

JMCM

JOURNAL of MANAGED CARE MEDICINE

A PEER-REVIEWED PUBLICATION

Vol. 7, No. 2

**The Cost of Gastroesophageal Reflux Disease:
It's What You Don't See That Counts**

**Immunomodulatory Therapy for Multiple Sclerosis:
Glatiramer Acetate**

Managed Care's Role in Influencing Appropriate Asthma Therapy

The Official Journal of the
NATIONAL ASSOCIATION OF MANAGED CARE PHYSICIANS
AMERICAN ASSOCIATION OF INTEGRATED HEALTHCARE DELIVERY SYSTEMS
AMERICAN COLLEGE OF MANAGED CARE MEDICINE

A Publication for Medical Directors and Healthcare Executives

AD

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The Cost of Gastroesophageal Reflux Disease: It's What You Don't See That Counts

Bonnie B. Dean, MPH, PhD; Joseph A. Crawley, MS; Jerry D. Reeves, MD; Daniel Aguilar, MPH;
Sean Sullivan; Robert Berglund; Robert Dubois, MD, PhD

Summary

The authors' objective was to assess the impact of gastroesophageal reflux disease (GERD) on work productivity, health-care utilization, and cost in an employed U.S. population. A cross-sectional survey evaluating the impact of GERD on work productivity was administered to employees at a major service industry employer. Work productivity loss was assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire. Administrative data were analyzed to determine costs and mean annual rates of utilization. The overall self-reported productivity loss as well as health-care and pharmacy utilization among eligible employees were compared between GERD and non-GERD participants. A total of 1,186 employees (16 percent) participated in the survey with complete information available for 956 participants; 273 (28.6 percent) met criteria for GERD.

Key Points

- Total potential work productivity among participants with GERD was reduced by an additional 10 percent compared with non-GERD participants. For a typical 40-hour per week employee, this translated to more than four hours per week missed or lost due to reduced productivity.
- Mean medical care costs were \$841 per year for participants with GERD, compared to \$601 for those without GERD, while pharmacy costs were \$895 and \$581 for participants with and without GERD, respectively.
- For GERD participants, lost productivity costs of \$5,193 exceed the combined direct costs of medical care and pharmacy use of \$1,736.
- Chronic conditions affecting employees impact productivity by causing absenteeism and reducing productivity while working. Chronic conditions like GERD can cost employers much more in lost productivity than in direct medical and pharmacy costs of treatment.

GASTROESOPHAGEAL REFLUX DISEASE (GERD) is a common digestive disorder characterized by symptoms of heartburn and acid indigestion.¹⁻³ It is estimated that approximately 60 percent of the population may experience either heartburn or acid regurgitation at least once per month; and of these people, 19 percent are believed to experience such symptoms on a daily basis.⁴

As with most highly prevalent chronic diseases, GERD is responsible for inflicting a significant economic burden on society. It is estimated that GERD is responsible for approximately \$9.6 billion (year 2000 dollars) in direct medical costs per year. The high prevalence of GERD makes it by far the most costly digestive disorder.⁵

The direct costs of GERD encompass primarily physician office visits, prescription medication costs, diagnostic procedures such as upper gastrointestinal endoscopy, and inpatient health service utilization. GERD is among the top three diagnoses for outpatient physician visits with direct outpatient costs estimated at \$603.1 million per year,⁵ but this is less than a quarter of the cost of inpatient treatment (\$2.5 billion per year).⁵ In addition, with the availability of safe and effective prescription medications, the cost of pharmaceutical treatment (estimated at \$5.9 billion annually), exceeds the cost of outpatient and inpatient direct costs combined.⁵ In the absence of

effective outpatient therapy, the cost of inpatient care would likely be substantially higher.

Although previous cost estimates for GERD have focused on direct medical costs, there is increasing interest in the “indirect” costs associated with this gastrointestinal disease. A 2001 report released by the American Gastroenterology Association (AGA) estimates that more than 75 percent of the 18.7 million suspected GERD cases in the U.S. are working-age people.⁵ The study further estimates indirect costs of GERD at nearly \$14.6 billion from absenteeism and productivity losses.⁵ This AGA report cites the findings from an earlier study by Henke et al (2000),⁶ which was the first to indicate that indirect costs may be significantly more than were previously estimated, and that lost productivity and absenteeism costs may greatly exceed direct medical costs of treating GERD in a working-age population.

The suggestion that the cost of work productivity loss due to GERD may greatly exceed direct medical costs is of increasing concern to employers in the U.S. who rely heavily on a healthy workforce. However, while the direct costs of GERD can be quantified from utilization data, pharmacy sources, and health surveys, the indirect costs associated with GERD (specifically those attributable to reduced worker productivity and absenteeism) are less easily quantified.

Drossman et al (1993)⁷ conducted a U.S. household survey assessing the relationship between gastrointestinal disorders and work status, absenteeism, and healthcare use. Findings for participants reporting gastrointestinal symptoms demonstrated that gastrointestinal symptoms affected absenteeism; respondents with either full-time or part-time employment missed nearly nine days of work (or school) due to illness, while respondents without gastrointestinal symptoms reported a mean of five days missed. Moreover, respondents with functional gastrointestinal disorders had a greater risk for work absenteeism (OR = 1.85; 95 percent CI: 1.40–2.45).

Henke et al (2000)⁶ used patient records and self-reported work productivity and absenteeism to assess indirect costs associated with work time and productivity loss in a population of managed care plan patients previously diagnosed with either peptic ulcer disease or GERD. Over 40 percent of patients with GERD reported work time loss due to their gastrointestinal problem, with cost due to productivity loss estimated to be substantial (\$237 per patient over a three-month period) and exceeding estimates of direct medical costs among the same population.^{6,8}

In validating a GERD-specific work productivity and activity impairment assessment tool, Wahlqvist et al (2002),⁹ measured the impact of GERD on work productivity and Health Related Quality of Life in a working Swedish population seeking consultation with a general practitioner. Findings revealed that patients with mild-to-severe heartburn symptoms experienced a mean

of 2.5 absent work hours due to GERD during the previous seven days, compared to 0.1 work hours absent reported by the non-GERD group. Likewise, productivity while at work was approximately 17 percent lower in employees with GERD. In a previous report on the same patients, the estimated cost of lost productivity for patients with GERD was estimated to be \$365 per patient for the week prior to seeking medical attention.¹⁰

These previous studies collected data from household or managed care plan enrollees while, in contrast, the present study examined productivity impact within a defined workforce in the service industry. Moreover, this study examined both direct and indirect costs, enabling a comparison of the importance of each. An employer in the service industry was chosen as a research partner because of the important role that each employee in this industry sector has in delivering the company’s product, i.e., service to the customers. Absenteeism and lost productive time while working are costs that can be compared to the direct medical costs employers pay as an investment in their employees’ health.

Methods

The protocol for this research project was approved by the Lovelace Institutional Review Board based in Las Vegas.

Participants were employees at multiple sites of a large hotel casino company in Las Vegas. Between March and May 2002, an Internet-based survey was offered to all employees of the collaborating employer. The questionnaire was constructed to compare participants with and without GERD for reductions in work productivity associated with this disease. The survey also included questions designed to assess the impact of other common conditions on work productivity. These comparisons were cross-sectional in nature, derived from data collected in a one-time survey of employees.

The survey was available online at a password-protected web site for WorldDoc Inc., an online health decision support services company with confidential and secure access provided by the employer to all employees. Employees could access the survey from any personal computer with Internet access. Employees were also provided Internet access at computer kiosks set up in the employee break rooms at each of the four company properties. Additionally, a small subset of participants completed a paper and pencil version of the survey on days when survey recruiters were available at each of the locations, to minimize non-participation due to wait time for computer access.

The Reflux Disease Diagnostic Questionnaire (RDQ)

Employees received The Reflux Disease Questionnaire (RDQ), a validated and reliable tool for assessing the presence of GERD.¹¹ The RDQ is a self-administered, 12-item diagnostic tool that assesses reflux and dyspeptic

symptoms over the preceding four weeks. The survey contains six component questions assessing frequency and severity of symptoms for each of three domains: regurgitation (acid taste and movement of materials), heartburn (burning and pain behind the breastbone), and dyspepsia (upper stomach pain and burning). Frequency and severity is assessed for each symptom using a scale of zero (did not have) to five (daily or severe). Scores for GERD are summed across the domains of regurgitation and heartburn, and a diagnosis of GERD is defined as having a continuous measure score of five or greater.

Work Productivity and Activity Impairment (WPAI)

The Work Productivity and Activity Impairment (WPAI) questionnaire is an instrument used to assess absenteeism and lost productivity from work and daily activities.¹² Multiple questions pertain to the number of days and hours worked, number of days with health-related problems, and number of missed hours of work due to health problems and for other reasons within the preceding seven days. Productivity impairment while

working and during regular activity is assessed as the degree to which health problems are affecting participants using a scale from zero to 100 and reported as a proportion. Productivity and absenteeism measures relevant to the current analysis and derived from WPAI questions included absence from work and impairment while working and during regular activities. We also calculated the work productivity score (WPS), which enumerates reduced productivity due to GERD symptoms as a percent of potential total work productivity during a full-time workweek. The WPS was calculated as follows:

$$\text{WPS} = \frac{[(\text{Hours absent from work} + \text{Percentage of reduced productivity at work} \times \text{Hours actually worked}) / (\text{Hours missed due to health} + \text{Hours missed due to non-health} + \text{Hours worked})] \times 100}{100}$$

Utilization Data

The service industry employer participating in the study maintains company-based health insurance and pharmacy benefits for eligible employees. For each inpatient and outpatient visit during the 12-month period

Exhibit 1: Description of Sample

Characteristic	Participants with GERD	Participants without GERD	P-value
Total number	273	683	—
Mean age	39.8 (12.5)	38.6 (12.3)	0.15
Gender			0.89
Male	128 (47.2)	326 (47.7)	
Female	143 (52.8)	357 (52.3)	
Education			0.12
Did not complete HS	15 (5.6)	59 (8.7)	
Completed HS	79 (29.6)	216 (32.1)	
Some college	128 (47.9)	312 (46.3)	
Completed college	36 (13.5)	57 (8.5)	
Graduate degree	9 (3.4)	30 (4.5)	
Format of survey			0.08
Web-based	198 (72.5)	456 (66.8)	
Paper version	75 (27.5)	227 (33.2)	
Language of survey			0.03
English	649 (95.0)	268 (98.2)	
Spanish	34 (5.0)	5 (1.8)	
Race/Ethnicity			<0.001
African American	10 (3.7)	44 (6.5)	
Asian/Pacific Islander	17 (6.3)	80 (11.8)	
Caucasian	206 (75.7)	425 (62.8)	
Hispanic	26 (9.6)	114 (16.8)	
Native American	7 (2.6)	10 (1.5)	
Other/Unknown	6 (2.2)	4 (0.6)	
Wage type			0.47
Salaried	36 (13.3)	79 (11.6)	
Hourly	235 (86.7)	602 (88.4)	

prior to survey participation, information collected for each included diagnosis code [International Classification of Disease Revision 9 (ICD-9)], procedure code [Current Procedural Terminology (CPT)], and cost (paid claims). This information was used to calculate averages for the total cost per year, the number of outpatient visits, the number of inpatient visits, the number of all procedures, and the number of GERD-related procedures. GERD-related procedures included those coded as abdominal exploration, abdominal ultrasound, abdominal X-ray, endoscopy, laparoscopy, esophagogastric fundoplasty, motility manometry, esophageal motility test, and 24-hour pH monitoring.

