apparent rate of about 1 in 1,000 prescriptions.[51] Pharmacy customers also expect to obtain drug therapy and pharmacy services through a process that is convenient, approachable, and affordable.

Pharmacy has an increasingly large opportunity to help patients and clinicians sort through the mountains of data and "information" available in journals, the lay press, and the Internet. The *Framework* Project, with its interviews of customers, revealed a nearly self-evident fact—patients expect pharmacists to help them sort through the data to find the information that will lead to optimal drug therapy outcomes, including efficacy and safety.[41] However, the challenge to pharmacists and other health care professionals to differentiate truth from pseudoscience is, quite simply, daunting. The explosion of material available through the Internet makes this challenge to define evidence nearly impossible for individuals. In addition to the challenge of differentiating good information from bad data, the advent of DTC advertising in the late 1990s increased customer awareness of and demand for the promoted drugs.

Pharmacy customer interviews show that the scope of the information expected by patients extends beyond drug information to health information. A survey of patients with hypercholesterolemia, who had a lipoprotein profile performed within the 6 months preceding the survey, showed that patients want to be involved in their drug therapy; 94% of the survey respondents preferred to receive notification of all lab test results, whether normal or abnormal, and desired that recommendations for health management changes accompany abnormal test results.[52] Research results have established that patient involvement in care decisions improves patient satisfaction and adherence to therapy, in part by reducing decisional conflict and indecision about the value of treatment.[53] Quality improvement as measured by adherence to therapy can occur as a result of soliciting patient treatment preferences prior to the selection of initial therapy.[54]

Core Focus Area 5: Patient Response to Drug Therapy Is Monitored for Effectiveness, Adherence, Avoidance of Adverse Effects, and Drug Therapy Is Adjusted to Achieve Optimal Outcomes

Components within this core focus area present perhaps the most significant opportunities for effective drug therapy management. Critical elements to improve outcomes include a systematic process to track drug errors and prevent, detect, and resolve ADEs as well as measure patient response to therapy and adjust drug therapy based on this feedback. From this perspective, patients who do not return for care are potential failures, not successes.

From a care-flow perspective, a care treatment plan is a necessary part of every episode of drug therapy and is the first step in drug therapy management. The plan permits continuous quality improvement in the care of each patient, achieved through application of the P-D-C-A (plan, do, check, act) quality-improvement tool. Patient progress can then be assessed relative to the care treatment plan and appropriate adjustments made to initial drug and dose selections. Reliance on evidence in the care process will lead to more-predictable and higher-quality patient outcomes. Monitoring intermediate and ultimate patient outcomes and making continuous adjustments increases favorable outcomes and reduces undesirable outcomes. Continuous assessment includes the prevention, identification, and treatment of ADEs.

Routine access to a patient's entire drug history by his or her pharmacist and physicians is necessary to help avoid drug-induced disease as well as attain optimum drug therapy outcomes. But the need and expectation remain unfulfilled. For patients who see more than one physician, their multiple prescribers seldom have efficient access to information on the entire drug-use history. Core Focus Area 5 includes assessment of pharmacist access to sufficient patient information to support decisions on the effectiveness of drug therapy, development of drug-induced disease, ADEs, and the need to make dosage or drug selection changes. In pharmacy customer interviews in the *Framework* Project, academicians, drug manufacturers, employer-purchasers, patients, health plan administrators, and, to a more limited extent, physicians and government administrators, agreed that pharmacists should have access to complete patient clinical data.[55]

Construction of the care treatment plan for each patient should be specific to patient diagnosis and individual patient characteristics (e.g., age, ethnicity, socioeconomic status, and living environment) and reflect current standards of care. By definition, care guidelines, clinical practice models (CPMs), and treatment protocols are not static and should be subject to continuous quality improvement. Unfortunately, even high-profile sources of clinical practice guidelines (CPGs) may not be reliable. Work published in September 2001 in the *Journal of the American Medical Association* found that only 3 of 17 (18%) of the CPGs published by AHRQ were judged to be still valid.[56] Seven (41%) of the CPGs were found to require a major update to reflect new evidence, and 6 CPGs were judged to require a "minor update." In other words, at the time of the report in September 2001, three quarters of the AHRQ guidelines needed updating. Early in 2003, AHRQ launched the Web-based National Quality Measures Clearinghouse to function as a repository for evidence-based quality measures and measure sets.[57] In addition to the

shortfall in maintaining and updating available CPGs and CPMs, a major challenge for pharmacy and medicine in the 21st century involves delivery of the clinically relevant information to the practitioner at the point of care. Even the best clinical guidelines will have no effect on patient outcomes if not used. Unfortunately, research has shown that the development and dissemination of practice guidelines has minimal effect on clinical practice.[58-61]

The Committee on Quality of Health Care in America of the IOM recommended in its *Chasm* report in 2001 the development of a clinical-information infrastructure that would eliminate most handwritten clinical data by 2010. Brent James, MD, has long advocated the placement of clinically relevant information not only at the time of service but also in the *process of care* such that a clinical information system generates reminders for each patient, in a manner that makes the information unavoidable to the clinician.[62] Research by Dexter et al. showed in a randomized controlled trial that a computerized clinical-information system that generated preventive care reminders at the point of patient discharge increased significantly the use of subcutaneous heparin for patients at risk for venous thromboembolism, instructions to take aspirin for patients hospitalized for acute myocardial infarction, and the use of pneumococcal or influenza vaccine for eligible patients.[63]

An information technology-based clinical decision support system may not be necessary to improve the quality of care, but such a system is necessary to reduce significantly the variance in practice and to maximize favorable therapeutic outcomes. This perspective is consistent with the observation attributed to Mark Twain: "We cannot possibly know everything we need to know, the subject is simply too large." Lawrence Weed observed in 1997, "Until now, we have believed that the best way to transmit knowledge from its source to its use in patient care is to first load the knowledge into human minds . . . and then expect those minds, at great expense, to apply the knowledge to those who need it. However, there are enormous 'voltage drops' along this transmission line for medical knowledge."[64]

Core Focus Area 6: Medical Benefits Are Provided Through a System That Has an Appropriate Drug-Use Policy and Benefit Design

This core focus area concentrates on the management of processes and the collating and sharing of information to assure that health benefits are adequate, make sense, and are generally straightforward to use. The health benefit should facilitate the provision of appropriate drug therapy such that practitioners have adequate time to develop professional relationships with patients, collect key-critical monitoring data, record this information, and make midcourse changes to improve drug therapy outcomes. To achieve this goal, the health benefit should include coverage for tasks and interventions that generate maximum output and best outcomes with limited resources.

Organizations measure effective drug therapy management, as all health service functions, by efficiency—achieving a *better* outcome at the *same* cost, the *same* outcome at lower cost, a *better* outcome at lower cost, or a *significantly better* outcome at moderately higher cost. "Cost" is a necessary consideration in this *value* determination since health care resources are finite, and a dollar spent on one good or service potentially reduces availability for spending on an alternate good or service. Second, whether commercial health insurance plans, government programs, or personal resources finance drug therapy, its cost affects the entire population. From the payer perspective, effective drug therapy management depends on more than the medical benefit to finance tasks and interventions. It also depends on responsible and effective management and leadership. Effective leaders and managers develop tools, procedures, and processes to generate maximum output with limited resources.

Commonly, the medical benefit and drug benefit design specific to a patient influence the selection of the most preferred drug therapy for that patient. Drug benefit designs commonly have financial incentives such as different copays for use of generic drugs and preferred drugs, and multi-tier plans with additional copays for "nonpreferred" or nonformulary branded drugs. Pharmacy and therapeutics (P&T) committees make these decisions regarding preferred drugs long before the individual patient encounter. From this perspective, health care systems must recognize all of the expectations of pharmacy's customers regarding fair-balance and absence of bias in evaluating alternate drug therapies. Just as the prescriber selects the best drug therapy for an individual patient, health care systems that operate P&T committees have the same or greater responsibility to protect preferred therapy decisions from bias and to base decisions on the best available evidence on clinical, service, and cost outcomes.[65]

However, drug-cost considerations are not as simple as the cost of the drug itself. The occurrence of an *avoidable* ADE increases the cost of therapy. An *avoided* ADE may reduce the cost of therapy. Aspirin prevents coronary heart disease, and even after accounting for the costs associated with the increased incidence of major bleeding, it is the most cost-effective therapy for reducing the medical and hospital costs associated with coronary events accross patients at a wide range of coronary risks.[66] Ultimately, drug costs are not "pharmacy" costs but health care costs, where cost "silos" for pharmacy versus physicians versus hospitals or home care are melded. Prescription drug benefits and pharmacy benefit managers contribute to total health care costs and should not be divorced or carved out from the larger perspective.

Core Focus Area 7: The Health System Performs Ongoing Assessment to Ensure That the Results of Drug Therapy Management Lead to Healthy Individuals and Populations

The emphasis in Core Focus Area 7 is on the evaluation of col-

lective, aggregate data to improve outcomes and processes for individual patients and across the hundreds, thousands, and even millions of patients, care-encounters, and care management plans. The determination of favorable patient care outcomes includes the development of quality measures for health care services and participation in their continuous development as well as continuous improvement in the processes of collecting data and the measurement of performance against available standards. Reliable clinical data are necessary for the conduct of valuable studies of the effects of interventions on population health. Readers should be critical of "quality standards" since these standards are always evolutionary. Readers should also strive to be informed of the criticisms of others and knowledgeable about shortcomings in existing quality measures. For example, the Health Plan Employer Data and Information Set (HEDIS) 2000 quality standard for asthma control was criticized for having little to do with true asthma *control*.[67]

Widespread use of integrated electronic medical records will facilitate the capture of patient clinical values in a more reliable manner, improving data quality as well as increasing efficiency in the collection and analysis of patient clinical data. The opportunity looms large. Consider that in 2001 just 33% of MCOs and integrated health networks (IHNs) reported using an integrated electronic medical record. This represented a very modest increase over previous years when 31% of MCOs and IHNs reported using an electronic medical record in 1999 and 27% in 1997.[68] As for the magnitude of the chasm between current practice and quality standards established by the Leapfrog Group, in 2001, only 3.3% of hospitals reported operational physician electronic order entry systems, and, in 2002, fewer than 5% of hospitals had computerized order-entry systems to permit detection of possible medication errors.[69]

Finally, it is not possible to do all things for all people. Resource consumption and return on investment must be fundamental considerations in quality improvement in health care and pharmacy services. To achieve the promise of disease management, health care systems must invest in higher-quality databases of medical encounter information combined with more valid and reliable descriptions of patient characteristics. Application of the principles of continuous quality improvement will ensure continual reassessment of the soundness of the resource allocation decisions and permit changes in medical and pharmacy intervention methods, processes, and procedures to cross the quality chasm. Somehow, we must continually strive to measure and improve health care quality and the measures of health care quality without diverting resources from other efforts that have better potential to actually improve quality. This is not a temporal concern and deserves our attention far into the 21st century.

Discussion

The IOM *Chasm* report set forth in useful detail the gap between the desired health care system of the 21st century and the deficiencies in the present health care system. As useful as the IOM *Chasm* report is, it could have defined more clearly the fundamental cause of many of the deficiencies of the present system. That is, the current health care system is directed primarily by market forces that do not reward or invest in quality. Arnold Relman, MD, of Harvard Medical School, observed, "The multiple independent private insurers (mostly investor-owned) constantly seek to reduce their payments to providers and their financial obligations to sick patients. . . . In all parts of the system, the providers of care (i.e., hospitals and physicians) see themselves as competing businesses struggling to survive in a hostile economic climate, and act accordingly. The predictable result is a fragmented, inefficient, and expensive system that neglects those who cannot pay, scrimps on support of public health services and medical education, and has all of the deficiencies in quality that are so well described and analyzed in this *[Chasm]* report. It is a system that responds more to the financial interests of investors, managers, and employers than to the medical needs of patients."