For each pharmacy prescription filled during the 12-month period prior to survey participation, information collected included prescription, dosage, number of days supplied, and cost. This information was used to calculate the annual means for the cost of all prescriptions, the cost of GERD-related prescriptions, and the number of days of GERD-related medication supplied.

Statistical Analysis

Participants with and without GERD were compared on socio-demographic and key clinical variables. Comparisons were made using chi-square tests for categorical variables and t-tests for continuous variables. Two-sided p-values were calculated with statistical significance set at the $P \leq 0.05$ level.

Reduced productivity due to GERD was measured using the WPAI measures. Participants with and without GERD were compared on their mean percent reductions across measures of productivity. Mean estimates of productivity loss were calculated and compared for employees with and without GERD. The mean differences in percent reduction associated with productivity and their associated 95 percent Wald confidence intervals were calculated. Bootstrapping, a non-parametric method, was also used to calculate mean estimates of productivity along with 95 percent confidence intervals, as this method allows for comparison across variables with highly skewed distributions.

Mean percent reductions in productivity were converted into their corresponding total number of hours with absenteeism and with reduced productivity per week or per year. These hours were also transformed into costs based on the mean Bureau of Labor Statistics year 2000 wages for U.S. employees.¹³ The mean cost of reduced productivity per year due to gastrointestinal symptoms in dollars was calculated as the difference in cost of productivity between employees with versus without GERD.

Additional work productivity analyses were conducted on participants with GERD who were stratified by self-reported symptom severity as measured by the RDQ. Mean severity scores were calculated across all four RDQ

symptoms, each measured on a five-point scale (zero representing absence of symptom and five representing "severe"). Participants were then categorized into severity groups as follows: scores between zero to one were classified as mild; greater than one but not greater than two were moderate; and greater than two were severe. The bootstrapping method was used to calculate, for each severity group, mean estimates of percent reductions in productivity. The mean differences in percent reduction associated with productivity and their associated 95 percent confidence intervals (CI) were calculated.

Participants with and without GERD were also compared on mean utilization and cost data for medical and pharmacy claims. Differences in annual means were assessed using t-tests. Two-sided P-values were calculated with statistical significance set at the $P \leq 0.05$ level. Additional utilization analyses were conducted on participants with GERD who were stratified by self-reported symptom severity. Differences in means across severity groups were assessed using ANOVA, and Tukey's studentized range test was used to calculate p-values for pair-wise differences, with statistical significance set at the $P \leq 0.05$ level.

Results

At the start of data collection, there were 7,212 individuals employed at four locations for this service industry employer. A total of 1,186 (16 percent) employees voluntarily participated in the survey. Complete information on GERD status and work productivity was available for a subset of 956 participants (80.6 percent), who were included in this analysis. More than 68 percent of respondents participated in the web-based version of the survey.

A comparison of the 956 survey participants with the general employee population revealed that respondents were similar to the total population in gender (48 percent versus 53 percent) and age (mean age 38.9 versus 39.8). Participants of the survey were more likely to be Caucasian (66 percent versus 52 percent) while the total population was more Hispanic (18 percent versus 26 percent) and a larger proportion of participants were salaried (12 percent versus four percent).

Among the 956 respondents, 273 (28.6 percent) met the RDQ criteria for GERD. When participants with GERD were categorized by reported symptom severity level, 107 (39.2 percent) were identified as mild, 97 (35.5 percent) as moderate, and 69 (25.3 percent) as severe.

Participants with GERD were similar to those without GERD in age, gender, education, and wage type (salary versus hourly) ($P > 0.05$) (*Exhibit 1*). Participants with GERD were more likely to respond to the survey in Spanish ($P = 0.03$) and were more likely to be Caucasian, compared with participants without GERD who were more likely to be African American, Asian/Pacific Islander, and Hispanic ($P < 0.0001$).

Worker Productivity

Exhibit 2 provides measures of work productivity among respondents with and without GERD. Mean differences and 95 percent confidence intervals are presented. Similar results were obtained with the bootstrapping methodology.

The percent of work time missed (absenteeism) was significantly higher among participants with GERD (2.7 percent work time absent) compared to 1.0 percent work time missed among participants without GERD (mean difference = 1.7 percent; 95 percent CI, 0.6–2.8 percent; P=0.03). For a full-time 40-hour per week worker, this amounts to almost one additional hour per week missed among respondents with GERD compared to those without GERD, or almost three additional hours per month.

The impact of health conditions on productivity while at work was more pronounced than that on absenteeism. Productivity while working was reduced by 14.5 percent among participants with GERD compared to only 5.2 percent among participants without GERD (P<0.0001). The mean difference of 9.3 percent (95 percent CI, 7.8–10.7 percent) of work time impaired can be quantified as an additional four hours per week of lost productivity for participants with GERD. On a monthly basis, reduced work productivity accounts for almost two additional days of impairment among GERD participants.

The health-related reductions in productivity are also reflected in general activity impairment. As shown

(Exhibit 2), the mean percent reduction in activity impairment was significantly higher in GERD than in non-GERD participants (mean difference=13.6; 95 percent CI, 11.8–15.5 percent; P<0.0001).

The WPS score combines measures of absenteeism and reduced productivity into a single value. On average, the total potential work productivity was reduced by 15.8 percent among GERD participants, or an additional 10 percent (95 percent CI, 8.3–11.6 percent) potential work productivity loss above the 5.8 percent for participants without GERD. For a full-time 40-hour per week employee, this translates to more than four hours per week of lost productivity. On a monthly basis, lost productivity among GERD employees was an additional two days more than that of a typical non-GERD employee.

Using the average annual income of U.S. employees of \$32,864, absenteeism and reduced work productivity were transformed into employer costs (Exhibit 3). On average, absenteeism resulted in \$887 and \$329 lost to the employer for individuals with and without GERD, respectively. Employees with GERD who have an income equal to the U.S. average would cost an employer an additional \$558 (95 percent CI, \$197–\$920) per year in lost productivity due to absenteeism. However, when absenteeism and lost productivity are combined, total work productivity losses resulted in an average loss of \$5,193 and \$1,906 in employees with and without GERD, respectively. Thus, the additional annual cost of

Exhibit 2: Reduced Productivity by GERD Status

Productivity measure	Mean Percent Reduction		
	Participants with GERD (n=273)	Participants without GERD (n=683)	Mean Difference (95% CI)
Work time absent	2.7	1.0	1.7 (0.6-2.8) ^a
Impairment while working	14.5	5.2	9.3 (7.8-10.7) ^b
Activity impairment	19.3	5.7	13.6 (11.8-15.5) ^b
WPS (Total reduced work productivity)	15.8	5.8	10.0 (8.3-11.6) ^b

^a P<0.05 ^b P<0.0001

Exhibit 3: Annual Cost of Reduced Productivity by GERD Status among an Average Income Employee

Productivity Measure	Cost of Reduction		Mean Difference in Cost (95% CI)
	Participants with GERD	Participants without GERD	
Work time absent	\$ 887	\$ 329	\$ 558 (\$197-\$920)
Impairment while working	\$4,765	\$1,709	\$3,056 (\$2,564-\$3,517)
WPS (Total reduced work productivity)	\$5,193	\$1,906	\$3,287 (\$2,787-\$3,812)

productivity lost among individuals with GERD was \$3,287 (95 percent CI, \$2,787–\$3,812) per year above that expected among non-GERD employees.

Work productivity reductions among GERD participants were also stratified by symptom severity level (*Exhibit 4*). Across all productivity measures evaluated, the percent impairment was higher among the severe group compared with that among the mild group; however, only the percent reduction in activity impairment was statistically significant ($P < 0.0001$). Similarly, percent impairments were higher among GERD participants with moderate severity compared with mild in all measures except absenteeism. Thus, although statistical significance was not achieved, an increasing trend of reduced productivity and impairment was seen with rising levels of symptom severity.

Utilization

A subset of survey participants provided consent for inclusion in an analysis of company-based health insurance claims and pharmacy data from the previous 12 months. A total of 430 respondents (30.7 percent with GERD) who provided consent were eligible and covered under the insurance plan and 405 had coverage under the pharmacy benefits plan.

Exhibit 5 displays the comparison of utilization measures and direct cost data for GERD cases and controls. The mean number of outpatient visits per year was significantly greater among participants with GERD (4.6 per year) compared with non-GERD respondents (2.6 per year) ($P = 0.01$). Additionally, GERD patients had a non-significant trend toward higher costs (\$841 versus \$601). The mean cost per year, mean number of inpatient visits per year, and mean number of GERD-related and non-related procedures per year were not significantly different across the groups ($P > 0.05$).

Results for pharmacy benefits and costs indicated additional differences between GERD and non-GERD participants (*Exhibit 5*). The mean cost of all prescriptions and GERD-related prescriptions, and number of days supplied for GERD-related prescriptions were significantly higher among participants with GERD ($P < 0.05$). Interestingly, GERD-related prescriptions were found among both GERD and non-GERD patients.

Discussion

This study is the first evaluation of the combined impact of GERD on work productivity loss, medical utilization, and pharmacy costs in an employed U.S. population. Employees with GERD were found to have higher medical utilization and pharmacy costs. However, the indirect costs due to reduced work productivity in participants with GERD were even higher, greatly exceeding the cost of medical care to the employer.

Reduced productivity while at work was the major contributor to total work productivity loss. Employees

with GERD reported pronounced reductions in productivity (15 percent) resulting in an additional two days of lost productivity per month more than that reported by their non-GERD counterparts. This reduction is comparable to reduced work productivity due to GERD reported among cases with mild heartburn among a Swedish working population.¹⁰ Absenteeism, while significantly higher among participants with GERD, was not a major contributor to reductions in total work productivity in the study population. GERD participants reported more than one hour of missed work time per week—about half a day absent per month. Although absenteeism was not responsible for a large proportion of total work productivity loss, the proportion was comparable to absence from work due to GERD among workers with moderate heartburn severity among a Swedish population and well above the levels reported by workers with mild heartburn.¹⁰

When transformed into costs, work productivity losses of the magnitude measured in this study are substantial and can have a great impact on total employer costs. The incremental increase in cost to the employer due to productivity loss exceeded \$3,200 per year per individual with GERD-related symptoms. This amount greatly exceeds the incremental increase in cost to the employer of \$240 for average annual medical costs and \$314 for annual pharmacy costs per year per individual with GERD-related symptoms.

As expected, employees with GERD had higher health-care utilization rates, which were primarily due to the greater number (almost two-fold higher) of outpatient visits per year. However, no statistical differences were observed in mean cost per year, mean number of inpatient visits per year, or mean number of GERD-related or non-related procedures per year. Employees with GERD also had higher pharmacy costs. Our findings indicate that direct medical costs may be due in large part to increased outpatient visits and to prescription drug costs, which were more costly among participants with GERD.

Comparisons with other health-care utilization data indicate that total patient care costs in this study were lower than projected one-year costs reported in earlier studies,^{8,14,15} as were the annual number of inpatient visits.¹⁶ However, the mean number of outpatient visits for participants with GERD in this study (4.6 visits per year) were within the one-year range previously reported in GERD populations receiving care (2.3 to 7.2 visits per year).¹⁷ The total number of days supplied for GERD-related prescriptions in this study (6 to 63 days supplied) were far below the figures previously reported in a GERD population receiving medical attention (123 to 339 days supplied),¹⁷ with costs of GERD-related prescriptions in this study (\$448 to \$508) substantially lower than the adjusted GERD-related drug costs reported elsewhere (\$736 to \$872, extrapolated to one year).¹⁴ Thus it is possible that

Exhibit 4: Reduced Productivity Among GERD Cases by Symptom Severity

Productivity measure	Mean Percent Reduction by Symptom Severity Level		
	Mild (n=107)	Moderate (n=97)	Severe (n=69)
Work time absent	2.8	1.9	3.9
Impairment while working	12.9	15.2	16.1
Activity impairment ^{ab}	13.9	17.9	29.9
WPS (Total reduced work productivity)	13.7	16.2	18.6

^a P < 0.05 for mild to severe ^b P < 0.05 for moderate to severe

Exhibit 5: Comparison of Utilization Measures for GERD Cases and Controls

Utilization Measure	Mean Scores		
	Participants with GERD	Participants without GERD	P-value
	n=132	n=298	
Mean total cost per year (U.S. \$)	\$841	\$601	0.32
Mean number of outpatient visits per year	4.6	2.6	0.01
Mean number of inpatient visits per year	0.1	0.1	0.24
Mean number of procedures per year	8.8	9.7	0.69
Mean number of GERD-related procedures per year	1.3	1.1	0.41
Pharmacy Utilization Measure	n=123	n=282	
Mean cost of all prescriptions	\$895	\$581	0.02
Mean cost of GERD-related pharmacy prescriptions per year	\$111	\$40	< 0.01
Mean number of days supplied for GERD-related pharmacy prescriptions per year	35	13	0.01

either GERD-related healthcare costs are lower among this employed population or that lower symptom severity among these participants may explain these differences.

This study has several potential limitations. Selection bias could affect the estimates, since the researchers had a 16 percent response rate in this employee population. However, prior research has shown that work impairment may be measured accurately regardless of survey response rates. Wang et al evaluated the accuracy of prevalence and work impairment data from health risk appraisal surveys with varying response rates and found that the levels of work impairment and effects of chronic conditions on work impairment did not vary by response rate. Thus, they concluded that useful data on work impairments could be ascertained by survey even if response rates are low.¹⁸ In addition, survey participants were similar in age and gender when compared to the general employee population.

Although the survey sample had more Caucasians and more salaried workers than the whole population, these are not likely to have an impact on the productivity or cost estimates comparing participants with and without GERD, as no published data have indicated differences in GERD severity by wage type or differences in productivity losses associated with race, ethnicity, or wage type.

The proportion of participants with GERD (29 percent) was higher than expected given the prevalence range of 7 percent to 19 percent previously reported among the general population, and assuming that daily and weekly GERD-like symptoms are indicative of disease status.⁴ Given the nature of the study and of the communication with employees, a higher number of individuals with heartburn might have participated. However, the similarity of participants with and without GERD along demographic and work-related variables

(i.e., salaried versus hourly) suggests that study results are unlikely to be biased by socio-demographic differences between participants with and without GERD that might have occurred as a result of voluntary participation and the self-selection of participants.

Although the method used to address the objectives of this study was to compare participants with and without GERD on work productivity and utilization and to measure the cost impact on the employer, a secondary aim was to evaluate differences in outcomes across GERD symptom severity levels. Among this employed population, the majority of participants with GERD reported symptomology of mild or moderate severity, thus reducing the researchers' power to detect potential differences across severity levels.

Interestingly, GERD-related prescriptions were found among both GERD and non-GERD patients. Since the RDQ assesses GERD based on current symptomology (over the past month), the researchers may have underestimated the economic impact of GERD. Patients who actually have GERD but received treatment for it, might be misclassified as non-GERD because their current symptoms were relatively controlled. Thus, the non-GERD group might have artificially higher pharmacy costs since they may have contained individuals with treated GERD. This limitation could have minimized the pharmacy cost differences between the GERD and non-GERD groups.

Similarly, among those identified with GERD, there is also potential heterogeneity in disease severity and treatment. Within the group of participants identified with GERD, it is likely that some had not been diagnosed by their physician and may not have received treatment. Moreover, others with a diagnosis may not have received adequate treatment to resolve their symptoms. Across this group, those undiagnosed or not managed, or those diagnosed but inadequately managed are likely to have greater symptom severity (and productivity impairment) than those receiving adequate treatment. The potential heterogeneity within the "non-GERD" and "GERD" groups might have lowered the actual impact of GERD on productivity as compared to a study, which compared a pure group of untreated GERD patients with a matched group of control individuals.

Employers have focused increasing attention on the costs to diagnose and treat GERD. However, lost work productivity due to illness may have an even more substantial impact on an employer and a company's overall business profitability. This study found annual indirect costs of \$5,193, which are three-fold higher than the direct costs of \$1,736 per year. Quantifying the impact on employers of this highly prevalent disease may lay the foundation for significant efforts to improve the quality of care for employees with GERD, including earlier and more aggressive lifestyle modification and pharmaceutical interventions. The researchers of this study estimate that an employer

with 10,000 employees might sustain productivity losses of \$3.3 million solely due to individuals with GERD. The results indicate that GERD significantly affects worker productivity. Further efforts by employers to ensure that such patients are identified and given appropriate treatment could pay dividends in the form of improved employee productivity and employer profitability. **JMCM**

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Acknowledgments

The authors would like to acknowledge the cooperation of Coast Casinos Inc. and their staff for their participation.

This research was supported by a grant from AstraZeneca LP, in Wilmington, Del.

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Immunomodulatory Therapy for Multiple Sclerosis: Glatiramer Acetate

Thomas Morrow, MD, and Ben Thrower, MD

Summary

One challenge facing managed care systems today is treatment of chronic diseases, such as multiple sclerosis (MS). Healthcare providers and managed care administrators must take many variables into consideration when making treatment decisions for these patients.

Immunomodulatory therapies have been shown to be effective in reducing the rate of relapse in MS. The beta interferons work by mediating the entire immune system, while glatiramer acetate has a more disease-specific mechanism of action and also works directly in the CNS. In addition to reducing the relapse rate in MS, glatiramer acetate also reduces the percentage of irreversible brain tissue damage and can delay the onset of disability. Unlike treatment with the beta interferons, treatment with glatiramer acetate is not impaired by the development of neutralizing antibodies. Glatiramer acetate also produces less severe side effects than do the beta interferons, which may improve adherence to treatment. Early treatment and adherence to therapy have been proven to delay disease progression and are an important part of controlling MS-related costs. Specialty pharmacy distributors may also work with managed care organizations to lower costs related to chronic diseases, including MS.

Key Points

- Early treatment and adherence to therapy have been proven to delay the progression of MS and are an important part of controlling MS-related costs.
- Given its proven efficacy, lack of need for laboratory monitoring, and long-term tolerability, glatiramer acetate is an appropriate choice for treatment of MS, both as first-line therapy and for more advanced cases.
- Specialty pharmacy distributors may work with managed care organizations to lower costs related to chronic diseases, including MS.

MULTIPLE SCLEROSIS (MS) is a chronic demyelinating neurodegenerative disease of the central nervous system (CNS), with potentially devastating consequences for affected individuals: approximately 350,000 in the United States.¹ Common symptoms include motor weakness, spasticity, nystagmus, depression, fatigue, vision changes, ataxia, and tremor; there are also secondary complications such as respiratory infections and muscle contractions.^{2,3} In the relapsing-remitting form of MS (RRMS), which affects 80 percent of MS patients, random intervals of relapse, full or partial recovery, and disease progression result in some degree of neurologic disability in about 75

percent of patients.³ Because MS typically develops in early adulthood, disability often occurs during the most productive years of life and makes lost earnings the greatest cost burden of the disease.² Also burdensome are direct costs of medical services, which range from \$7,000 to \$13,000 per patient per year,⁴ and these costs may increase as the severity of MS increases. Direct costs are influenced by the specific practice patterns and reimbursement rates in different treatment settings, including, for many patients, the managed care organization (MCO).²

Definitive solutions to MS are aptly described as attainable yet elusive. For many years, treatments

focused on more achievable goals such as relieving symptoms and preventing acute disability from relapses, mainly through use of corticosteroids to shorten relapse duration.³ In the 1990s, however, the introduction of immunomodulatory drugs redefined MS treatment by offering the means to reduce the rate of relapses and potentially decrease the disability that is acquired through disease progression. In the United States, these disease-modifying therapies now comprise glatiramer acetate and three beta interferons: interferon β -1a intramuscular (IM), interferon β -1a subcutaneous (SC), and interferon β -1b. All of the beta interferons work in the same general way, primarily in the peripheral immune response of T cells and at the blood-brain barrier. Glatiramer acetate differs from the beta interferons in several important ways including in its mechanism of action and related long-term tolerability. The efficacy and safety of glatiramer acetate are now supported by eight years of prospective data,⁵ the longest follow-up period for any of the immunomodulators, and by data from placebo-controlled magnetic resonance imaging (MRI) studies.^{6,7} Glatiramer acetate's tolerability, lack of need for laboratory monitoring, and costs relative to the beta interferons are all germane to the delivery of MS therapy in the MCO setting. This article looks at the mechanism of action of the beta interferons and glatiramer acetate, as well as the importance of treatment adherence in the MS population and in chronic disease management generally. It also describes the emerging role of specialty pharmacy distributors in chronic disease management programs.

Pathology and Pathogenesis of Multiple Sclerosis

Demyelinated plaque and inflammation are hallmarks of MS pathology. Demyelination affects optic nerves and the periventricular white matter, brain stem, cerebellum, and spinal cord white matter. Inflammatory cells, usually found around blood vessels, primarily include lymphocytes and (in active lesions) macrophages. Axonal denudation and disrupted conduction are responsible for the early symptoms of MS—for example, “cross-talk” between demyelinated axons may cause trigeminal neuralgia and ataxia, and increased mechanical sensitivity causes flashes of light with eye movement (phosphenes). During the initial course of the disease, remyelination of early lesions and corresponding regression of symptoms can occur in association with reduced inflammation. After repeated episodes of disease activity and incomplete recovery, however, lesions become permanent and resist

further remyelination. This marks the transition to permanent axonal loss, persistent neurologic deficits, and disease progression.^{3,8}

MS is an autoimmune disease caused by the interaction of environmental and genetic factors. What triggers MS is unclear, but more than one pathogenetic mechanism may be involved, given that its clinical and pathologic characteristics vary. The basic immune dysfunction probably involves a T cell-mediated attack on one or more antigenic fragments of myelin. Myelin-reactive T cells produced in response to initial antigen presentation enter the peripheral circulation and gain entry to the CNS through the blood-brain barrier. In the CNS, local factors sustain further antigen presentation as well as an inflammatory response against myelin basic protein (MBP) and possibly several other myelin fragments. Antibodies to these antigens can cause demyelination directly, but damage appears to depend largely on the presence and function of two subsets of T cells, the T helper (Th) cells Th1 and Th2, in the periphery and CNS. Th1 cells produce inflammatory cytokines such as interferon- γ , interleukin (IL)-2, IL-12, and tumor necrosis factor (TNF)- α , all of which are believed to upregulate antigen presentation and mediate injury to the myelin. By contrast, Th2 cells produce anti-inflammatory cytokines such as IL-4, IL-5, and IL-10; these can inhibit the inflammatory cytokines produced by Th1 cells or macrophages.^{8,9} Relapses in the course of MS are associated with an elevation of Th1 cells and a reduction in Th2 cells. It follows that alteration of the Th cell/cytokine milieu may be a productive approach to controlling relapses and slowing disease progression.

Immunomodulatory Drugs

Mechanisms of Action

The immunomodulatory drugs glatiramer acetate and the beta interferons all manipulate antigen presentation and cytokines, but they do so by fundamentally different mechanisms. Beta interferons do not act directly within the CNS. Rather, they act in an indirect, “antigen-nonspecific” way in the periphery, mediating the entire immune system. By acting on their receptors on T cells and antigen-presenting cells, these drugs downregulate the expression of class II major histocompatibility complex (MHC) molecules needed to sustain antigen presentation. The beta interferons inhibit T cell expansion and survival, with the net result of decreasing the generation of myelin-reactive T cells.⁹ Beta interferons also stem the migration of inflammatory cells from the periphery across the blood-brain barrier. This antimigratory effect, accomplished by suppressing

the adhesion molecules, chemokines, and proteases needed for entry, may be the most crucial activity of beta interferons for altering MS pathology.