From another perspective, efficiency is one of the valuable outcomes of quality improvement, and tools such as *Pharmacy's Framework* will permit individual pharmacists and pharmacies and managed health care systems in the 21st century to focus investments in quality to increase efficiency and improve patient outcomes. The great strides in the 21st century in managed care pharmacy will involve less focus on pharmacy provider discounts and more emphasis on methods to reduce *overuse* and *misuse* of pharmacy services and improve *underuse* of pharmacy services. This quality improvement will occur, in part, through enhanced 2-way communication between managed health care systems and pharmacy providers. PBMs will become coordinators of care and less brokers of pharmacy provider discounts.

In the *Framework* portfolio white paper, "Organization Culture and Effecting Change in Pharmacy in the 21st Century," Jeanine Mount writes, "Optimizing drug therapy management presents the greatest challenge to pharmacy as it enters the 21st century. Meeting this challenge requires seizing opportunities and overcoming obstacles that limit pharmacy's current contribution to health care. In short, it requires changing pharmacy practice. "Initiating change can be daunting, however this is a time when the amount and pace of change is unprecedented. Observe this for long enough and it becomes clear that one's choices are simple: actively manage change, reactively respond to change, or be left behind."[70]

Within Pharmacy's *Framework for Drug Therapy Management in the 21st Century* is a new structure to identify and meet the needs of pharmacy's customers and optimize drug therapy. The *Framework* authors view it as a roadmap that can guide change. Pharmacy is more than managing the care of individual patients. Pharmacy involves organized efforts to continuously improve common methods and processes to attain better patient out-

comes. Certainly no pharmacist, pharmacy, or health care system carries out all of the activities enumerated in the *Framework*. It is also safe to say that every pharmacist, pharmacy, and health care system engages in some of the *Framework* activities, although which and to what extent will vary considerably.

Conclusion

Using the *Framework*, every pharmacist, pharmacy, and health care system has the potential to bridge the quality gap through continuous self-assessment of performance in core focus areas and in the specific tasks and functions that comprise these core focus areas. The *Framework* tool can help better define the opportunities for quality improvement, narrow the focus for the interventions, and help in the measurement of the progress to goal.

The *Pharmacy's Framework for Drug Therapy Management in the 21st Century* is available at www.fmcpnet.org.

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REFERENCES

1. Chassin MR, Galvin RW, and the National Roundtable on Health Care Quality. The urgent need to improve health care quality. *JAMA.* 1998; 280(11):1000-05.

2. Chassin MR. Is health care ready for six-sigma quality? *Milbank Q.* 1998;76(4):565-91.

3. Schuster MA, McGlynn EA, Brook RH. How good is the quality of healthcare in the United States? *Milbank Q.* 1998;76(4):517-63.

4. Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err Is Human: Building a Safer Health System.* Institute of Medicine Committee on Quality of Health Care in America. Washington, DC: National Academy Press; 2000.

5. Kohn LT, Corrigan JM, Donaldson MS, eds. *Crossing the Quality Chasm: A New Health System for the 21st Century.* Institute of Medicine Committee on Quality of Health Care in America. Washington, DC: National Academy Press; 2001.

6. Wertheimer AI. Shaping the profession of pharmacy: an overview of seminal events that helped transform pharmacy education and practice during the twentieth century [Appendix A]. In: *Pharmacy's Framework for Drug Therapy Management in the 21st Century*. Alexandria, VA: Academy of Managed Care Pharmacy; 2002.

7. Midwest Business Group on Health. Reducing the costs of poor-quality health care through responsible purchasing leadership. April 2003. Available at: www.mbgh.org. Accessed May 15, 2003.

8. *Medical Errors: The Scope of the Problem* [fact sheet]. Rockville, MD: Agency for Healthcare Research and Quality; February 2000. AHRQ publication 00-P037 Available at: http://www.ahrq.gov/qual/errback.htm. Accessed August 18, 2002.

9. Leape LL, Institute of Medicine error figures are not exaggerated. *JAMA.* 2000;284:95-97.

10. MacCondald CJ, Weiner M, Jui SL. Deaths due to medical errors are exaggerated. *JAMA.* 2000;284:93-95.

11. Weingart SN, Wilson RM, Gibberd, RW, et al. Epidemiology of medical error. *BMJ.* 2000;320:774-77.

12. Aspinall MB, Whittle J, Aspinall SL, et al. Improving adverse-drug-reaction reporting in ambulatory care clinics at a Veterans Affairs hospital. *Am J Health Syst Pharm.* May 1, 2002:841-45.

13. Anonymous. FDA handling of ADR reports needs improvement. *Am J Health Syst Pharm.* February 1, 2000:201-02.

14. Bates DW, Boyle DL, Vander Vliet MB, Schneider J. Leape L. Relationship between medication errors and adverse drug events. *J Gen Intern Med.* 1995; 10:199-205.

15. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention: ADE Prevention Study Group. *JAMA.* 1995;274:29-34.

16. Gurwitz JH, Field TS, Avorn J, et al. Incidence and preventability of adverse drug events in nursing homes. *Am J Med.* 2000;109:87-94.

17. Gurwitz JH, Rochon P. Improving the quality of medication use in elderly patients: a not-so-simple prescription. *Arch Intern Med.* 2002;162(15):1670-72.

18. Zhan C, Sangl J. Bierman AS, et al. Potentially inappropriate medication use in community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. *JAMA.* 2001;286:2823-29.

19. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA.* 2003;289(9):1107-16.

20. Milstein A, Galvin RS, Delbanco SF et al. Improving the safety of health care: the Leapfrog initiative. *Eff Clin Pract.* 2000;3:313-16.

21. National Quality Forum Consensus Report: *Safe Practices for Better Healthcare.* May 2003. Available at: http://www.qualityforum.org/txsafeexecsumm+order6-8-03PUBLIC.pdf. Accessed December 6, 2003.

22. Pew Health Professions Commission. Critical challenges: revitalizing the health professions for the twenty-first century. The third report of the Pew Health Professions Commission. December 1995. Available at: http://www.futurehealth.ucsf.edu/summaries/challenges.html. Accessed December 6, 2003.

23. Anonymous. Professional issues, whom do you trust? *Am Med News.* January 20, 2003. (Amednews.com Quick View). Available at: http://www.ama-assn.org/sci-pubs/amnews/pick_03/prca0120.htm. Accessed January 22, 2003.

24. Malone DC. Determining the value of pharmacy services—the search for rigorous research designs. *J Manag Care Pharm.* 2002;8(2):152-55.

25. Malone DC, Carter BL, Billups SJ, et al. An economic analysis of a randomized, controlled, multicenter study of clinical pharmacist interventions for high-risk veterans: the IMPROVE study. Impact of managed pharmaceutical care resource utilization and outcomes in Veterans Affairs medical centers. *Pharmacotherapy*. 2000;20:1508-16.

26. Malone DC, Carter BL, Billups SJ, et al. Can clinical pharmacists affect SF-36 scores in veterans at high risk for medication-related problems? *Med Care.* 2001;39:113-22.

27. Heaton AH, Hansten PD, Martin SL, et al. High frequency of itraconazole prescriptions with potentially interacting medications in a large health care plan. *J Manag Care Pharm.* 2002;8(3):199-203.

28. Leape LL, Cullen DJ, Clapp MD, et al. Caring for the critically ill patient—pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA.* 1999;282:267-70.

29. Adams C. The fine print: are too many doctors missing safety alerts on drugs? *Wall Street Journal.* March 24, 2000:B1.

30. Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD. Contraindications to metformin therapy in patients with type 2 diabetes: a population-based study of adherence to prescribing guidelines. *Diabet Med.* 2001;18:483-88.

31. Holstein A, Nahrwold D, Hinze S, Egberts EH. Contraindications to metformin therapy are largely disregarded. *Diabet Med.* 1999;16:692-96.

32. Horlen C, Malone R, Bryant B, et al. Frequency of inappropriate metformin prescriptions. *JAMA.* 2002;287:2504-05.

33. Wojcik J. Disease management success prompts second program. *Bus Insurance.* March 1998;30:6.

34. Connolly C. In N.C., improving worker health—and cutting costs. *Washington Post.* August 20, 2002:A1, A3.

35. Cranor CW, Christensen DB. The Asheville Project: short-term outcomes of a community pharmacy diabetes care program. *J Am Pharm Assoc.* 2003; 43(2):149-59.

36. Cranor CW, Bunting BA, Christensen DB. The Asheville Project: long-term clinical and economic outcomes of a community pharmacy diabetes care program. *J Am Pharm Assoc.* 2003;43(2):173-84.

37. Aventis Managed Care Digest Series 2002. *Medical Group Practice Digest:*12. Bridgewater, NJ: Aventis; 2002.

38. Isetts BJ, Brown, LM, Schondelmeyer SW, Lenarz LA. Quality assessment of a collaborative approach for decreasing drug-related morbidity and achieving therapeutic goals. *Arch Intern Med.* 2003;163:1813-20.

39. Institute for Safe Medication Practices. ISMP Medication Safety Self-Assessment for Community-Ambulatory Pharmacy. Available at: www.ismp.org. Accessed March 3, 2004.

40. Supporting documents, *Pharmacy's Framework for Drug Therapy Management in the 21st Century.* June 2002. Available at: http://www.fmcpnet.org/data/resource/Framework_Supporting_Documents.pdf. Accessed March 3, 2003.

41. Lopez L. First steps to building pharmacy's framework for drug therapy management in the 21st century: interviews with customers about pharmacy's role in drug therapy management. Supporting documents, *Pharmacy's Framework for Drug Therapy Management in the 21st Century.* Alexandria, VA: Academy of Managed Care Pharmacy; 2002. Available at: http://www.fmcpnet.org/data/resource/Framework_Supporting_Documents.pdf. Accessed March 3, 2003.

42. The Self-Assessment Tool. *Pharmacy's Framework for Drug Therapy Management in the 21st Century*—A Quality Improvement Tool. Alexandria, VA: Academy of Managed Care Pharmacy; 2002. Available at: http://www.fmcnet.org/data/resource/Framework_Self_Assessment_Tool.pdf. Accessed December 6, 2003.

43. de Brantes F, Galvin RS, Lee TH. Bridges to excellence: building a business case for quality care. *J Clin Outcomes Manage.* 2003;10(8):439-46.

44. Shojania KG, Duncan BW, McDonald KM, et al, eds. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices.* Rockville, MD: Agency for Healthcare Research and Quality; 2001. Evidence Report/Technology Assessment No. 43. AHRQ publication 01-E058.

45. Fortescue EB, Kaushal R, Landrigan CP, et al. Prioritizing strategies for preventing medication errors and adverse drug events in pediatric inpatients. *Pediatrics.* 2003;111(4):722-29.

46. Oks D, Westcott RT, eds. *Certified Quality Manager Handbook.* 2nd ed. 2001. Available at: http://qualitypress.asq.org/perl/catalog. Accessed March 29, 2003.

47. Berwick DM. *As Good As It Should Get: Making Health Care Better in the New Millennium*. Boston, MA: Institute for Healthcare Improvement; 1998. Available at: http://www.ihi.org/newsandpublications/articles/ci0801asgoodas.asp. Accessed August 15, 2002.

48. Koretz BK, Moore AA. Assessment of the geriatric patient: a practical approach. *J Clin Outcomes Manage.* July 2001;8(7):35-40.