In some patients, the beta interferons may induce the formation of antibodies, some of which neutralize the biological activity of the drug and cause therapeutic failure.^{8,9} Neutralizing antibodies to the beta interferons have also been shown to be cross-reactive, which can reduce the efficacy of the drug when patients switch from interferon β -1b to interferon β -1a.¹⁰ In patients, the antibodies are detectable by a variety of laboratory techniques, including enzyme-linked immunosorbent assay (ELISA) and cytopathic effect (CPE) assay (most often used by diagnostic labs).¹¹ Conversely, the antibodies seen with glatiramer acetate treatment do not interfere with treatment response or tolerability, although their significance is unknown.¹²

The actions of glatiramer acetate are more selective immunologically. This drug is an amino acid copolymer designed to be an analogue of MBP. As such it has high affinity for the MHC class II molecules associated with MS on antigen-presenting cells, and it competes with them for binding to the T cell receptor. Presentation of glatiramer acetate leads to the generation of T cells specific to glatiramer acetate. Glatiramer acetate does not inhibit their migration across the blood-brain barrier along with other immune cells. The CNS milieu supports reactivation and expansion of glatiramer acetate-reactive Th2 cells and the release of anti-inflammatory cytokines, which then limit the expansion of myelin-reactive T cells. This process is called bystander suppression.^{9,13,14} Glatiramer acetate-reactive T cells have also been found to produce brain-derived neurotrophic factor, one of the most potent factors supporting neuronal survival and regulating neurotransmitter release.¹⁵ BDNF has also been shown to rescue injured or degenerating neurons and induce the remyelination and regeneration of axons.^{16,17}

Clinical Data

The National Multiple Sclerosis Society (NMSS) recommends the use of immunomodulatory therapy for patients following a diagnosis of RRMS.¹⁸ There is lessening debate among neurologists about the most appropriate timing of therapy. Some believe that initiation of therapy upon diagnosis of RRMS, or soon thereafter, will have the greatest impact on early inflammation, permanent axonal injury, and the progression of disease. They take the position that “time is brain,” and that to wait for recurrent attacks before starting therapy is to squander the opportunity to preserve neurologic func-

tion. Others argue for delayed therapy—beginning only after recurrent relapses—by noting that 10 percent to 20 percent of MS cases follow a benign course after diagnosis or a first attack, and that immunotherapy has not been proven to reduce early axonal injury if indeed it occurs. They hypothesize that if beta interferons are started early, there is a risk that formation of neutralizing antibodies could render the drugs useless later in the disease process.⁸ Of course, a key issue in the argument is patient willingness to accept the expense and possible side effects of immunomodulatory therapy and to comply over the long term.^{8,19}

Much of the uncertainty about treatment strategy has been sustained by the absence of long-term clinical data on the immunomodulatory drugs. At present, the beta interferons have efficacy data supporting their use for up to five years, while glatiramer acetate has efficacy data supporting its use beyond eight years (*Exhibit 1*). Six-year data on safety and the development of neutralizing antibodies with interferon β -1a SC have recently become available. Although assumptions about lifetime efficacy are unavoidable in clinical decision-making, it is helpful to proceed with knowledge of the pivotal clinical trials and follow-up studies for each drug.

Long-term efficacy findings

Two-year data are available for interferon β -1a IM from a randomized, placebo-controlled trial with 301 patients with RRMS. At entry, patients had an Expanded Disability Status Score (EDSS) of 1.0 to 3.5 and had experienced at least two relapses in the prior three years. Compared with placebo, interferon β -1a IM, 30 μ g (6 million IU) once weekly, significantly ($P=0.02$) slowed the EDSS progression rate (the primary endpoint) and reduced the rate of relapses by clinical and MRI criteria. In the subpopulation of patients ($n=172$) for whom two-year data were available, the annual relapse rate was 0.90 in the placebo arm and 0.61 with active treatment.²⁰

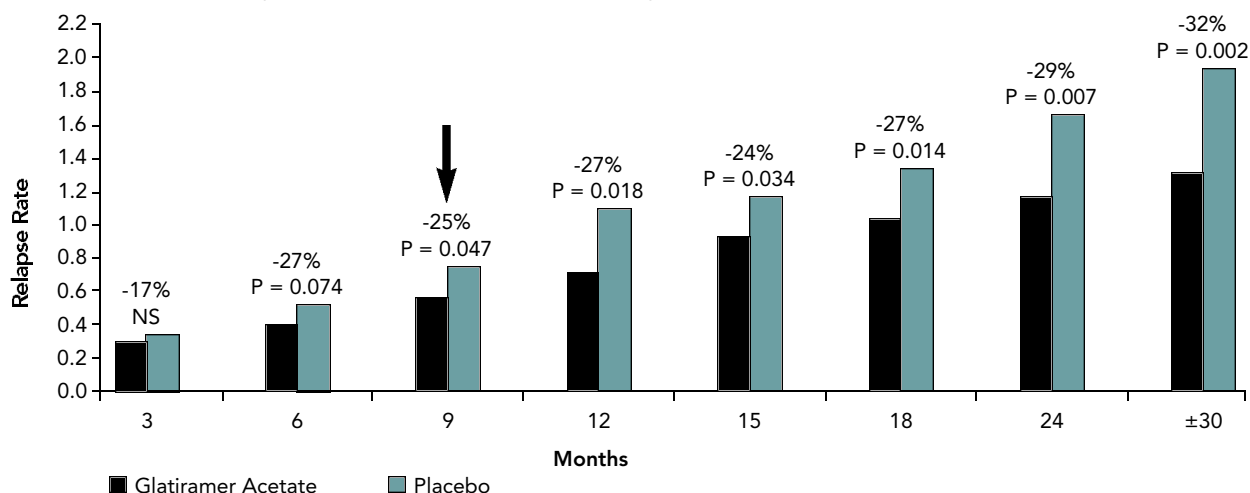
Four-year data have been reported for interferon β -1a SC, which became available in the United States in 2002. The original randomized, placebo-controlled trial, known as PRISMS (Prevention of Relapses and Disability by Interferon- β -1a Subcutaneously in Multiple Sclerosis)-2, involved 560 patients with RRMS. At entry, all patients had an EDSS score ≤ 5.0 and all had experienced at least two relapses in the prior two years. Interferon β -1a SC was administered three times weekly in doses of either 22 μ g (6 million IU) or 44 mg (12 million IU). At two years, the number of relapses per person was 1.82 for the 22 μ g group, 1.73 for

Exhibit 1: Immunomodulatory Treatments for Multiple Sclerosis

	Glatiramer Acetate (Copaxone®)	Interferon β-1a IM (Avonex®)	Interferons Interferon β-1a SC (Rebif®)	Interferon β-1b (Betaseron®)
Type	Polypeptide mixture	Recombinant protein	Recombinant protein	Recombinant protein
Use	Reduction of relapse frequency	Slow accumulation of disability and reduce relapse frequency	Reduce relapse frequency and slow accumulation of disability	Reduce relapse frequency
Injection	SC	IM	SC	SC
Administration	Daily	Weekly	3 x/week	Every other day
Dosage	20 mg	30 µg	44 µg	0.25 mg (8 MIU)
Duration of follow-up	8+ years	2 years	4 years	5 years

SC = subcutaneous; IM = intramuscular.

Exhibit 2: Change in Relapse Rate in Patients Receiving Glatiramer Acetate versus Those Given Placebo²⁷



From commencement of therapy, the glatiramer acetate group tended to have a lower rate of relapse than did the placebo group. At month nine, the difference between groups was significant (P=0.047), and the difference remained significant for up to 30 months. NS, not significant.

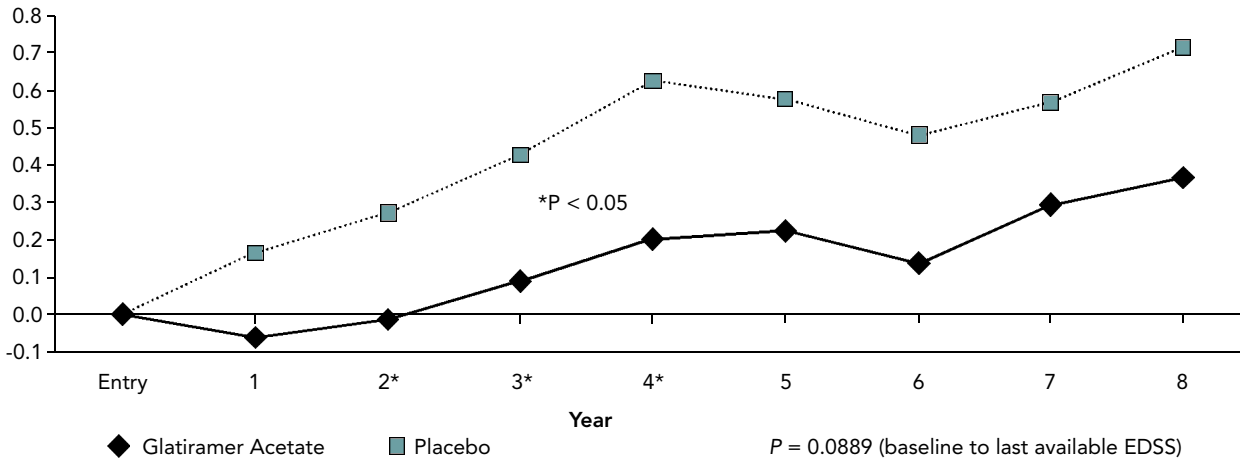
Adapted with permission from Johnson.²⁷ Courtesy of Kenneth P. Johnson, MD.

the 44 mg group, and 2.56 for the placebo group (P<0.005 for both active treatment groups versus placebo). Patients who were originally given placebo were then randomly assigned to one of the active treatment regimens. The remaining patients continued interferon β-1a SC as originally assigned. At four years, the relapse rates were 1.02 for the crossover group, 0.80 for the 22 µg group (P<0.001), and 0.72 for the 44 µg group (P<0.001). Time to sustained disability progression was prolonged by 18 months in the 44 µg group compared with the crossover group (P<0.001). Development of neutralizing antibodies in 14.3 percent of patients in the 44 µg group was associated with reduced efficacy. During years three and

four, the relapse rate was 0.50 for patients in the 44 µg group without neutralizing antibodies, compared with 0.81 for those on the same dose regimen who developed antibodies (P=0.002).²¹⁻²³

Data from patients followed for four years and from some of the five patients seen through five years are available for interferon β-1b, the first of the immunomodulatory drugs for MS to be approved in the United States. This drug is administered as 250 µg (8 million IU) SC every other day; a lower dose of 50 µg (1.6 million IU) was also tested but not approved. The original two-year, randomized, placebo-controlled trial enrolled 372 patients with RRMS, an EDSS score of ≤5.5, and at least two relapses in the prior two years. Compared with

Exhibit 3: Expanded Disability Status Score (EDSS) Change from Baseline Over Eight Years⁵



Yearly EDSS change from baseline for patients on glatiramer acetate continuously and patients who received placebo in the first two to two and a half years and then switched to active treatment. Differences are significant in years two, three and four. By year five, the effect of treatment appears to have influenced the patients originally given placebo.

Adapted with permission from Johnson et al.⁵ Courtesy of Kenneth P. Johnson, MD.

placebo, the high-dose interferon β -1b regimen reduced the clinical attack rate (primary endpoint) by 28 percent ($P=0.03$) and reduced progression of disease burden on MRI. However, neutralizing antibodies, present in 38 percent of patients by year three, weakened the impact on relapse rate.²⁴

Glatiramer acetate now has an eight-year record of sustained efficacy. The original randomized, double-blind, placebo-controlled trial of this drug enrolled 251 patients with RRMS, an EDSS score of ≤ 5.0 , and a history of at least two relapses in the prior two years. After two years, the mean relapse rate for glatiramer acetate, 20 μg SC once daily, was 1.19 compared with 1.68 for the placebo group ($P=0.007$). In addition, significantly more patients treated with active drug improved on the disability scale, whereas those who received placebo were more likely to worsen ($P=0.037$).²⁵ At the completion of the controlled phase of the trial (approximately 30 months), 208 patients continued on open-label glatiramer acetate (101 originally randomized to active drug and 107 who crossed over from placebo).²⁶ Of this group of 208 patients, 152 (73 percent) were still participating after six years. Those patients who received glatiramer acetate from randomization through year six experienced an annual relapse rate of 0.42 (within year six, it was 0.23). The relapse rate declined each year and by the sixth year was 0.23. In the patient group who received glatiramer acetate all along, 26/101 patients remained free from relapse for more than five years.²⁶ Continuous use of glatiramer acetate

over five years also stabilized or improved disability scores in 69.3 percent of patients.²⁶

The reported eight-year follow-up of the glatiramer acetate study represents the longest period of prospective observation in MS treatment trials.⁵ For 72 continuing patients who had always received active therapy, the annual relapse rate was 0.16 in year eight; for 70 patients who had switched from placebo, the rate was 0.23—a rate of approximately one relapse every five years. For all patients, the mean EDSS score after eight years in the study (and approximately 15 years of clinical MS) was 3.14. Neurologic status was unchanged or improved from baseline in almost two thirds of patients on continuous active therapy compared with approximately half of those who originally received placebo. The clear conclusion is that the delay in starting active therapy with glatiramer acetate meant a loss of benefits in terms of long-term clinical status and the progression of disability.⁵

Another perspective on the timing of clinical benefits comes from the placebo-controlled phase of the glatiramer acetate trial. The mean annual relapse rate tended to be lower in the active-treatment arm at months three and six. A significant ($P=0.047$) between-group difference emerged at month nine (relapse rate reduction of 25 percent) and was maintained throughout the study (*Exhibit 2*).²⁷ At 12 months, the difference in rates was 27 percent, and by 30 months, it was 32 percent.²⁷ The beneficial effects of early treatment with glatiramer acetate on neurologic disability remained

stable for more than six years.²⁶ It is important to emphasize that the placebo recipients did subsequently benefit from the switch to glatiramer acetate. By year eight, their annual relapse rates were similar to those of patients always on active therapy (about 0.2). Moreover, their relatively steep rise in EDSS scores during years two and three plateaued by year four. By year five, their pattern of change resembled that of the patients who had always been on glatiramer acetate, although the delay in starting active therapy meant the absolute EDSS score was higher (*Exhibit 3*).⁵

MRI findings with glatiramer acetate

A placebo-controlled trial of glatiramer acetate focused on MRI outcomes but also evaluated clinical results. The European/Canadian study enrolled 239 patients with RRMS and an EDSS score of ≤ 5.0 , and who had at least one relapse in the prior two years. This study was unique because all patients had at least one gadolinium-enhancing lesion on the screening brain MRI; most trials don't require enhancements as an entry criterion. The mean number of enhancing lesions was 4.2 for the glatiramer acetate group and 4.4 for the placebo group. Scans were repeated monthly over nine months. The mean number of cumulative enhancing lesions was 36.8 in the placebo group compared with 26.0 in the glatiramer acetate group, a 29 percent reduction ($P=0.003$). Treated patients also had significantly fewer new enhancing lesions and a smaller monthly change in the volume of enhancing lesions. At the end of nine months, they had 33 percent fewer clinical relapses over the study period. The EDSS scores did not differ significantly from baseline for either group.⁶ After completing the nine-month placebo-control phase, patients were enrolled in a nine-month, open-label extension where patients who had received placebo received glatiramer acetate. There was a 54 percent reduction in the mean number of enhancing lesions for the patients who changed treatment from placebo to glatiramer acetate, and a 24.6 percent reduction for the patients who continued on glatiramer acetate. All patients experienced relapse rate reductions in the open-label phase and there were no major changes from baseline EDSS scores.⁷ Patients who received active treatment with glatiramer acetate had a continuous and sustained effect on gadolinium-enhancing lesions.

The European/Canadian trial was also unique because it was the first trial to assess the effects of immunomodulatory treatment on the proportion of new lesions that became chronic "black holes," which are areas of severe tissue disruption that become persistently hypointense on MRI after

gadolinium enhancement. Initial MRI evaluation found that approximately three quarters of 1,772 new lesions were hypointense in the glatiramer acetate and placebo groups. Over nine months, fewer lesions evolved into permanent black holes in the patients treated with glatiramer acetate versus placebo. By month seven, the percentages were 19 percent and 26 percent, respectively ($P=0.04$). By month eight, the percentage of lesions evolving into permanent black holes in the glatiramer acetate group was approximately half that in the placebo group (16 percent and 31 percent, respectively; $P=0.002$). This effect of glatiramer acetate on permanent tissue disruption probably underlies the drug's efficacy in slowing disability.²⁸

These results are in contrast to those seen with the beta interferons. A 36-month longitudinal study evaluating the effect of interferon β -1b on permanent black holes concluded that the drug had no effect on these lesions.²⁹ This conclusion is consistent with the presumed mechanism of action of the beta interferons. The authors note, "although the drug decreases the inflammatory activity, the events that follow the acute lesion formation appear not to be affected [by] IFN β -1b." Furthermore, another study demonstrated that, although the beta interferons showed a rapid and robust decrease in the number of gadolinium-enhancing lesions on MRI, the decrease in enhancing lesions did not necessarily correlate with clinical response to the beta interferons in the long term.³⁰

Comparative data

Prospective trials comparing the efficacy of all of the immunomodulatory drugs for MS have not been conducted. However, a recent analysis of retrospective clinical and cost data provides limited insight on the use and relative impact of these drugs in a managed care setting.³¹ Information on 8,457 MS patients treated between 1996 and 2001 at 47 health plans across the United States was obtained from a proprietary database. In terms of age, sex, type of health plan, and other demographic variables, the patients were considered representative of an MCO population. Clinical course was compared according to the first prescribed immunomodulatory drug. During the study period, 10 percent of patients who received interferon β -1a IM and 5.5 percent of patients who received interferon β -1b switched or added to their regimens, and the change usually involved glatiramer acetate. By contrast, there were no switches or additions among patients receiving glatiramer acetate. The cumulative incidence of relapses was similar regardless of type of immunotherapy being used, but the time to

first relapse was longer with use of glatiramer acetate, and the 1-year risk of relapse was significantly higher ($P < 0.01$) with use of interferon β -1a IM (hazard ratio of 1.15) or interferon β -1b (hazard ratio of 1.51). Mean annual MS-related costs favored glatiramer acetate (\$9,522) in comparison with interferon β -1a IM (\$9,957) and interferon β -1b (\$10,185), mainly because of the cost difference between the immunomodulatory drugs themselves (respectively \$6,740, \$7,547, and \$7,648).³¹

Safety considerations

Although all of the immunomodulatory drugs for MS are clinically effective, their safety profiles may ultimately affect treatment value by promoting or discouraging patient adherence or increasing the costs of care. Side effects of the beta interferons include flu-like symptoms, such as fever, chills, and myalgias, which may affect approximately half of patients with initial therapy.^{20,21,24} These symptoms often resolve after weeks to months of therapy or they can be managed with use of acetaminophen or nonsteroidal anti-inflammatory medications; a small percentage of patients (3 percent to 8 percent) may remain symptomatic for years. Blood counts and liver function tests, usually performed at three- or six-month intervals in patients receiving beta interferons, may reveal mild abnormalities in liver function, mild lymphopenia, or (rarely) severe hepatotoxicity. One Canadian postmarketing surveillance analysis reported elevated liver enzymes for each interferon β group reviewed: interferon β -1a IM, interferon β -1b, and interferon β -1a SC.³² All groups showed significant ($P < 0.005$) de novo grade 1 (greater than upper limit of normal) or more elevations in amino transferase levels compared to baseline values for 846 patients on drug a mean of 23.1 months. Patients who received interferon β -1b and interferon β -1a SC had significant ($P < 0.0005$) grade 2 (> 2.5 upper limit of normal to 5 upper limit of normal) elevations in amino transferase levels. Interferon β -1a SC had significant ($P = 0.031$) grade 3 (> 5 upper limit of normal) amino transferase levels compared to baseline. De novo grade 1 alanine aminotransferase (ALT) elevations occurred in 39.4 percent (138/350) of interferon β -1b patients, 37.6 percent (97/258) of interferon β -1a SC patients, and 25 percent (13/52) of interferon β -1a IM patients.³²

Muscle abscesses are reported rarely with injections of interferon β -1a IM and SC injections can cause redness, induration, or skin necrosis at the injection site.^{21,24} These side effects are generally more severe with higher drug doses. Depression, increased spasticity, and mental abnormalities have been reported but may be related to MS itself.

Postmarketing data concerning interferon β -1a IM suggests an increased risk of depression, suicidal ideation, and other psychiatric disorders, as well as infrequent reports of possible cardiac and hepatic toxicity, autoimmune disorders, thyroid disorders, and seizures.³³ The beta interferons, which are each Pregnancy Class C, can cause miscarriages,^{11,19} whereas glatiramer acetate, which is Pregnancy Class B, has not been shown to affect fetal development in animal studies³⁴ and, in clinical trials and postmarketing surveillance, has not been shown to induce a higher rate of miscarriages than in the general population.³⁵ As always, any patient who is pregnant or considering becoming pregnant should discuss treatment with her physician.

Because the side-effect profile of glatiramer acetate therapy does not include laboratory abnormalities,^{25,26} routine monitoring of blood and liver function is not needed during treatment. Mild redness or rash may occur at the injection site but these symptoms usually subside with continued therapy. In the pivotal trial of glatiramer acetate,²⁵ approximately 15 percent of patients at some time experienced an immediate postinjection-type reaction shortly after injection involving shortness of breath, chest tightness, palpitations, and anxiety. This was self-limiting and did not recur in the majority of patients. If such a reaction does occur, patients who have been cautioned about it in advance are typically able to tolerate it.^{11,19} This reaction rarely leads to discontinuation of therapy.