49. Medicare Payment Advisory Commission (MedPAC). *Report to the Congress— Medicare Coverage of Nonphysician Practitioners.* June 2002:23. Available at: www.medpac.gov/publications/congressional_reports/jun02_NonPhysCoverag.pdf. Accessed June 29, 2002.

50. Anonymous. Let's collaborate. *Drug Top.* September 1, 2003:58-64, 67.

51. Flynn EA, Barker KN, Carnahan, BJ. National observational study of prescription dispensing accuracy and safety in 50 pharmacies. *J Am Pharm Assoc.* 2003;43(2):191-200.

52. Meza JP, Webster DS. Patient preferences for laboratory test results notification. *Am J Manag Care.* 2000;6(12):1297-1300.

53. Murray E, David H, Tai SS, et al. Randomized controlled trial of an interactive multimedia decision aid on hormone replacement therapy in primary care. *BMJ.* 2001;323:490-93.

54. Dwight-Johnson M, Unutzer J, Sherbourne C, et al. Can quality improvement programs for depression in primary care address patient preferences for treatment? *Med Care.* 2001;39:934-44.

55. Lopez L, Wertheimer AI. Designing a framework for pharmacy practice: a look at consumer reactions and expectations. *J Manag Care Pharm.* 2001; 7(3):193-200.

56. Shekelle PG, Ortiz E, Rhodes S, et al. Validity of the Agency for Healthcare Research and Quality Clinical Practice Guidelines—how quickly do guidelines become outdated? *JAMA.* 2001;286:1461-67.

57. Agency for Healthcare Research and Quality. National Quality Measures Clearinghouse (NQMC). Available at: http://www.qualitymeasures.ahrq.gov/. Accessed March 1, 2003.

58. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA.* 1999;282(15): 1458-65.

59. Hayward RS. Clinical practice guidelines on trial. *Can Med Assoc J.* 1997;156:1725-27.

60. Lomas J, Anderson GM, Karin D-P, et al. Do practice guidelines guide practice? The effect of a consensus statement on the practice of physicians. *New Engl J Med.* 1989;321(19):1306-11.

61. Woolf SH. Practice guidelines: a new reality in medicine. III. Impact on patient care. *Arch Intern Med.* 1993;153:2646-55.

62. James B. Quality improvement opportunities in health care—making it easy to do it right. *J Manag Care Pharm.* 2002;8(5):394-99.

63. Dexter PR, Perkins S, Overhage JM, et al. A computerized reminder system to increase the use of preventive care for hospitalized patients, *New Engl J Med.* 2001;345(13):965-70.

64. Weed LL. Opening the black box of clinical judgment—an overview. *BMJ.* 1999;319:1-4. Available at: www.bmj.com/cgi/reprint/319/7220/1279.pdf. Accessed March 5, 2003.

65. Sullivan SD, Lyles A, Luce B, et al. AMCP guidance for submission of clinical and economic evaluation data to support formulary listing in U.S. health plans and pharmacy benefits management organizations. *J Manag Care Pharm.* 2001;7(4):272-82.

66. Marshall T. Coronary heart disease prevention: insights from modeling incremental cost effectiveness. *BMJ.* 2003;327:1264-66.

67. Glauber JH. Does the HEDIS asthma measure go far enough? *Am J Manag Care.* June 2001;5(6):575-79.

68. Knapp K, Blalock SJ, Black BL. ASHP survey of ambulatory care responsibilities of pharmacists in managed care and integrated health systems—2001. *Am J Health Syst Pharm.* November 15, 2001:2151-66.

69. Landro L. Hospitals' technology gap widens. *Wall Street Journal.* July 16, 2002:D3. Available at: www.hhnmag.com. Accessed July 16, 2002.

70. Mount JK. Organization culture and effecting change in pharmacy in the 21st century. Supporting documents, *Pharmacy's Framework for Drug Therapy Management in the 21st Century.* Alexandria, VA: Academy of Managed Care Pharmacy; 2002. Available at: http://www.fmcpnet.org/data/resource/Framework_Supporting_Documents.pdf. Accessed March 3, 2003.

AMCP DOCUMENTS PRECEDING *FRAMEWORK*
(SEE ABSTRACT)

• *Catalog of Pharmacy Quality Indicators.* Alexandria, VA: Academy of Managed Care Pharmacy; 1997.

• Pharmacy Quality Council. *Summary of National Pharmacy Quality Measures.* Alexandria, VA: Academy of Managed Care Pharmacy; February 1999.

Evaluating the Cost-Effectiveness of Statins

It is not easy to synthesize the available evidence on medication pricing, treatment costs, drug safety, potency, outcomes evidence, and epidemiology to derive appropriate and cost-effective treatment guidelines for hypercholesterolemic patients. Cost-effectiveness analyses that consider only narrow intermediate measures of clinical effectiveness to derive cost per percentage low-density lipoprotein (LDL) reduction ignore many key issues.[1] They simplify away many of the factors that should be considered by clinicians and health plans in attempting to obtain value for money spent on lipid therapy. For each lipid medication, these factors should certainly include (1) the available disease outcomes evidence from randomized controlled studies (RCTs), (2) the safety evidence from RCTs and from actual market usage, and (3) given that hypercholesterolemia is a lifetime chronic condition, the potential impacts of generic competition on treatment costs.

We are only beginning to see the results of comparative trials of competing statin agents. To infer that there is a direct proportional relationship between LDL lowering and potency (even holding other coronary heart disease [CHD] risk factors constant) and CHD event reduction across statins, without head-to-head trials, is to take a leap of faith. As discussed by Sacks et al. for the Cholesterol and Recurrent Events (CARE) study, pravastatin (Pravachol) appeared to reduce CHD events as much or more in the Scandanavian Simvastatin Survival Study (4S)-eligible CARE study population as simvastatin (Zocor) did in the 4S for comparable patients, even though pravastatin did not lower LDL cholesterol (LDL-C) as much in CARE as simvastatin did in 4S.[2,3]

The first head-to-head statin trial—PROVE IT—(pravastatin versus atorvastatin) to evaluate actual CHD endpoints will be released early in 2004.[4] However, based on invasive ultrasound measurement of atherosclerotic plaque progression, a smaller Cleveland Clinic study of 502 patients with preexisting CHD presented at the most recent American Heart Disease conference found that atorvastatin (Lipitor) halted CHD progression, while pravastatin did not.[5] Hopefully, additional active-drug RCT comparison trials will enhance our understanding and better guide therapy choices.

The National Cholesterol Education Program (NCEP) cholesterol treatment guidelines and LDL targets are designed to be used by clinicians as simple indicators for initiation of therapy.[6] The NCEP guidelines do not recommend specific medications nor do they predict the mortality and CHD morbidity outcomes associated with alternative cholesterol medications. They cannot be overinterpreted to provide more evidence than the existing and extensive randomized controlled trial data on statins and other lipid therapies.[7-14] One cannot infer from NCEP guidelines that because one statin is less expensive than another for a given patient in "reaching the NCEP LDL goal" that it is a more cost-effective treatment. Only head-to-head RCTs comparing actual medications can establish such definitive results.

Even setting aside differences in statin medication outcomes, a reduction in LDL-C to 131 mg/dL will have about the same effect on CHD risk as a reduction to 129 mg/dL, but the NCEP effectiveness metric would consider the former as a "failure" and the latter as a "success" in achieving target LDL-C. Ironically, if managed care organization quality metrics (e.g., health maintenance organization report cards) focus on arbitrary NCEP LDL-C guidelines, physician, pharmacist, and other medical resources may be wasted on monitoring to ensure a maximum number of patients achieve these arbitrary LDL targets (e.g., by ensuring that patients slightly above LDL targets are brought under the targets) while high risk "failed" patients may be ignored. The result could easily be more heart disease than if medical resources were explicitly allocated to maximize CHD risk reduction in the managed care organization patient population.

If a clinician really believed that LDL reduction is the *only* thing that matters, then over-the-counter (OTC) niacin would dominate any statin on the basis of price per LDL lowering. Niacin is potent, cheap, and available without prescription (niacin 300 mg costs $0.03 per day, reduces LDL cholesterol by 17%, and raises high-density lipoprotein cholesterol by 27%). Diet is available even more cheaply, and diet can achieve a 10% to 20% LDL reduction. Compliance is a concern with all lipid therapies, including statins. While compliance is more problematic with diet or niacin, a stepped-care approach with patients initiating niacin therapy and then switching to lovastatin if niacin cannot be tolerated has been found to be economically viable and dominates statin therapy alone.[15] Unfortunately, RCT data on disease outcomes with niacin or with (niacin + statin) stepped-care regimens is extremely limited.

Rosuvastatin (Crestor) is a potent statin and achieves favorable cost-per-LDL results at higher LDL reduction targets. However, in comparison with well-established statins, there is limited evidence on rosuvastatin safety over longer terms and in large populations.[16] The last new potent statin on the market was cerivastatin (Baycol), and it was withdrawn after 3 years on the market due to safety concerns (which went undetected in the premarketing clinical trials). While there is no reason to assume that rosuvastatin will have a similar fate, additional value should be incorporated in any cost-effectiveness study for those statins with millions of patient-years of history of safe use, given that one potent statin has already failed in the market. For example, the difference in daily price of atorvastatin 80 mg (LDL-C reduction 60%/$3.07) and rosuvastatin 40 mg (LDL-C reduction 63%/$2.22) is $0.85.[1] For many patients and providers, this $310 annual price differential could be a small premium to pay for atorvastatin's proven safety record in millions of patients worldwide during the past decade and for its proven CHD outcomes evidence.[7]

Generic competition will have an increasingly important effect on the statin therapy market. Morrison and Glassberg's analysis shows generic lovastatin 10 mg to already be a domi-

nant treatment for lowering LDL cholesterol by 25% or less.[1] This result is underscored by the favorable heart disease reduction and safety evidence for lovastatin developed in the AFCAPS/TEXCAPS clinical trial and its world-wide safety record since its market introduction in the mid-1980s.[12] The majority of Americans requiring medication to lower cholesterol under NCEP guidelines fall into this moderate LDL-lowering category.

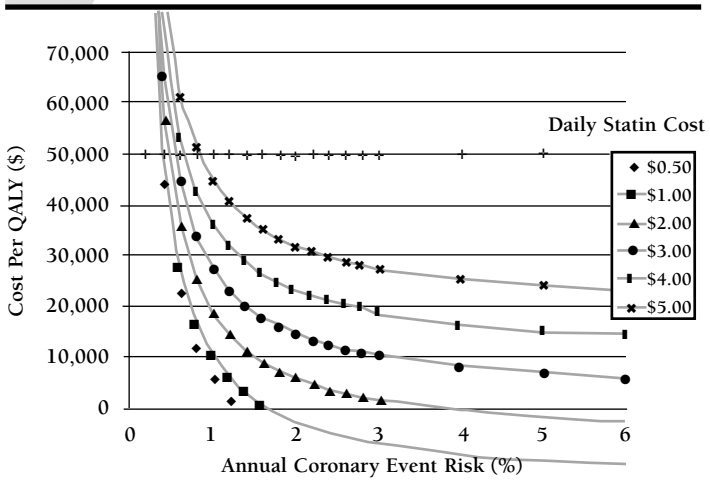
However, the price of generic lovastatin can be expected to fall dramatically over the next few years. Generic lovastatin was FDA-approved in 2002. During the first 6 months following patent expiration, the FDA allows only the first approved generic manufacturer to compete with the brand name (in this case, Mevacor). This first competitor has little incentive to lower prices (particularly published average wholesale price [AWP]). After this point, many generic competitors are allowed into the market, and the generic prices drop precipitously, usually by 70% or more when 8 to 10 generic competitors are available.[17] This should happen fairly soon in the statin market.