An important difference between glatiramer acetate and the beta interferons is the development of neutralizing antibodies with beta interferons, which necessitate expensive, time-consuming testing.¹⁹ Formation of neutralizing antibodies to glatiramer acetate has not been reported. Conversely, a significant number of patients who receive beta interferon therapy become positive for antibodies. Some, but not all, antibodies interfere with the receptor-mediated functions of the drugs, thereby diminishing the drugs' biologic activity and reducing clinical response.¹¹ For example, in the pivotal trial of interferon β -1b,²⁴ 38 percent of patients who received the high-dose regimen had evidence of neutralizing antibodies by the end of year three. The attack rate was 1.08 in the antibody-positive patients versus 0.56 in the antibody-negative patients ($P < 0.001$). In the pivotal trial of interferon β -1a IM,²⁰ neutralizing antibodies developed in 14 percent of patients after one year and 22 percent after two years of receiving active drug. Similarly, treatment with high-dose interferon β -1a SC in the PRISMS trial led to neutralizing antibodies in 14 percent of patients through year four²³; this percent-

age remained consistent through year six.³⁶ Although the low-dose regimen led to a higher incidence of antibodies—24 percent—the attenuated impact on relapse rate was felt more strongly in the high-dose group. Neutralizing antibodies to any of the beta interferons are cross-reactive;¹⁰ a patient with antibodies and treatment failure should not be switched to another beta interferon.¹⁹

Disease Management

Beyond recommending early and continued use of immunomodulatory drugs for patients with RRMS, the NMSS cites obstacles to such use that require remedy. One is patient accessibility to the drugs, which may be hindered if both major therapeutic classes of treatment for MS (glatiramer acetate and interferon) are not included in formularies or covered by insurers. Although not necessarily related to managed care restrictions, referral to specialists is inadequate and the fault of inadequate information reaching primary care physicians, the NMSS says. Moreover, policymakers and insurers need to better understand the concept and benefits of chronic disease management. Some insurers see the absence of attacks as reason to discontinue immunomodulatory therapy, for example, or consider two attacks in the prior year a prerequisite for therapy. Others place a ceiling on treatment costs.³⁷ NMSS figures show glatiramer acetate to be the least expensive therapy, with a wholesale cost per year of \$12,939.25. The most expensive is high-dose interferon β -1a SC (44 μ g, which is the dose approved for use in the United States), at \$17,392.25, followed by interferon β -1b at \$14,034.25, and interferon β -1a IM at \$14,029.69.³⁸

The NMSS also cites nonadherence and discontinuation by patients on therapy as obstacles to optimal management of chronic diseases in general and MS in particular. Nonadherence is especially common in patients with chronic conditions, of whom only about 50 percent maintain therapy to the degree associated with the best outcomes. Nonadherence increases the costs of care and complicates the course and success of treatment. Factors that lead to nonadherence include drug side effects, the unpredictability of MS itself, and perhaps disappointment if patients have undue expectations of therapy. Improved adherence, on the other hand, may lower costs by reducing hospital stays and the need for surgery and invasive care.³⁹⁻⁴¹ This is a chief goal of disease management: a treatment model focused on helping patients understand their condition, change their behavior, and coordinate their caregiver relationships, all in the interest of adherence.⁴²

Glatiramer acetate may improve adherence,

especially for patients who start treatment early in the MS disease course, because of its tolerability relative to the beta interferons.⁸ This feature may have accounted for the findings of a recent survey of 700 MS patients in the United States who took immunomodulatory drugs. Their average duration of disease was nine years. Among patients who took interferon β -1b, 71 percent discontinued and 43 percent changed to another drug; among those on interferon β -1a IM, 40 percent discontinued and 28 percent switched therapy; and among those patients who took glatiramer acetate, 21 percent discontinued and 8 percent switched. The main reasons given overall for discontinuance were a lack of obvious benefit from therapy, an increase in MS symptoms, and flu-like symptoms. It is interesting that some factors expected to affect adherence did not, such as injection-site pain, abnormal blood tests, and travel-related disruptions.⁴³ Nor was the inconvenience of injections cited. Nevertheless, half the respondents reported preferring SC injections to IM injections.⁴³ As noted above, glatiramer acetate, interferon β -1b, and interferon β -1a SC are administered SC. Only glatiramer acetate and interferon β -1a SC can be administered in prefilled syringes, another possible advantage for improving adherence.

Specialty Pharmacy Distributors

The chasm between the clinical results of adherent versus less-adherent patients has been widely discussed in the literature but until recently, little has been done on a population basis to improve adherence. MCOs have embraced and formalized the philosophy of disease management for common diseases such as diabetes, asthma, and coronary artery disease. However, the actual application of disease management processes and techniques to less common diseases has been minimal at best. Part of the reason is the high cost to health plans and providers to maintain disease management programs for rarer diseases, such as MS. Although a few disease management companies have developed programs, acceptance by MCOs has been infrequent.

This situation is complicated by the high cost of the drugs used to treat diseases like MS. Many are biotechnology drugs, which currently carry a price tag of between \$6,000 and \$100,000 per year per patient. Most recently, this group of drugs represented an estimated \$27 billion market in the United States,⁴⁴ while total retail pharmacy expenditures were \$154 billion in 2001.⁴⁵ The injectable drug market share may be as high as \$2.29 per member per month.⁴⁶ If hospital, physician office, home care, and skilled nursing care distribution

channels are included, this number is likely to be closer to \$10 per member per month. As a group, the biotechnology drugs have other characteristics that may increase costs and nonadherence. Many (but not all) are high-cost polypeptides or proteins intended for treating chronic, rare, and complex disorders, sometimes at just a few academic medical centers. They are administered by injection. Many are temperature-sensitive and require precisely timed shipping and delivery. As a group, biotechnology drugs necessitate customized education. Their costs are reimbursed inconsistently from a mixture of pharmacy and medical benefits. Nonadherence may result in high direct medical costs and indirect personal and social costs.

In an increasingly popular approach to controlling costs while providing quality care, several companies have gone beyond merely dispensing drugs to working with patients within the disease management plan, helping them to self-manage and cope with the challenges of therapy. These specialty pharmacy distributors fill prescriptions, send refill reminders, counsel patients on topics such as side effects, and even screen for depression, and collect valuable data about patients receiving treatment. These services can benefit both patients and their insurers. One specialty pharmacy distributor showed that patients with MS in their program were able to reduce their hospital stays.⁴⁷ This ties in with the data on disease management that show that adherence and education can lead to better outcomes. The drugs that are most often distributed by these programs are for the treatment of MS, Gaucher's disease, growth hormone deficiency, pulmonary arterial hypertension, anemia, infertility, osteoarthritis, hepatitis C, hemophilia, respiratory syncytial virus prevention, rheumatoid arthritis, and immunoglobulin deficiency. Some companies distribute HIV drugs and immunosuppressants for use in organ transplantation.

Specialty pharmacy distributors and managed care organizations

The idea of specialty pharmacy distributors is now more than 10 years old. The idea has its roots in a variety of other industries including home healthcare companies, infusion companies, pharmacy benefits management, mail order companies, and even retail drug chains. Distributors have received the attention of Wall Street as their growth and profitability have accelerated.

For numerous business reasons, the specialty pharmacy distributors have become popular with MCOs. They offer aggregation of pharmacy costs to one data system; adjudication under either the medical or pharmacy benefit or both, as the MCO

wishes; prior authorization services; monitoring for drug availability and the ensurance of a steady supply; accepting assignment of benefits; and, of course, better pricing. One compelling reason these companies are becoming a part of the overall disease management strategy is that they appear to improve adherence. They are starting to design their business model to actually measure and improve the clinical, humanistic, and financial outcomes of the diseases and patients they focus on. Specialty pharmacy distributors will also allow insurers to take advantage of the competition as the manufacturers of the three interferons start to offer rebates and price concessions by directing care to the "preferred" drug during the prior authorization process.

Specialty pharmacy distributors include the following companies:

- Caremark Therapeutic Services (NYSE: CMX)
- Chronimed Inc. (NASDAQ: CHMD)
- Coram Prescription Services
- CuraScript Pharmacy (privately held)
- CVS Procure
- Accredo (Hemophilia Health Services, Nova Factor, Accredo Therapeutics) (NASDAQ: ACDO)
- Express Scripts International
- Priority Healthcare Corp. (NASDAQ: PHCC)
- OptionMed Inc. (NASDAQ: OPTN)
- MIM Corp., Script Pharmacy Solutions, (NASDAQ: MIMS)
- Theracom
- McKesson Specialty Rx
- IVPCare

Conclusions

Drugs that affect the course of MS are relatively new, but these immunomodulators (glatiramer acetate and the interferons) are building a promising track record in formal clinical studies; in the case of glatiramer acetate, the data extend beyond eight years. Neither glatiramer acetate nor the beta interferons are curative; relapses still occur and disability accumulates even when immunotherapy is given under controlled clinical trials. Use of drugs for MS is associated with the real-world challenges of side effects, costs, tolerability and inconvenience, which may deter physicians and patients from timely therapy. Initiation of immunotherapy early in the course of MS—before axonal loss is permanent and clinical progression established—is becoming a pivotal issue in disease management given current understanding of MS pathophysiology and the emerging data from the trials of glatiramer acetate. Glatiramer acetate has similar efficacy to the interferons and a milder side effect profile. Its effectiveness is not impaired by the formation of

neutralizing antibodies. It may be the most appropriate first-line choice when immunotherapy is started early in the course of disease, and its long-term tolerability and efficacy profile render it an appropriate choice for more advanced disease.

Medical costs of MS therapy may increase with the severity of disease and the development of disability,² so preventing disease progression is vital to controlling costs. To that end, improving adherence to therapy is a key target of disease management, a tenet which has been adopted by MCOs. Specialty pharmacy distributors have emerged with the goals of controlling drug costs and improving adherence by educating and assisting patients within the disease management framework. As they develop, these distributors are expected to lower the practical and economic obstacles faced by MS patients in the course of their disease, and optimize their management and outcomes as they are treated with immunomodulators. **JMCM**

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Managed Care's Role in Influencing Appropriate Asthma Therapy

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Summary

In 2002, the National Asthma Education and Prevention Program (NAEPP) Expert Panel released an update to its "Guidelines for the Diagnosis and Management of Asthma." These revisions and other issues of appropriate asthma treatment were discussed at the Spring 2002 Medical Director's Update, which was conducted by the Medical Director's Institute in conjunction with the National Association of Managed Care Physicians, the American Association of Integrated Healthcare Delivery Systems, and the American College of Managed Care Medicine.

Key Points

- With the NAEPP classification system, underclassification of asthma sufferers is still common and continues to result in undertreatment.
- A growing body of evidence indicates that many asthma patients probably have a more severe form of asthma than originally determined by assessment of pulmonary function and symptom recall.
- Managed care has significant opportunities to employ a variety of methods to increase physician compliance with the updated NAEPP guidelines.

CME Credit

This article was developed from the proceedings of the National Association of Managed Care Physicians (NAMCP) 2003 Spring Update, held in Atlanta. The meeting was supported by an unrestricted educational grant from GlaxoSmithKline. **To receive CME credit, see instructions for the post-test and evaluation starting on pages 31.**

EFFECTIVELY TREATING A DISEASE depends first on classifying the patient in the most accurate diagnostic category. For example, a patient who actually has a viral form of pneumonia will not benefit from a course of antibiotics. Similarly, the condition of a Type I diabetic will not be improved with a regimen of sulfonylureas. Classifying the asthma patient into a diagnostic category for treatment purposes can be far more complex than determining if a diabetes patient has Type I or Type II diabetes, or if a pneumonia patient has a viral or bacterial form of pneumonia.

Diagnostic Difficulties

The "Guidelines for the Diagnosis and Management of Asthma," which were developed by an expert panel under the auspices of the National Heart,

Lung, and Blood Institute's National Asthma Education and Prevention Program in 1991 and revised in 1997 and 2002, designate four classifications based on disease severity.^{1,2} These disease severity categories are summarized in Exhibit 1. Though a patient with severe persistent asthma is easily distinguished from a patient with moderate or mild asthma, it is difficult to clearly label patients as having moderate persistent, mild persistent, or mild intermittent asthma and to distinguish them from each other. What's more, asthma patients do not remain consistently within one disease category throughout the course of their illness. These variables vastly affect treatment regimens.

As more is learned about the inflammatory response and what happens to cells that line the

bronchial airways, it is becoming apparent that there are more similarities, rather than differences, among moderate persistent, mild persistent, and mild intermittent asthma patients. A recent study found that both mild persistent and moderate persistent asthma patients responded with similar inflammation to a segmental allergen challenge.³ Even among mild persistent asthmatics, airway remodeling occurs.