It would be misleading to use 2003 generic lovastatin prices to talk about the cost of lifetime lovastatin therapy. Under any reasonable scenario over the next few years, generic lovastatin will dominate other statin therapies on a cost-per-LDL-lowering basis, except in high-LDL patients who can't achieve treatment goal on lovastatin monotherapy. In the United States, these patients comprise fewer than 20% of those at risk.[18]

According to Morrison and Glassberg,[1] lovastatin 40 mg achieves a 31% reduction in LDL cholesterol at a cost of $1.97 per pill (per day). With 10 generic competitors, and a 70% discount resulting from generic competition, this price can be expected to drop to only $0.50 to $0.70 per day in the near future. Rosuvastatin can achieve a 63% LDL reduction at a cost of $2.22 per pill (per day). But by further combining generic lovastatin (10 mg to 40 mg) with diet, OTC niacin, generic gemfibrozil, or generic bile acid resins, patients will be able to achieve even greater LDL reduction than this, with proven safe and effective therapies at a cost substantially lower than with the relatively new and unproven rosuvastatin. Even factoring in $200 to $400 per year for compliance, tolerability, and safety monitoring, a stepped-care combination regimen with these older medications would be less expensive than rosuvastatin—not to mention that, in an increasingly competitive statin market, all manufacturers are willing to consider substantial discounts from AWP or other published drug pricing sources for preferred customers.

In a meta-analysis of statin outcomes evidence, Larosa et al. found that the proportional risk reduction in coronary events (31%; 95% CI: 26% to 36%), cardiovascular deaths (27; 95% CI: 19% to 34%), and all-cause mortality (21%; 95%CI: 14% to 28%) is roughly equivalent across primary and secondary prevention clinical trials of statin therapy, despite differences in statin potency and baseline annual cardiovascular disease risks ranging from 1.1% (AFCAPS/TexCAPS) to 5.2% (4S).[19] These outcomes results are further underscored by the more recent RCT findings from the ASCOT, PROSPER, and Heart Protection Studies.[7,13,14] There is no evidence that this proportional risk reduction changes with patient age, gender, or underlying cause of cardiovascular disease risk (e.g. diabetes, smoking, hypercholesterolemia, etc.).[19] While such outcomes evidence has already been established for several of the available cholesterol medications, it needs to be verified for all statin medications and further refined in head-to-head statin comparison trials. Given the ranges of confidence intervals for CHD endpoints in the various statin trials, it is spuriously precise to claim that medications that achieve different LDL reductions per dollar spent translate into specific cost-effectiveness differences.

FIGURE 1 Relationship Between Cholesterol Medication Cost-Effectiveness and Initial Coronary Event Risk*



** This analysis assumes that the medication achieves a 30% reduction in CHD relative risk. QALY = quality-adjusted life-year.*

Given these meta-analysis results, Figure 1 summarizes my estimates of the current relationship between statin prices and statin cost-effectiveness as a function of baseline annual coronary event risk, assuming a 30% CHD event reduction with a statin treatment.[19,20] Figure 1 suggests that, at a price of $0.50 per day, generic lovastatin (or other therapy) will be cost effective for any patient with annual CHD risk exceeding 0.5% per year, and cost saving (i.e., reduces average direct medical costs) for patients with annual CHD risk exceeding 1.5%. Since these risk categories includes millions of American adults who are not currently receiving therapy, it is important to ensure that any statin therapy administered to such large numbers of patients has solid evidence of safety and CHD event reduction.

Increased generic and brand competition in the statin and cholesterol medication markets will dramatically lower the price of these medications in the near future. This is excellent news because many of these drugs do have a good track record of safe-

ty, efficacy, and effectiveness. Saving lives with statins is increasingly one of the greatest pharmaceutical bargains available today.

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DISCLOSURES

The author states that he has no financial conflicts or interests regarding the drugs or manufacturers mentioned in this article.

REFERENCES

1. Morrison A, Glassberg H. Determinants of the cost-effectiveness of statins. *J Manag Care Pharm.* 2003;9(6):544-51.

2. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996;335:1001-09.

3. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383-89.

4. Cannon CP. McCabe CH. Belder R. Breen J. Braunwald E. Design of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial. *Am J Cardiol.* 2002;89(7):860-61.

5. Kolata G. Study finds differences in 2 cholesterol-lowering drugs. *New York Times.* November 12, 2003. Available at: http://www.nytimes.com/2003/11/12/health/13HEART.html?ex=1069682201&ei=1&en=0bb7ee7b2e2d1567. Accessed November 12, 2003.

6. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486-97.

7. Sever PS. Dahlof B. Poulter NR, et al. (ASCOT investigators). Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 2003;361(9364):1149-58.

8. The Long-term Intervention with Pravastatin Group in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339:1349-57.

9. Athyros VG, Papageorgiou AA, Mercouris BR. The Greek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. *Curr Med Res Opin.* 2002;18:220-28.

10. Messerli AW. Aronow HD. Sprecher DL. The Lescol Intervention Prevention Study (LIPS): start all patients on statins early after PCI [comment]. *Cleveland Clin J Med.* 2003;70(6):561-66.

11. Shepherd J, Cobbe SM, Ford I, et al., for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 1995;333:1301-07.

12. Downs JR, Clearfield M, Weis S, et al., for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA.* 1998;279:1615–22.

13. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:7-22.

14. Prosper Study Group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet.* 2002;360:1623-30.

15. Gold M, Siegel J, Russell L, Weinstein M. *Cost-Effectiveness in Health and Medicine.* New York: Oxford University Press; 1996.

16. Pfeffer MA. Keech A. Sacks FM, et al. Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. *Circulation.* 2002;105(20):2341-46.

17. Frank R, Salkever D. Generic entry and the pricing of pharmaceuticals. *J Econ Manage Strategy.* 1997;6(1):75-90.

18. Hay J, Yu W. Prevalence, patient awareness, and treatment of dyslipidemia in the diabetes mellitus population. *Drug Benefit Trends.* 1999;(suppl):6-11.

19. LaRosa J, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA.* 1999;282:2340-46.

20. Hay J, Yu W, Ashraf T. Pharmacoeconomics of lipid-lowering agents for primary and secondary prevention of coronary heart disease. *Pharmacoeconomics.* 1998;15(1):47-74.

Challenges in Evaluating the Cost-Effectiveness of Statins

The article by Morrison and Glassberg[1] and the editorial by Hay[2] highlight the challenges encountered when attempting to assess the cost-effectiveness of drug therapies for chronic diseases, particularly new drugs. Efficacy data from randomized clinical trials (RCTs) often pertain to intermediate endpoints in the form of surrogate markers of risk for the ultimate clinical endpoints of interest. In the case of drugs for hypercholesterolemia, intermediate endpoints in RCTs often relate to changes in serum lipids, such as low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), but the ultimate goal of therapy is to reduce the risk of coronary heart disease (CHD) events. In cost-effectiveness analyses, it is common practice to use risk prediction models such as the Framingham model to translate changes in lipids into predicted changes in the risk of CHD events. However, this prediction amounts to an "educated guess" that may well be wrong. A case in point is the Women's Health Initiative (WHI) RCT that reported that the CHD event rate in the estrogen-progestin treatment group was 29% higher than in the placebo group over 5 years.[3] The decrease in LDL-C and increase in HDL-C associated with estrogen-progestin therapy in prior RCTs had translated into a predicted decrease in CHD event risk of about 25%.[4]

In the case of statins, since a relationship between LDL-C reduction and CHD risk reduction has been established for several statins, it may be reasonable to assume a "class effect" for newer statins such as rosuvastatin, at least on a qualitative level. However, using these intermediate endpoints to quantify the impact of therapy on CHD endpoints requires a leap of faith. Hay cites evidence suggesting that statins that produce the same percentage change in LDL-C need not produce the same percentage change in CHD event risk, because different statins may affect CHD risk through pathways other than LDL-C reduction. If definitive efficacy data in terms of CHD endpoints from head-to-head RCTs were available, decision models would have limited value. However, such RCTs are enormously expensive and time consuming and, as such, are rarely available,

especially for new drugs. In the absence of head-to-head CHD endpoint RCTs, a model that makes explicit "leaps of faith" has the potential to inform decision making, as long as the decision maker appreciates the limitations of the model.

While RCTs certainly represent the "gold standard" of evidence regarding efficacy, the limitations of RCTs as models for effectiveness in usual clinical practice, specifically with respect to compliance, is a crucially important issue for drug therapies targeted at chronic diseases. Hay refers to a model by Stinnett et al. that concludes that niacin dominates lovastatin as a first-line therapy for hypercholesterolemia.[5] In this model, the authors assume essentially "ideal" compliance (discontinuation rates observed in RCTs). However, numerous studies have shown that compliance with niacin in clinical practice is poor relative to statins.[6,7] This can have a huge impact on cost-effectiveness, as noted in a recent review by Hughes and colleagues.[8] The relatively few published cost-effectiveness evaluations that attempt to assess the impact of noncompliance usually focus on discontinuation of drug therapy. In all of these studies, lower continuation rates are associated with lower incremental effectiveness. Poor compliance is associated with higher incremental cost in some studies and lower incremental cost in others, but poor compliance usually increases incremental cost-effectiveness ratios. Thus, it is quite possible that seemingly inexpensive niacin would have been dominated by the more expensive (but better-tolerated) statin in the Stinnett et al. model, if the substantial differential in compliance had been taken into account.

Another issue is the choice of an effectiveness metric to use in the denominator of the cost-effectiveness ratio. Gold et al.[9] recommend the use of QALYs, though they acknowledge that other effectiveness measures may have value in particular settings or for particular audiences. In the case of formulary decision makers, it is common to consider "within class" cost-effectiveness issues as an adjunct to "which class" cost-effectiveness issues. In the context of statins, a cost-effectiveness ratio expressed as "cost per percent LDL-C reduction" will tend to preserve the rank-order of cost-effectiveness for alternative statins if the error is small in the projection of LDL-C change onto CHD risk change. But the results using this effectiveness metric may be difficult to interpret. For example, Morrison and Glassberg report that rosuvastatin 5 mg yields an incremental improvement in LDL-C reduction of about 6 percentage points over atorvastatin 10 mg, at an additional cost of about $80 in annual drug costs. What criterion may be used to conclude that rosuvastatin is (or is not) worth this additional cost?

Morrison and Glassberg also report results using the percent of patients meeting National Cholesterol Education Program III treatment thresholds as an effectiveness measure. This "treatment success" metric has an intuitive appeal and may be relevant to managed care organizations, to the extent treatment success rates are reflected in organizational quality metrics. However, similar issues of interpretation remain: What is a "reasonable" incremental cost per treatment success? As Hay notes, a related issue is that the threshold approach often employed in treatment guidelines or Health Plan Employer Data and Information Set scores can produce incentives for waste. For example, there is no meaningful difference in CHD risk for a patient with LDL-C of 131 mg/dL and a patient with LDL-C of 129 mg/dL, but incremental resources consumed to achieve "success" might have provided greater benefit elsewhere. Although this is a legitimate concern, it is not possible to base quality performance metrics on "hard" endpoints for chronic diseases because of the lag time from quality of care received to hard endpoints, coupled with the turnover in managed care populations. Managed care organizations operate in competitive markets where payers want quality metrics in one form or another. Threshold quality metrics probably will continue to be used in the absence of a viable and superior alternative. Clearly, standard effectiveness metrics like QALYs are essential to make assessments of relative value, but additional metrics may provide additional information that may be helpful to managed care organizations.

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DISCLOSURE

The author discloses current work as a consultant for AstraZeneca in a study of the patterns of treatment of bipolar disorder. This research is not drug-specific and is unrelated to rosuvastatin.

REFERENCES

1. Morrison A, Glassberg H. Determinants of the cost-effectiveness of statins. *J Manag Care Pharm.* 2003;9(6):544-51.

2. Hay J. Evaluating the cost-effectiveness of statins. *J Manag Care Pharm.* 2004;10(1):79-81.

3. The Writing Group for the Women's Health Initiative Investigators. Risk and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized clinical trial. *JAMA.* 2002;288:321-33.

4. The Writing Group for the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA.* 1995;273:199-208.

5. Stinnett AA, Mittleman MA, Weinstein MC, et al. The cost-effectiveness of dietary and pharmacologic therapy for cholesterol reduction in adults. In: MR Gold, JE Siegel, LB Russell, MC Weinstein, eds. *Cost-Effectiveness in Health and Medicine.* New York: Oxford University Press; 1996.

6. Andrade SE, Walker AM, Gottlieb LK, et al. Discontinuation of antihyperlipidemic drugs: do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med.* 1995;332:1125-31.

7. Hiatt JG, Shamsie SG, Schectman G. Discontinuation rates of cholesterol-lowering medications: Implications for primary care. *Am J Manag Care.* 1999;5(4):437-44.

8. Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: A review of the literature. *Health Econ.* 2001;10:601-615.

9. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine.* New York: Oxford University Press; 1996.

3-Tier Drug Benefit Designs Based on Sound Drug Formulary Principles Will Maximize Favorable Outcomes

Employer-sponsored drug benefit plans have embraced the 3-tier drug benefit design in dramatic fashion, with 63% of covered workers subject to a 3-tier copay design in 2003 compared with 27% just 3 years earlier (in 2000) and 55% in 2002.[1] Use of the 2-tier copay design, the predominant drug benefit design in 2000 (with 49% of covered workers), fell to just 23% of covered workers in 2003. One major reason for this enthusiasm for 3-tier copay designs is that plan sponsor cost generally declines as member cost-share rises.[2-4] However, when multi-tier copay designs are based upon sound drug formulary principles in which low (favorable) cost-effectiveness ratios determine formulary (tier-2 copay) versus nonformulary (tier-3 copay) status, both beneficiaries and plan sponsors can enjoy lower costs as lower-cost drugs replace the utilization of higher-cost drugs. The use of lovastatin, a tier-1 cholesterol-lowering drug at a cost before copay of approximately $2 per day of therapy (with 40 mg), is about one half the cost for the same outcomes as the tier-3 drug, Mevacor (brand-name equivalent of lovastatin), at about $4 per day of therapy at year-end 2003.[5]

In the Kaiser Family Foundation survey of employer-sponsored drug benefit plans, the average member cost-share for tier-1 drugs such as lovastatin rose by $2 in the 3-year period from 2000 to 2003. The average tier-1 copay was $7 in 2000 and $9 in 2003, while the cost-share for tier-3 drugs such as Mevacor rose by $12, from an average of $17 in 2000 to $29 in 2003. Clearly, raising tier-3 copays can reduce the proportion of plan-sponsor costs for tier-3 drugs, but how much do these financial incentives and penalties influence drug utilization? The more precise question is, perhaps, how much of a financial incentive is necessary to cause a significant change in the use of preferred versus nonpreferred drugs? A collateral question is how much *change* in copayments in a drug benefit design is necessary to cause a change in behavior in the use of preferred versus nonpreferred drugs?

There is a growing body of evidence to support our hypothesis that financial incentives in the form of tiered copayments do reduce plan sponsor costs and reduce aggregate drug costs by causing a shift in utilization to generic drugs and lower-cost brand-name drugs.[6,7] But there is still much to learn about the magnitude of copay differentials necessary to influence a significant proportion of drug plan beneficiaries to change behavior and use preferred (i.e., tier-1 and tier-2 copay) drugs versus nonpreferred (generally nonformulary, tier-3 copay) drugs. In addition to questions surrounding the timing of copayment changes and the magnitude of copayments necessary to influence behavior, other questions that continue to beg for definitive answers include (a) do some patients discontinue useful and valuable drug therapy when faced with tiered copays and (b) what are the clinical and health economic outcomes from discontinued drug therapies, whether these drug therapies are perceived as valuable or of marginal value?

Looking outside prescription drug benefits, data from several studies, including the findings of the Health Insurance Experiment, suggest that (a) copayments reduce the use of medical services, (b) small copayments reduce the use of apparently unnecessary services, and (c) large amounts of cost-sharing reduce the use of medical services such as office visits without selectivity as to the appropriateness of the office visit.[8] For example, the introduction of a $5 copayment for an office visit in the mid-1980s caused an 11% reduction in visits and 14% reduction in physical exams, but the $5 copayment per office visit had no effect on the immunization of children, screening for cancer in women, or the use of cardiovascular medications.[9] More than a decade ago, researchers found that, in response to the requirement of a copayment of $1.50 for prescriptions, patients selectively reduced the use of discretionary drugs more than their use of drugs deemed essential.[10] More recently, increases in brand-drug copayments were found to not affect compliance with maintenance medications,[11] and higher cost-sharing (average 25%) in employer-sponsored drug plans was associated with higher, not lower, drug utilization compared with lower cost sharing (average 15%).[6]

In the early 1990s, it was found that a $10 increase in copayment, from a copayment of $25 to $35 per emergency room (ER) visit, resulted in a 14.6% drop in hospital ER use among a group of 30,276 health maintenance organization members in northern California compared with 2 control groups (60,408 and 37,539 members) without ER copayments.[12] A separate study of ER patients at 19 hospitals who presented with myocardial infarction (MI) found that an ER copayment requirement ranging from $25 to $100 did not have an effect on the median length of time from onset of symptoms to arrival at the hospital compared with patients with no ER copayment requirement.[13]

Wogen and Frech in their letter to the editor in this issue of the *Journal* are correct in their assertion that there is a lack of evidence that higher copayments for prescription drugs result in clinically significant discontinuation rates.[14] This statement is true despite the recent publication of a study that captured headlines by suggesting that copayments could cause discontinuation of the use of drugs.[15] In fact, the results of this recent study are mixed and even contradictory. Like many things in life, the truth and wisdom are in the details.

There is a score of shortcomings in the recent study of 3-tier copay designs (for 2 employers), including (a) the significant differences in the age demographics between the intervention and comparison groups, (b) a 2.3-fold difference in the enrollment size between one intervention group and its comparison group, and (c) nondisclosure of the actual dates of implementation of the 3-tier benefit design interventions ("in order to protect the employers' anonymity"). Most important among the findings, however, there were opposite, contradictory effects in discontinuation rates for one of the 3 drug classes that were studied. The rate of discontinuation of angiotensin-converting enzyme (ACE) inhibitors was 16.2% of tier-3 users in employer 1 versus 6.4% in its comparison group ($P<0.001$), but there was an opposite effect for employer 2 in which 8.3% discontinued use of tier-3 ACE inhibitor drugs versus 15.8% in the comparison group ($P=0.03$) This contradictory finding is muddied further by the examination of several alternate therapies, including beta-blockers and calcium channel blockers (as well as histamine-2 receptor antagonists; agents other than statins to lower cholesterol, including cholestyramine, gemfibrozil, or niacin) but

not examination of the one alternate therapy most likely to explain discontinuation rates of ACE inhibitors, the most logical therapeutic alternative to ACE inhibitors, the angiotensin II receptor blockers (ARBs).

For the other 2 drug classes studied, proton-pump inhibitors (PPIs) and statins, the results of implementation of 3-tier copay designs were inconsistent among the 2 employer groups and their matched comparisons. There was a higher rate of discontinuation of statins for employer 1 versus its comparison (P=0.04) but not for employer 2 and its comparison (P=0.45). There was a higher rate of discontinuation of PPIs for employer 1 versus its comparison (P<0.001) but not for employer 2 versus its comparison (P=0.79). Part of the reason for these apparently disparate findings may lie with the magnitude of the copays and the type of change. Beneficiaries of the employer 1 drug plan were converted from a single-tier copay ($7 for generic or brand-name drug for community pharmacy) to a 3-tier copay design (community pharmacy copayments of $8 for generic, $15 for preferred brand drugs and $30 for nonpreferred brand drugs) compared with a comparison group with an unchanged 2-tier plan of $8 copay for generic drugs and $15 copay for brand-name drugs. Beneficiaries in employer 2 were confronted with a smaller magnitude and extent of change, transitioned from a 2-tier plan of $6 copay for a generic drug and $12 for a brand-name drug to a 3-tier plan design with the same copays for tier-1 and tier-2 drugs and simply the addition of a third-tier copay of $24 for nonpreferred drugs. The comparison group for employer 2 had an unchanged 2-tier plan design of $6 and $12. Some consumer research suggests that copay differences of as much as $35 per prescription are necessary to influence consumer behavior in use of PPIs,[16] a dollar amount more than twice the tier-3 copayment "penalty" in the 3-tier drug benefit designs in this study of PPIs, ACE inhibitors, and statin drugs.

So, there is much that remains to be answered about the effects of 3-tier drug benefit copay designs on clinical, service-humanistic, and cost outcomes. The important and useful answers will come from carefully designed studies, but even these results will require interpretation since drug formularies upon which 3-tier copay plans are based differ markedly in content from one managed care organization to another. For example, the inconsistent and even contradictory results in the recent study might be explained, in part, by characteristics unique to the study population. The formulary of the pharmacy benefit manager (PBM) contained only 2 statins in tier 3 throughout the study, fluvastatin and lovastatin, and the latter became available by generic name in the middle of the study period. Readers might be better able to judge the importance of this variable if the authors had disclosed the actual patient counts for each of the 3 statin drugs in tier-3, one of which (Mevacor) became available by generic name in December 2000, the midpoint of the study period, and cerivastatin (Baycol), which changed tier-copay status from nonformulary (tier-3 copay) to formulary status (tier-2 copay) in October 2000, also in the midpoint of the study period. Baycol was withdrawn from the market in August 2001, about 5 months prior to the completion of the postintervention study period and 10 months after changing from nonformulary (tier-3 copay) to formulary (tier-2 copay) status for this PBM.

Due, in part, to the content of the tier-3 (nonformulary) statin drugs for this PBM, the utilization of tier-3 statin drugs in this study population was exceptionally low and not generalizable to other patient populations in drug benefit plans. The highest utilization of tier-3 statin drugs was found not in the comparison groups but, ironically, in the intervention (3-tier copay) groups, 3.5% of 933 patients for employer 2 and 3.4% of 2,608 statin patients for employer 1 versus 3.1% of 3,391 statin patients for the comparison group to employer 1 and 1.7% of the comparison group to employer 2. Therefore, measurement of the effect of the tier-3 plan design change on discontinuation of statin drugs was undertaken on a very small number of patients: 3 (9.1%) discontinued statin therapy versus 1 patient (4.0%) for the comparison group (P=0.45) and 19 patients (21.3%) for employer 1 versus 11 patients (10.6%) for the comparison group (P=0.04).

Other nuances further complicated the comparisons for the 3 drug classes in this study. In addition to the dual-tier copay status for lovastatin (tier-3 copay [Mevacor] and tier-1 copay effective December 2000) and the switch in copay for Baycol, followed by its withdrawal from the market, for the PPIs, esomeprazole was a tier-3 PPI before November 2001 but changed to a tier-2 copay in the latter part of the postintervention period, on November 1, 2001. For the ACE inhibitors, captopril was both a tier-1 copay drug and a tier-2 (Capoten) copay drug (and most MCOs would place the multiple-source brand drug Capoten in tier-3).