One study that measured subepithelial layer thickness, the reduction of which predicts the presence of airway remodeling, found no statistical difference between the subepithelial layer thickness of mild persistent versus moderate persistent asthma patients.⁴ The subepithelial layers of both categories were significantly reduced, indicating that for both categories of patients, the smooth muscle cells that line the airways were significantly hypertrophied.

A growing body of evidence indicates that many asthma patients probably have a more severe form of asthma than originally determined by assessment of pulmonary function and symptom recall. Pulmonary function is assessed by measuring the maximal volume of air that is forcibly exhaled during the first second (FEV₁) after maximal inhalation. This value is then compared to reference or predictive values to determine the presence of airway obstruction. Although a diminished FEV₁ signals the need for immediate treatment, a normal FEV₁ does *not* indicate an absence of risk of suffering an acute asthma episode. In fact, one retrospective study determined that 20 to 25 percent of pediatric patients with a normal FEV₁ (>90 percent predicted) would be treated for an acute asthma episode during the ensuing year.⁵

Shortcomings of Symptom Recall

The NAEPP classification system's reliance on symptom recall to establish disease severity further compounds the problem of asthma underclassification. Two studies in particular show that assessing disease severity based on quality of life or functional impact significantly—and drastically—changes the disease distribution.^{6,7}

French investigators with the National Institute for Health and Medical Research in Paris used the Global Initiative for Asthma guidelines to assess disease severity in 4,362 patients. Researchers first determined disease severity based on symptoms and FEV₁, using similar criteria to the NAEPP guidelines. They then reclassified patients according to an additional parameter of medication use. Based on how often they used their albuterol

inhalers as a form of rescue therapy, 40 percent of the 953 patients originally classified as having mild intermittent asthma were shifted into a more severe disease category, with 18 percent jumping two categories or more.⁷

Anne Fuhlbrigge and her team of researchers from Brigham and Women's Hospital and Harvard Medical School in Boston, asked an additional quality-of-life question when assessing disease severity of a randomized sample of adult asthmatics and parents of children with asthma in a cross-sectional telephone survey. When asthma severity was defined by these measures of symptom burden, the proportion of individuals with mild intermittent asthma decreased by 35 percent, while the proportion of individuals with moderate or severe persistent asthma increased by 35 percent. The proportion of individuals with mild persistent asthma remained the same.⁷

Underclassification Results in Undertreatment

With the NAEPP classification system, underclassification of asthma sufferers is still common and continues to result in undertreatment. As evidence accumulates, experts in the field are concluding that the classification system itself may be flawed. Under the current system, mild intermittent, mild persistent, and moderate persistent asthmatics are virtually indistinguishable based on airway inflammation and airway remodeling.

A study conducted by Canadian researcher Paul O'Byrne of McMaster University in Hamilton, Ontario, also showed that mild intermittent and mild persistent asthmatics significantly benefited from stepped-up therapy.⁸ O'Byrne and others now question whether placing people in a mild intermittent or mild persistent category facilitates proper treatment. Future guideline revisions are likely to address this issue as it continues to be examined.

Evidence-Based Treatment Recommendations

Mounting evidence examined by the NAEPP's expert panel also suggests that treatment recommendations for those who have been *accurately* diagnosed with moderate persistent asthma are not intensive enough. This evidence is further explored in the "NAEPP Expert Panel Report Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002" which included updated treatment recommendations.² The update also addresses recommendations for long-term management of asthma in children.

Exhibit 1: Classification of Asthma Severity—Clinical Features Before Treatment*

	Symptoms**	Nighttime Symptoms	Lung Function
STEP 4 Severe Persistent	<ul style="list-style-type: none"> • Continual Symptoms • Limited Physical Activity • Frequent Exacerbations 	Frequent	<ul style="list-style-type: none"> • FEV₁ or PEF ≤ 60% predicted • PEF variability > 30%
STEP 3 Moderate Persistent	<ul style="list-style-type: none"> • Daily symptoms • Daily use of inhaled short-acting beta₂-agonist • Exacerbations affect activity • Exacerbations ≥ 2 times a week; may last days 	>1 time a week	<ul style="list-style-type: none"> • FEV₁ or PEF ≤ 60% predicted - < 80% predicted • PEF variability > 30%
STEP 2 Mild Persistent	<ul style="list-style-type: none"> • Symptoms > 2 times a week but < 1 time a day • Exacerbations may affect activity 	>2 times a month	<ul style="list-style-type: none"> • FEV₁ or PEF ≥ 80% predicted • PEF variability 20%-30%
STEP 1 Mild Intermittent	<ul style="list-style-type: none"> • Symptoms ≤ 2 times a week • Asymptomatic and normal PEF between exacerbations • Exacerbations brief (from a few hours to a few days) 	≤ 2 times a month	<ul style="list-style-type: none"> • FEV₁ or PEF ≥ 80% predicted • PEF variability <20

Source: Guidelines for the Diagnosis and Management of Asthma, p. 8 Figure 1-3.

*The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this figure are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.

**Patients at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

These updates are summarized in Exhibits 2 and 3.

Most importantly, systematic reviews of the published literature on these issues further established long-acting inhaled corticosteroids as the backbone of therapy across all age and severity continuums. During the late 1970s, experts began to realize the importance of controlling the inflammatory response that occurs in patients with asthma. It is now known that even mild asthmatics without symptoms and with normal pulmonary function exhibit some degree of inflammatory response. It is also known that uncontrolled inflammation leads to irreversible airway remodeling and airway smooth muscle hypertrophy.

The goal of asthma treatment, then, is to control inflammation so that airway remodeling and airway smooth muscle hypertrophy is prevented or curtailed. In study after study, long-acting inhaled corticosteroids (ICS) have been shown to be the most effective anti-inflammatory agents.

The most popular alternative to a long-acting ICS is, in fact, not an anti-inflammatory agent. Leukotriene receptor antagonists (LTRAs) have an anti-inflammatory effect in rodent species but have a bronchodilatory effect in humans. Nevertheless, since LTRAs were approved in the

United States in 1997, annual sales have increased, while annual sales of ICS have decreased. Comprehensive reviews of both randomized controlled trials and observational studies in the published literature have demonstrated the superiority of inhaled corticosteroids over the use of LTRAs in virtually all instances.^{9,10}

In a 2003 study appearing in the *British Medical Journal*, Canadian researcher Francine Ducharme reviewed 13 randomized controlled trials, in which patients received a single agent for the long-term control of asthma. These patients received either LTRAs or ICSs. All outcomes—including rate of acute asthma exacerbations, FEV₁, peak flow, frequency of nocturnal awakening, use of rescue medication, number of days without symptoms, and risk of treatment failure—favored ICS as the preferred single agent therapy for the long-term control of asthma.⁹

Large-scale cohort studies also reflect the effectiveness of using an ICS as a single agent in the treatment of asthma. One study, identifying more than 96,000 patients with asthma in the United Kingdom, determined that a dramatic reduction in the relative risk of death could occur when persistent asthmatics using only rescue therapy were properly treated with a low-dose ICS. Patients who refilled their prescriptions for a short-acting

beta agonist at least once a month were 52 times more likely to die than patients who refilled their prescription once or twice a year. When these same patients were placed on low-dose ICSs, their relative risk of dying was reduced to 0.4—even lower than the mildest asthmatics.¹⁰

Cohort studies have also compared the economic impact of various single agent asthma treatment regimens. Claims data consistently show that asthma costs per patient per year are higher for those using LTRAs compared to those using ICSs. Costs include inpatient admissions, emergency room and outpatient visits, and pharmacy costs.¹¹ A major component of pharmacy costs, according to one

study recently appearing in *Pharmacotherapy*, is refill prescriptions for short-acting beta agonists (SABA), or rescue medications. Patients using LTRAs refilled their SABA prescriptions 10 times a year, as compared to fewer than five times a year for those using ICSs.¹² This finding is significant because repeated SABA refills indicate a substantial loss of symptom control.

Inhaled corticosteroids are the backbone of treatment for even more severe disease, in which combination therapy is recommended. Through its review of a substantial body of research, the NAEPP expert panel has concluded that an ICS, preferably the third-generation agent fluticasone

Exhibit 2: Stepwise Approach for Managing Infants and Young Children (5 Years of Age and Younger) with Acute or Chronic Asthma

Classify Severity: Clinical Features Before Treatment or Adequate Control		Medications Required to Maintain Long-Term Control
<u>Symptoms/Day</u> <u>Symptoms/Night</u>		Daily Medications
STEP 4 Severe Persistent	<u>Continual</u> Frequent	<i>Preferred treatment:</i> <ul style="list-style-type: none"> • High-dose inhaled corticosteroids AND <ul style="list-style-type: none"> • Long-acting inhaled beta₂-agonists AND, if needed <ul style="list-style-type: none"> • Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
STEP3 Moderate Persistent	<u>Daily</u> > Night/Week	<i>Preferred treatment:</i> <ul style="list-style-type: none"> • Low-dose inhaled corticosteroids and long-acting inhaled beta₂-agonists OR <ul style="list-style-type: none"> • Medium-dose inhaled corticosteroids. <i>Alternative treatment:</i> <ul style="list-style-type: none"> • Low-dose inhaled corticosteroids and either leukotrine receptor antagonist or theophylline. If needed (particularly in patients with recurring severe exacerbations) <i>Preferred treatment:</i> <ul style="list-style-type: none"> • Medium-dose inhaled corticosteroids and long-acting beta₂-agonists. <i>Alternative treatment:</i> <ul style="list-style-type: none"> • Medium-dose inhaled corticosteroids and either leukotrine receptor antagonist or theophylline.
STEP 2 Mild Persistent	<u>> 2/week but < 1 x day</u> > 2 nights/month	<i>Preferred treatment:</i> <ul style="list-style-type: none"> • Low-dose inhaled corticosteroids (with nebulizer or MDI with holding chamber with or without face mask or DPI). <i>Alternative treatment (listed alphabetically):</i> <ul style="list-style-type: none"> • Cromolyn (nebulizer is preferred or MDI with holding chamber) or leukotrine receptor antagonist.
STEP 1 Mild Intermittent	<u>≤ 2 days/week</u> ≤ 2 nights/month	No daily medication needed. Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is recommended.