Nevertheless, this recent study of the effects of 3-tier drug copay designs for 2 employers provides a valuable reminder that the answers to the important questions regarding tier-copay drug benefit designs will depend in significant part upon how we ask the questions. It should come as no surprise that neither the answers nor the questions are simple. Behavioral change, including discontinuation rates, will likely depend upon the magnitude of the financial incentive(s) as well as the degree of change from the previous design to the new drug benefit design. When interpreting the results of research conducted on the effects of multi-tier drug benefit plan designs, readers, at a minimum, should assess 2 key variables: (a) the content of the drug formulary tiers and (b) the dollar magnitude of the financial incentives/penalties and the degree of change that are imposed by the new benefit design.

Managed Care Pharmacy—Weighing Clinical, Service, and Cost Outcomes

The creation of drug benefit plan designs that result in improvement in clinical, service-humanistic, and cost outcomes requires competent and experienced design architects. Managed care pharmacists possess unique knowledge for this task—the combination of information gleaned from clinical trials, experience with assessment of service outcomes, and the ability to identify precisely the price per day of drug therapy. Admittedly, better knowledge of total cost (e.g., direct drug and

medical costs and indirect costs) is needed, but managed care pharmacists can identify precisely the actual net cost per day of drug therapy among alternate products used for the same indication.[17] A recent survey of 100 pharmacy and medical directors in health plans found that 78% of the plans that preferred pantoprazole did so because it was the low-price leader among the proton-pump inhibitors (PPIs).[18] This fact reflects an opinion among pharmacy and medical directors that the 5 PPIs are relatively equivalent in safety and efficacy, and the preference in formulary position defers to price, for which pantoprazole at the time of the survey had a clear and distinct advantage over the 4 competing agents, including generic omeprazole.

Drug Formulary Decisions—Evaluating the Risks and Benefits of Hormone Replacement Therapy

A randomized controlled trial (RCT) found that 0.625 mg of estrogen plus 5 mg medroxyprogesterone hormone replacement therapy (HRT), was approximately 2 times as effective as 5 mg of alendronate in preserving or building bone mineral density in postmenopausal women.[19] The favorable effect of HRT on mineral density is manifest in dental bone as well as skeletal bone. A review of the medical literature found 1,518 articles on estrogen and osteoporosis, of which 20 were deemed relevant to the subject of HRT on mandibular bone or other dental bone effects of HRT and clinical or cost outcomes. The 20 studies involved data collection for 13,735 women for whom dental, HRT, or osteoporosis outcomes were collected, and the conclusion was that HRT has favorable effects on dental outcomes and dental costs.[20]

The favorable effects of HRT in osteoporosis appear to be offset by adverse effects in breast cancer. The results from the HRT portion of the Women's Health Initiative (WHI) RCT was announced on July 9, 2002. This study enrolled 16,608 postmenopausal women without coronary heart disease (CHD) and randomized them to combination HRT or placebo. The study was designed to examine the effect of combination HRT on the prevention of heart disease and hip fractures and to identify any associated risk for breast and colon cancer. Originally, the study was to continue until 2005, but the data safety monitoring board stopped the trial after finding that the risk of therapy began to outweigh the benefit when they analyzed accumulated data at the end of May 2002. With an average of 5.2 years of follow-up (a range of 3.5 years to 8.5 years), researchers found a higher rate of invasive breast cancer in the treatment arm: 38 versus 30 cases of invasive breast cancer per 10,000 person-years. Any prior use of HRT was associated with 114 cases of breast cancer over the average 5.2 years of follow-up, (a rate of 1.34%), compared with 102 cases (a rate of 1.26%) for women who had never taken HRT. In other words, WHI found that HRT was associated with 8 additional cases of breast cancer per 10,000 women treated per year.

The results from the Heart and Estrogen/progestin Replacement Study (HERS), HERSII,[21] WHI,[22] and Womens' Estrogen Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART)[23] suggest that combination estrogen and progestin is not associated with favorable effects on the progression of atherosclerosis or the prevention of CHD events. In WHI, HRT was associated with increases in CHD events (29%; 37 versus 30 per 10,000 person-years; most of the excess was in nonfatal myocardial infarction [MI] with no significant differences in CHD deaths or revascularization procedures [coronary artery bypass graft and percutaneous transluminal coronary angioplasty], stroke [41%; 29 versus 21 events per 10,000 person-years; most of the difference in nonfatal stroke], and pulmonary embolism [a doubling of the rate in the placebo group]). On the positive side, combination HRT was shown to result in 37% fewer cases of colon cancer (10 versus 16 per 10,000 person-years), 33% fewer hip fractures (10 versus 15 per 10,000 person-years), 24% fewer fractures overall, and 23% fewer osteoporotic fractures. There was no difference in mortality between the 2 groups. It should be noted that the overall risk of the negative events was quite low (i.e., an individual's risk of any of the events was less than 0.1%); however, from a population basis, there is significant risk relative to minor benefits. For a small subset of women with CHD (who would have been eligible for HERS; i.e., prior MI or revascularization procedure; N=400), there were 19 CHD events versus 16 events (hazard ratio 1.28), and, for the remaining women, the identical hazard ratio of 1.28, 145 CHD events for HRT versus 106 CHD events for placebo. Researchers concluded that the use of combination HRT should not be initiated or continued for the primary prevention of CHD. Also noteworthy, 42% of HRT users and 38% of placebo users stopped taking study drugs at some time.[24]

Others have helped explain the sometimes divergent data on postpmenopausal HRT from the more than 50 observational studies and RCTs,[25] one with a table that compares the findings from WHI versus HERS versus observational studies of estrogen with progestin in 6 key outcomes (breast cancer, colorectal cancer, hip fracture, stroke, pulmonary embolism and CHD).[26] HRT, while relatively inexpensive, may not be the best choice for osteoporosis. Estrogen alone may be effective in primary prevention of cardiovascular disease (CVD) but may not be effective in secondary prevention (in women with established CHD). Estrogen or HRT may help retard memory loss in women and might prevent Alzheimer's disease.[27] HRT might increase the risk of breast cancer, but the cancers associated with HRT may be more benign tumors, possibly explaining the observation of lower breast cancer mortality rates among HRT users compared with nonusers. Estrogen unopposed by progestin has a more favorable effect on high-density lipoprotein (HDL),[28] but micronized progesterone in combination with estrogen maintains the benefits of estrogen on HDL,[29] and unopposed estrogen has been associated with favorable cardiovascular effects.[30,31] Estrogen alone may not be associated with an increase in breast cancer risk.[32] Research on clinical outcomes of estrogen alone continues in WHI and elsewhere, and, after nearly 20 years of research on estrogen and HRT, definitive answers remain elusive, in part due to the high ratio of subjects lost to follow-up in RCTs such as WHI.[33] However, the available information at this time suggests that there may be significant differences in outcomes

among different hormone formulations, different doses of hormones,[26] and even in the timing and duration of use in postmenopausal women,[34] increasing the challenge for pharmacy and therapeutics (P&T) committees in formulary decision making and in the development of clinical guidelines.

In this issue of the *Journal*, Deady presents a summary of safety, efficacy, and effectiveness data on the use of HRT.[35] It is an example of a clinical monograph presented to the members of a P&T committee of a managed care provider network. The article is presented in the *Journal* in the Formulary Management department and is not intended as a subject review, another department in *JMCP*. This clinical monograph on HRT is perhaps an ideal subject to initiate a focus on clinical monographs in *JMCP* because it is obvious in this subject area that decisions made today need to be revisited periodically to permit refutation or affirmation of the validity and reliability of the assumptions, information, and data that were paramount in the preceding decisions. Readers who prepare clinical monographs for formulary decision making by P&T committees are encouraged to submit manuscripts from actual experience. Ever-greater transparency in drug formulary decision making will benefit all stakeholders, including physicians, pharmacists, drug manufacturers, plan sponsors, and, ultimately, health plan members.

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REFERENCES

1. Kaiser Family Foundation 2003 Employer Health Benefits Survey. Exhibit 9.1, Section 9: Prescription Drug and Mental Health Benefits. Available at:www.kff.org/insurance/ehbs2003-11-chart.cfm. Accessed December 10, 2003.

2. Joyce GF, Escarce, JJ, Solomon, MD, Goldman DP. Employer drug benefit plans and spending on prescription drugs *JAMA.* 2002;288:1733-39.

3. Anonymous. Rx benefit represent 12% of employer health care costs, survey shows. *Drug Cost Manage.* October 2002:1-7.

4. Campbell G. Study gives three cheers for three tiers. *Manag Healthcare.* July 2000:27.

5. Prices from www.drugstore.com. Accessed December 12, 2003.

6. Parks TC, Wallack SS, Lee S, Ritter GA. Impact of health plan design and management of retirees' prescription drug use and spending, 2001. *Health Aff.* January/February 2003; posted as a Web exclusive December 4, 2002;:W408-19. Available at: http://www.healthafffairs.org/WebExclusives/Thomas_Web_Excl_120402.htm. Accessed December 9, 2002.

7. Curtiss FR. Unraveling the effects of tier-copayment drug benefit designs. *J Manag Care Pharm.* 2003;9(2):177-78.

8. Selby JV. Cost-sharing in the emergency department—is it safe? Is it needed? *N Engl J Med.* 1997;336:1750-51.

9. Cherkin DC, Grorhaus L, Wagner EH. The effect of office visit copayments on preventive care services in an HMO. *Inquiry.* 1990;27:24-38.

10. Harris BL, Stergachis A, Ried LD. The effect of drug co-payments on utilization and cost of pharmaceuticals in a health maintenance organization. *Med Care.* 1990;28:907-17.

11. Motheral BR, Henderson R. The effect of a copay increase on pharmaceutical utilization, expenditures, and treatment continuation. *Am J Manag Care.* 1999;5: 383-94.

12. Selby JV, Fireman BH, Swain BE. Effect of a copayment on use of the emergency department in a health maintenance organization. *N Engl J Med.* 1996,334:635-41.

13. Magid DJ, Koepsell TD, Every NR, et al. Absence of association between insurance copayments and delays in seeking emergency care among patents with myocardial infarction. *N Engl J Med.* 1997;336:1722-29.

14. Wogen J, Frech F. Patient adherence with hypertension medication [letter]. *J Manag Care Pharm.* 2004;10(1):90-91.

15. Huskamp HA, Deverka PA, Epstein AM, et al. The effect of incentive-based formularies on prescription-drug utilization and spending. *New Engl J Med.* 2003;349: 2224-32.

16. Buckley B. Higher co-pays. *Drug Top.* May 19, 2003:36-37.

17. Curtiss FR. Searching for drug benefit benchmarks—cost per day of therapy. *J Manag Care Pharm.* 2002;8(1):54-55.

18. WYE: primary research supports conclusion of declining Protonix sales in '04. *Bernstein Research Call,* New York, NY: Sanford C. Bernstein & Co., LLC; May 14, 2003:1-7.

19. Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with alendronate in post-menopausal women under 60 years of age. *N Engl J Med.* 1998;338:485-92.

20. Allen IE, Monroe M, Connelly J, et al. Effect of postmenopausal hormone replacement therapy on dental outcomes: systematic review of the literature and pharmacoeconomic analysis *Man Care Interface.* April 2000:93-99.

21. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/Progestin Replacement Study follow-up (HERS II) *JAMA.* 2002;288:49-57

22. Fletcher SW, Codlitz GA. Failure of estrogen plus progestin therapy for prevention. *JAMA.* 2002;288:366-68.

23. Hodis HN, Mack WJ, Azen SP, et al. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N Engl J Med.* 2003; 349:535-45.

24. The Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-33.

25. Biscup P. Risks and benefits of long-term hormone replacement therapy. *Am J Health Syst Pharm.* 2003;60:1419-25.

26. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med.* 2003;348:645-50.

27. Dick SE, DeWitt DE, Anawalt BD. Postmenopausal hormone replacement therapy and major clinical outcomes: a focus on cardiovascular disease, osteoporosis, dementia, and breast and endometrial neoplasia. *Am J Manag Care.* 2002;9:95-104.

28. The Writing Group for the PEPI Trial. Effects of estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. *JAMA.* 1995;273:199-208.

29. The Writing Group for the PEPI Trial. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. *JAMA.* 1996;276:1389-96.

30. Herrington DM, Reboussin DM, Brosnihan KB et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med.* 2000;342: 522-29.

31. Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study: a prospective observational study. *Ann Intern Med.* 2001;135:1-8.

32. Weiss LK, Burkman RT, Cushing-Haugen KL, et al. Hormone replacement therapy regimens and breast cancer risk. *Obstet Gynecol.* 2002;100:1148-58.

33. Bailar J. Hormone-replacement therapy and cardiovascular diseases. *N Engl J Med.* 2003;349:521-22.

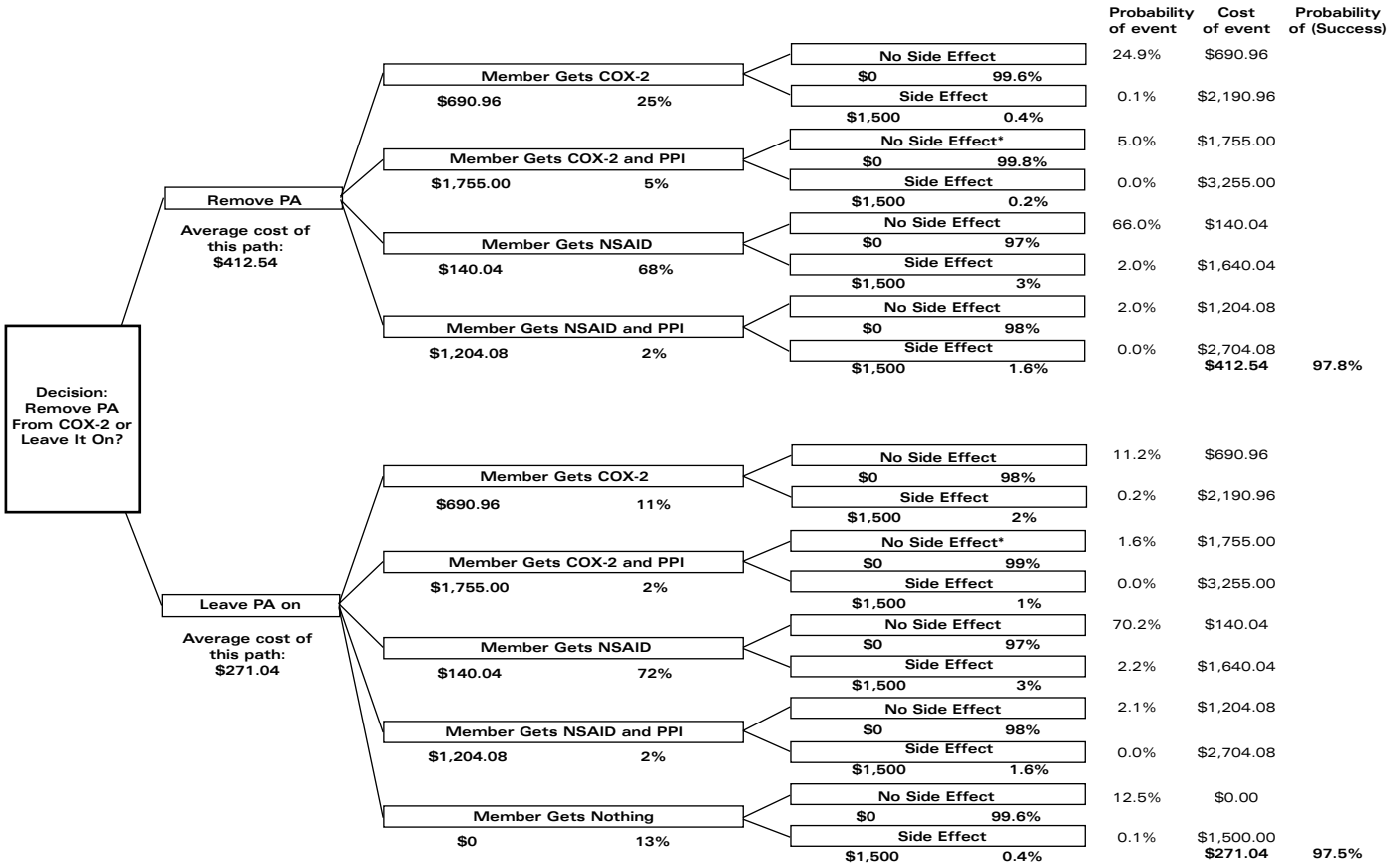
34. Schneider DL, Barrett-Connor EL, Morton DJ. Timing of postmenopausal estrogen for optimal bone mineral density. The Rancho Bernardo Study. *JAMA.* 1997; 277:543-47.

35. Deady J. Clinical monograph: hormone replacement therapy. *J Manag Care Pharm.* 2004;10(1):33-47.

CORRECTIONS

1. Stacy J, Shaw E, Arledge MD, Howell-Smith D. Pharmacoeconomic modeling of prior-authorization intervention for COX-2 specific inhibitors in a 3-tier copay plan. *J Manag Care Pharm.* 2003;9(4):330. The corrected Figure 1 appears below.

FIGURE 1 COX-2 Cost-Effectiveness Analysis Model



2. Parodi S, Rhew DC, Goetz MB. Early switch and early discharge opportunities in intravenous vancomycin treatment of suspected methicillin-resistant staphylococcal species infections. *J Manag Care Pharm.* 2003;9(4):323. The following correction to the "Limitations" section is made at the request of the authors:

> "The potential for patient noncompliance with outpatient oral linezoid treatment was not incorporated into our economic modeling assumptions."

Measuring Adherence to Antihypertensive Drug Therapy

To the Editor:

Adherence to therapy as measured in a controlled clinical environment may not reflect adherence in usual-care settings because of the multifactorial nature of adherence. Thus, for large population studies, where the more expensive and time-consuming methods like pill counts, assessment of drug levels, and patient self-report are not feasible, refill compliance (compliance as measured from pharmacy refill records) may provide otherwise unattainable information about the true nature of adherence to therapy.[1] In the article on patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting, the authors have assessed adherence and persistence from a pharmacy claims database utilizing a retrospective cohort study design with a 2-year follow-up.[2] Although this approach is appropriate and inexpensive for a large-population-based study, we would like to draw attention to certain points that may be relevant when interpreting the study results.

Data for the study were obtained from a large pharmacy benefits manager with a diverse payer mix. Although the authors address this issue as an advantage, probably pertaining to the external validity of the study, the diverse payer mix may have indirectly affected the outcome measure as different levels of coverage, copay-structures of different insurance systems may unduly have affected adherence to therapy.

Retrospective database research studies need to explicitly state the contents of data for the reader to be able to assess the absence of key variables that can affect the outcome measure.[3] In this case, for instance, since the underlying premise was that the relatively better side-effect profile of the angiotensin receptor blockers (ARBs) compared with the angiotensin-converting enzyme inhibitors and the calcium channel blockers may result in better adherence and persistence with ARBs, it would have been important to know the dosage provided for each of the therapy groups. Generally, most pharmacy databases include drug name, dose, quantity dispensed at each fill, and the dates of the fills.

Two different measures of adherence were used, one that has the duration of therapy as the denominator (called compliance) and the other that has 365 days as the denominator (called medication possession ratio [MPR]). Although there was only a 2% difference in the compliance measure, there was almost an 8% to 10% difference in the MPR measure. This difference has to be viewed with respect to the manner in which the MPR was measured. The authors state that "a patient may demonstrate high compliance but a lower MPR if the patient discontinues therapy at some point within the 12 months postinitiation of therapy."[1,p.425] Measurement of MPR, however, has not been explicitly defined in terms of whether discontinuers were included in the MPR calculation. If one looks at the compliance measure, MPR measure, and the proportion of discontinuers in each group, then it seems that discontinuers were included, resulting in a higher MPR for the ARB group because of the lower number of discontinuers.

For the persistence measure, these results emphasize the low discontinuation rate associated with being on the ARBs. In terms of adherence (compliance measure), however, there is only a 2% difference. Elaboration of the clinical significance of this difference is needed. Does this 2% difference translate into lower costs and improved blood-pressure control? Given that other studies[4,5] have already shown better adherence profiles for the ARBs, it begs the question as to whether there was really a need for this study. Perhaps the focus should now be on interpreting the meaning of the improved adherence.

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DISCLOSURES

The authors state that they have no conflict of interest or any potential bias regarding this letter.

REFERENCES

1. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity and applications. *J Clin Epidemiol*. 1997;50(1):105-16.

2. Wogen J, Kreilick, CA, Livornese, RC, Yokoyama K, Frech F. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting; *J Manag Care Pharm.* 2003;9(5):424-29.

3. Motheral B, Brooks J, Clark MA, et al. A checklist for retrospective database studies. Report of the ISPOR task force on retrospective databases. *Value Health.* 2003;6(2):90-97

4. Marentette MA, Gerth WC, Billings DK, Zarnke KB. Anti-hypertensive persistence and drug class. *Can J Cardiol.* 2002;18:649-56.

5. Conlin PR, Gerth WC, Fox J, Roehm JB, Boccuzzi SJ. Four-year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other anti-hypertensive drug classes. *Clin Ther.* 2001;23:1999-2010.

The Authors Respond

Ms. D'Souza and Dr. Miller raise some interesting points regarding our study, "Patient Adherence With Amlodipine, Lisinopril, or Valsartan Therapy in a Usual-Care Setting."[1] We would like to take the opportunity to respond to their comments in this letter.

Assessment of patient copay was not included in the original scope of the study so we cannot rule out the possibility that this had an impact on adherence results. However, one of the benefits of the large size of the pharmacy benefits manager data-

base used is that many different employer, retirement, and government plans were included, with many and vastly different drug benefit designs most likely represented in the patient mix. This diversity in benefit designs and associated drug copays is likely a strength of our study. In addition, as we pointed out in our response to Dr. Curtiss' editorial (page 90), there is no consensus regarding the impact of patient copay on therapy persistence and adherence. Some studies have found an impact of patient copay on therapy discontinuation,[2] while others have failed to find an association.[3,4]

We did not examine dosage for each of the agents included in the study, and it is theoretically possible that this may have had some impact on study results. Since dosages are not equivalent across study agents, this would have added considerable complexity to the study analyses and made interpretation of results difficult. Examination of the prescribing information reveals that for lisinopril and valsartan, no dose-related responses were seen for adverse experiences or drug discontinuation in clinical trials.[5] For amlodipine, some side effects (edema, dizziness, flushing, palpitation) were found to be dose related.[5] We cannot therefore exclude the possibility that daily drug dosage may have impacted adherence or persistence, at least for amlodipine patients.

One of the strengths of our study was that we did, in fact, use 2 distinct measures of adherence to examine the issue from different perspectives. We referred to "compliance" as the proportion of time that a patient had drug supply "on hand" to the patient-specific duration of therapy, as measured by the last prescription fill date minus the first prescription fill date. This measure, by definition, can only be calculated for those patients with at least 2 fills of the index prescription. Medication possession ratio (MPR) is calculated for all patients using the available follow-up (365 days for patients in the current study). Thus, patient persistence with therapy is reflected in the MPR calculation but not in the compliance calculation. The results of our study indicated significantly greater patient persistence with valsartan as compared with amlodipine or lisinopril, as reflected primarily in persistence rates and improved MPR. This is evident in a comparison of mean length of therapy, as valsartan patients remained on therapy about a month longer (mean = 270.1 days of therapy with valsartan as compared with 241.6 for amlodipine and 234.6 with lisinopril) than patients receiving amlodipine or lisinopril. We believe that this has important implications and agree that further research is warranted to fully explore the potential impact on blood pressure control and clinical outcomes.

D'Souza and Miller question the relevance of our study, citing that other studies have shown improved adherence profiles for angiotensin-receptor blockers (ARBs).[6,7] However, this is not an entirely accurate interpretation of these studies as they, in fact, investigated medication persistence, not adherence, and neither study was specific to valsartan. No other studies, to date, have investigated valsartan adherence and persistence. Furthermore, as valsartan is currently the most frequently prescribed ARB in the United States, we feel that this is a relevant and timely contribution to the literature.

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REFERENCES

1. Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. *J Manag Care Pharm.* 2003;9(5):424-29.

2. Huskamp HA, Deverka PA, Epstein AM, et al. The effect of incentive-based formularies on prescription-drug utilization and spending. *N Engl J Med.* 2003;349:2224-32.

3. Motheral B, Fairman KA. Effect of a three-tier prescription copay on pharmaceutical and other medical utilization. *Med Care.* 2001;39:1293-1304.

4. Motheral BR, Henderson R. The effect of a copay increase on pharmaceutical utilization, expenditures, and treatment discontinuation. *Am J Manag Care.* 1999;5:1383-94.

5. *Physicians Desk Reference.* 56th ed. Montvale, NJ: Medical Economics Company, Inc.; 2002.

6. Marentette MA, Gerth WC, Billings DK, Zarnke KB. Anti-hypertensive persistence and drug class. *Can J Cardiol.* 2002;18:649-56.

7. Conlin PR, Gerth WC, Fox J, Roehm JB, Boccuzzi SJ. Four-year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other anti-hypertensive drug classes. *Clin Ther.* 2001;23:1999-2010.

8. IMS America data, October 2003.

Patient Adherence With Hypertension Medication

To the Editor:

We are writing to discuss the paper entitled "Patient Adherence With Amlodipine, Lisinopril, or Valsartan Therapy in a Usual-Care Setting"[1] and the subsequent editorial, "Hypertension, Prescription Drug Copayments, and Drug Therapy Adherence,"[2] both published in the September/October 2003 issue of the *Journal of Managed Care Pharmacy*. Our retrospective database study found increased patient adherence and persistence with valsartan, an angiotensin-receptor blocker (ARB), as compared with the most frequently prescribed agents from the calcium channel blocker (CCB—amlodipine) and angiotensin-converting enzyme inhibitor (ACEI—lisinopril) classes, controlling for available patient baseline factors, including age, gender, and baseline comorbid conditions. We welcome the thoughtful evaluation and suggestions in the editorial and would like to clarify some of the issues that were raised.

As Dr. Frederic Curtiss mentioned in his editorial, plan information such as patient copay and drug formulary status was not included in the study results. His editorial discusses the small increase in U.S. sales of atorvastatin and decrease in sales of sertraline and amlodipine in Q1 2003 and analysts' speculation of a relationship to rising drug plan copayments as published in the *Wall Street Journal*[3] and suggests that patient copayment amounts and drug formulary status, which were not assessed in the study, may have impacted the study results. Recently, many insurers have adopted incentive-based ("tiered") formularies for prescription medication coverage. For example, a patient with a 3-tier formulary typically has the lowest copay for generic drugs (the first tier), a higher copay for preferred brand-name drugs (second tier), and the highest copay for third-tier brand-name drugs.

Relatively few peer-reviewed studies have been published examining the relationship between patient copay for pharmaceutical agents and associated patterns of therapy compliance and persistence. Results of a recent study using pharmacy claims data suggested increased ACEI, proton-pump inhibitor, and statin discontinuation rates subsequent to the implementation of a 3-tier copay formulary in a plan that had previously had a 1-tier structure as compared with a comparison plan with a stable 2-tier structure.[4] However, the same study found no increase on discontinuation rates for the same classes of drugs in a plan that implemented a less-drastic change in formulary structure (2-tier to 3-tier). Another study utilized an integrated medical and pharmacy claims database to examine drug continuation rates for members for which a 3-tiered copay system was implemented as compared with a control group that remained on a 2-tiered benefit and found significantly lower therapy continuation rates for only 1 therapeutic class out of 4 studied.[5] A different study found no increase in chronic branded medication discontinuation for patients with copay increases from $10 to 15 as compared with patients whose copay amount remained fixed at $10.[6] Thus, there is a lack of clear evidence in the peer-reviewed literature regarding the hypothesis that increased patient copay results in greater medication discontinuation rates or patient noncompliance.

The editorial inaccurately stated that one of the study medications, lisinopril, became available as a generic at the end of the study; in fact, the study analyzed data through July 31, 2000, and generic lisinopril did not become available in the United States until July 2002. While the introduction of generic lisinopril did not impact the results of this study, the introduction of generic ACEIs is an undeniably important factor for current studies of the hypertension market.

Curtiss also pointed out an important observation, namely that channel of delivery was not included in the published study. Members of most prescription plans are often limited to a 30-day supply of medication at a retail pharmacy but may often receive up to a 90-day supply if they receive the medication via home delivery. Thirty-four percent of patients included in the study filled one or more study medications via mail service (data not presented in our article). As would be expected, these patients were more adherent with the study agent than patients who received all study prescriptions via retail service only (overall medication possession ratio [MPR], mean of 59.7% for retail-only patients versus 85.3% for patients with one or more mail prescriptions). However, valsartan patients consistently demonstrated a higher mean MPR than patients prescribed amlodipine or lisinopril. Valsartan patients with one or more mail fills had a mean MPR of 89.0% compared with 84.2% for amlodipine and 83.8% for lisinopril; valsartan patients who received all fills via a retail pharmacy had a mean MPR of 66.1% compared with 57.9% for amlodipine and 58.6% for lisinopril. Thus, we agree that channel of prescription delivery can play an important role in patient adherence with therapy, though it was not directly addressed in the scope of our original study.

Information about blood-pressure control was not available for this study due to the nature of the administrative claims database employed, and this is an important study limitation. While research has shown that persistence with antihypertensive therapy is associated with lower rates of adverse long-term sequelae of hypertension[7] and decreased health care resource consumption,[8] there is little that is documented about the implied relationship between therapy compliance and persistence and their impact on blood pressure control in a usual-care setting. Additional research is needed to explore the relationship of the current study findings and others demonstrating superior compliance with ARBs to blood pressure control in a nonclinical trial setting.

In addition, the authors agree with Curtiss that the information provided by this study must be applied in the context of recent clinical studies. ALLHAT[9] followed 33,357 patients for a mean of 4.9 years and found that patients treated with amlodipine or lisinopril had the same incidence of combined fatal coronary heart disease or nonfatal myocardial infaction as a thiazide diuretic (chlorthalidone), but patients treated with the diuretic had lower rates of heart failure at 6 years than amlodipine patients, while lisinopril patients had higher 6-year rates of combined cardiovascular disease, stroke, and heart failure. Patients treated with chlorthalidone had a higher incidence of

diabetes at 2 and 4 years of follow-up as compared with amlodipine and lisinopril patients. The Second Annual Australian Blood Pressure (ANBP2) study[10] found results that are somewhat contradictory; in this study, which followed 6,083 patients for a mean of 4.1 years, the investigators reported reductions in the rates of total cardiovascular events, first cardiovascular event, and all-cause mortality for patients treated with ACEI as compared with diuretics. What are the differences between the 2 trials? ANBP2 used enalapril as the ACEI and hydrochlorothiazide as the diuretic, while ALLHAT used lisinopril and chlorthalidone. There is no information regarding a comparison of clinical efficacy of enalapril versus lisinopril or chlorthalidone versus hydrochlorothiazide, and there is not likely to ever be any.[11] Patients in ANBP2 were older (mean = 71.9 years versus 67 years for ALLHAT patients), had higher mean diastolic and systolic blood pressure readings at study baseline (168 ± 13/91 ± 8 versus 146 ± 16/84 ± 10 for ALLHAT), were more likely to be white than black or Hispanic (95% versus 46% for ALLHAT), and were less likely to have diabetes (7% versus 36% for ALLHAT). Thus, these critical differences in study populations and medications employed make comparing the results difficult and a definitive statement regarding the superiority of an ACEI versus a thiazide diuretic problematic.

Nevertheless, patient behavior during participation in a randomized trial differs from patient behavior in a real-world setting, where patients may not be as motivated to take prescribed medication exactly as instructed by their health care providers. It is in this context that studies such as the current one become important. While the authors agree that a difference in mean compliance (measured as the sum of total days' supply divided by the length of therapy) of 88.5% for valsartan as compared with 86.7% for amlodipine or 86.3% for lisinopril may be statistically significant only due to the very large sample size, the paper reported a greater length of therapy with valsartan compared with the other study agents that the authors believe is clinically very meaningful. This is reflected in both increased persistence rates, as 63% of valsartan patients remained on therapy at 12 months compared with 53% and 50% for amlodipine and lisinopril patients, respectively, and higher medication possession ratio for valsartan (mean = 75%) as compared with amlodipine (67%) or lisinopril (65%) patients. This is most evident in the study finding that patients stayed on therapy an average of a month longer with valsartan as compared with the other agents (mean = 270.1 days of therapy with valsartan as compared with 241.6 for amlodipine and 234.6 with lisinopril), which has the potential to positively impact patient outcomes.

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DISCLOSURES

See page 89 for Wogen's and Frech's disclosure information.

REFERENCES

1. Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. *J Manag Care Pharm.* 2003;9(5):424-29.

2. Curtiss FR. Hypertension, prescription drug copayments, and drug therapy adherence. *J Manag Care Pharm.* 2003;9(5):454-56.

3. Hensley S, Burton TM. Big drug makers report increase in sales. *Wall Street Journal.* April 23, 2003:B2.

4. Huskamp HA, Deverka PA, Epstein AM, et al. The effect of incentive-based formularies on prescription-drug utilization and spending. *N Engl J Med.* 2003;349:2224-32.

5. Motheral B, Fairman KA. Effect of a three-tier prescription copay on pharmaceutical and other medical utilization. *Med Care.* 2001;39:1293-1304.

6. Motheral BR, Henderson R. The effect of a copay increase on pharmaceutical utilization, expenditures, and treatment discontinuation. *Am J Manag Care.* 1999;5:1383-94.

7. Cramer JA. Consequences of intermittent treatment for hypertension: the case for medication compliance and persistence. *Am J Manag Care.* 1998:4: 1563-68.

8. McCombs JS, Nichol MB, Newman CM, Sclar DA. The costs of interrupting antihypertensive therapy in a Medicaid population. *Med Care.* 1994:32:214-26.

9. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA.* 2002;288:2981-97.

10. Wing LMH, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med.* 2003;348:583-92.

11. Frohlich ED. Treating hypertension—what are we to believe? *N Engl J Med.* 2003;348:639-41.

Letters to the Editor

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