Source: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002*

propionate, *and* a long-acting beta agonist (salmeterol) is the most effective treatment regimen for those with moderate and severe persistent asthma.³ Confirmation that long-acting beta agonists are preferable to LTRAs in combination therapy comes from studies throughout the trial design continuum. Different claims data sets have been evaluated by various investigators and supported by the claims data of individual medical groups across the country.^{13,14,15,16}

Managed Care's Role in Asthma Treatment Patterns

Managed care can help reverse the trend of asthma undertreatment. Managed care has significant opportunities to employ a variety of methods

to increase physician compliance with the updated NAEPP guidelines. In many instances, physicians don't know what the guidelines say, or in some cases, that they even exist. Physicians are inundated by guidelines for the diagnosis, management, and treatment of virtually every condition imaginable. And for some disease states, multiple guidelines exist, thereby making it difficult to recall a guideline's specific recommendations. In one study, 22 percent of medical school faculty members specializing in asthma could not recall the specifics of the 1997 NAEPP Expert Panel Report Update on Selected Topics.¹⁷ Nearly half of those with broader specialties, such as internal medicine or family practice residents, did not know the guideline's treatment recommendations.¹⁷

Exhibit 3: Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age (Treatment)

Classify Severity: Clinical Features Before Treatment or Adequate Control		Medications Required to Maintain Long-Term Control
<u>Symptoms/Day PEF or FEV₁</u> Symptoms/Night PEF Variability		Daily Medications
STEP 4 Severe Persistent	<u>Continual ≤ 60%</u> Frequent >30%	<i>Preferred treatment:</i> <ul style="list-style-type: none"> • High-dose inhaled corticosteroids AND <ul style="list-style-type: none"> • Long-acting inhaled beta₂-agonists AND, if needed <ul style="list-style-type: none"> • Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
STEP 3 Moderate Persistent	<u>Daily > 60% to > 80%</u> > Night / Week >30%	<i>Preferred treatment:</i> <ul style="list-style-type: none"> • Low-to-medium dose inhaled corticosteroids and long-acting inhaled beta₂-agonists <i>Alternative treatment:</i> <ul style="list-style-type: none"> • Increase inhaled corticosteroids with medium dose range OR <ul style="list-style-type: none"> • Low-to-medium dose inhaled corticosteroids and either leukotrine modifier or theophylline. If needed (particularly in patients with recurring severe exacerbations) <i>Preferred treatment:</i> <ul style="list-style-type: none"> • Increase inhaled corticosteroids within medium-dose range and add long-acting beta₂-agonists. <i>Alternative treatment:</i> <ul style="list-style-type: none"> • Increase inhaled corticosteroids within medium-dose range and add either leukotrine modifier or theophylline.
STEP 2 Mild Persistent	<u>> 2/week but < 1 x day = 80%</u> > 2 nights/month 20% to 30%	<i>Preferred treatment:</i> <ul style="list-style-type: none"> • Low-dose inhaled corticosteroids. <i>Alternative treatment (listed alphabetically):</i> <ul style="list-style-type: none"> • Cromolyn leukotrine modifier, nedocromil, or sustained release theophylline to serum concentration of 5–15 mcg/mL.
STEP 1 Mild Intermittent	<u>≤ 2 days/week = 80%</u> ≤ 2 nights/month < 20%	No daily medication needed.

Numerous methods for shifting provider practice patterns have been explored. These range from physician interventions, such as targeted mailings to asthma patients, to disease management approaches, to physician incentive programs. Each of these endeavors has met with varying results. A recent study appearing in the *Annals of Internal Medicine* evaluated the effectiveness of these and other methods.¹⁸ Lectures, review articles, and other large-scale academic activities, though effective conduits for disseminating knowledge, are not effective in influencing physician behavior. Establishing good communication channels, organizing physician-led, one-on-one education, and providing patient incentives and reminders have also met with limited success. Instituting system changes, however, has proven very effective.¹⁸

One area that holds promise, but for which limited data is available, is the development of physician incentive programs. Some managed care organizations are beginning to provide incentives for their providers based on quality improvement, rather than cost-control measures. Incentives based on measures of quality improvement or patient satisfaction are related to greater physician satisfaction than are incentives that tend to persuade one to compromise care and quality.¹⁹ The public's approval of these incentives is also higher than its approval of incentives based on cost control.²⁰

Incentive programs often take the form of report cards or score cards that rate individual physicians or an entire medical group in a number of categories, including patient satisfaction, preventive health activities, clinically effective healthcare, and prescribing patterns. Physicians or medical groups are then compensated according to their rankings.

Effecting Change: One Health Plan's Experience

As is the case with other health plans throughout the country, Blue Cross of California, operating under parent company WellPoint Health Networks, a conglomeration of five managed care organizations with more than 13 million medical members, has also experimented with various methods to alter provider practice patterns to reflect the most effective treatment of asthma.

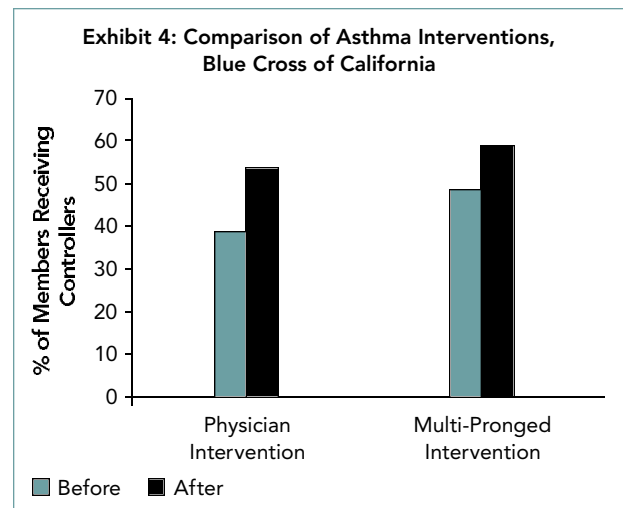
Blue Cross of California's foray into an in-house disease management program for asthma began in 1996.²¹ Its asthma disease management program, targeting low-risk and high-risk popu-

lations age two to 56, utilized interventions of various intensities for physicians and patients. Outcomes measured included emergency room and inpatient utilization, quality of life, and knowledge and usage of self-monitoring tools, as well as usage of ICSs and LTRAs. Most outcomes showed significant improvement, although controller medication prescribing patterns were still sub-optimal.

In 1997, Blue Cross of California initiated a targeted physician intervention using pharmacy claims data that was aimed at increasing the prescribing of controller medications.²¹ At this point, controller medications included inhaled corticosteroids, mast cell agents (e.g., cromolyn or nedocromil), and leukotriene receptor antagonists (LTRAs).

From pharmacy claims data, which represented more than 90 percent of Blue Cross of California members, those patients who received three or more canisters of SABAs in a six-month period who did *not* fill a prescription for a controller medication at least once in the past three months were identified. A letter and a prescription profile of these patients were then sent to the provider in an effort to encourage prescription of a controller medication for these patients.

Each quarter, the percentage of members on SABAs who received a controller medication was calculated. Over the course of three years, this intervention resulted in limited success. Overall, the percentage of members on SABAs who received a controller medication increased by less than 20 percent. Prescriptions of LTRAs increased by 10 percent, while prescriptions of ICSs increased by only seven percent. Prescriptions for mast cell agents actually decreased.²¹



Effecting Change with a Multi-pronged Intervention

In 2001 and 2002, Blue Cross of California designed and implemented a more intensive intervention based on HEDIS' (Health Plan Employer Data and Information Set) "Use of Appropriate Medications for People with Persistent Asthma" measure.²² HEDIS defines persistent asthma as disease that resulted in at least four asthma dispensing events during one year *or* disease that resulted in one or more emergency department visits with asthma as the principal diagnosis during one year *or* disease that resulted in at least one hospitalization during one year *or* disease that resulted in at least four outpatient visits *and* two dispensing events during one year.²² From pharmacy and patient claims data, Blue Cross of California identified all members with persistent asthma. It then determined the percentage of these patients who had received at least one prescription for an ICS, a LTRA, or a mast cell agent.²¹

Members with persistent asthma who had not received at least one prescription for a controller medication received a number of interventions. A letter was generated to the providers of these patients encouraging them to prescribe the appropriate medication. A reminder was sent to office staff. Providers who did not respond received telephone reminders. And members received letters and an incentive. These interventions increased the usage of controller medications somewhat, but after one year, 35 percent of members who needed controller medications still were not receiving the appropriate drugs.²¹ (See Exhibit 4.)

Effecting Change with a Physician Incentive Program

Blue Cross of California is now in the process of designing and implementing a physician incentive program²¹ that rewards those who demonstrate high-quality care and a high level of patient satisfaction. Both physician groups and individual providers are graded on a quality scorecard. While the physician incentive program assigns weighted values to a number of elements assessing the overall quality of care, appropriate asthma therapy may be one component of such an element in quality scorecards for medical groups and individual primary care providers.

For example, appropriate asthma therapy is a part of the preventive health element of the quality scorecard for medical groups. Medical groups are also rated on whether they measure and award

bonuses to their providers based on satisfaction and clinical quality indicators (e.g., HEDIS scores). Because "Use of Appropriate Medications for People with Persistent Asthma" is a HEDIS measure, individual physicians can then be rewarded for complying with evidence-based asthma therapy.

Although Blue Cross of California has not yet analyzed the change in behavior patterns this incentive program may generate, research suggests that incentive programs such as these may be influential in shifting provider practice patterns.¹⁹ **JMCM**

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CME/CEU:

Managed Care's Role in Influencing Appropriate Asthma Therapy

The preceding article in the *Journal of Managed Care Medicine*, Vol. 7, No. 2, was developed from the proceedings of the National Association of Managed Care Physicians (NAMCP) 2003 Spring Update, held in Atlanta. The meeting was supported by an unrestricted educational grant from GlaxoSmithKline. The release date of this article is Nov. 1, 2003, and CME is valid until April 1, 2004.

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INSTRUCTIONS FOR CME/CEU

After reading this article, complete the following Evaluation and Post Test, and send to Katie Eads at NAMCP, either by fax at 804-747-5316 or by e-mail: keads@namcp.org. CME will *not* be awarded without the submission of both the Post Test and the Evaluation. You must answer all post-test questions accurately.

The National Association of Managed Care Physicians is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education to physicians. NAMCP designates this activity for 1.5 credits in Category I toward the AMA Physicians Recognition Award. Each physician should claim only those credits he/she actually spent in the activity.

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LEARNING OBJECTIVES

Upon completion of this activity, the reader should be able to:

- Understand how underclassification of asthma sufferers occurs.
- Describe what indicators are present in the diagnosis of asthma severity.
- Review what managed care organizations can do to increase compliance with NAEPP guidelines.

EVALUATION

1. This article was well written and easily understandable.

- Strongly Agree
 Agree
 Disagree
 Strongly Disagree

2. This article achieved the learning objectives.

- Strongly Agree
 Agree
 Disagree
 Strongly Disagree

3. This article will change my practice patterns by

- a. Changing the method I use for initial intervention
 b. Changing the method I use for compliance with NAEPP guidelines
 c. Encouraging participation in disease management program
 d. Will not change my practice patterns

4. This article was fair, balanced, and did not show any commercial bias toward any organization or method.

- Agree
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POST TEST

CME/CEU: Managed Care's Role in Influencing Appropriate Asthma Therapy

1. What level of severity can have mild, moderate, or severe exacerbations? _____

2. What compounds the problem of asthma underclassification? _____

3. The goal of asthma treatment is _____

4. According to the NAEPP panel, what is the most effective treatment regimen for moderate and severe asthma?

- a. Third-generation agent fluticasone propionate
- b. Long-acting beta agonist (salmeterol)
- c. Short-acting beta agonist
- d. A & B
- e. A & C

5. How are some MCOs combating the lack of knowledge among providers regarding asthma treatment? _____

6. HEDIS defines asthma as a disease that resulted in at least

- a. Four asthma dispensing events during one year
- b. One or more emergency visits with asthma as principal diagnosis in one year
- c. At least one hospitalization during one year
- d. Four outpatient visits and two dispensing events in one year
- e. All of the above

AD

4 "Ps" LEADERSHIP FORUM AND DISEASE MANAGEMENT SUMMIT

April 15-16, 2004, Lake Buena Vista, FL

The Institute for Health and Productivity Management (IHPM) and the National Association of Managed Care Physicians (NAMCP) in conjunction with the American Association of Integrated Healthcare Delivery Systems (AAIHDS) and the American Association of Managed Care Nurses (AAMCN) invite you to attend the Second Annual 4 "Ps" Leadership Forum and Disease Management Summit. The 4 "Ps" Leadership Forum is the only meeting that engages health plans and medical providers in a dialogue with employers/purchasers about how to bring them greater value by implementing the Health and Productivity Management Model. The 2004 Forum adds a Fourth P—the patient—to last year's inaugural 3 "Ps" event, by means of a new survey designed to elicit fresh input from consumers on their health and functionality. The Second Annual 4 "Ps" Forum also adds a Disease Management Summit—the only disease management event to focus on the ability of such programs to help deliver higher-value health and productivity outcomes.

Who Should Attend

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About IHPM

The Institute for Health and Productivity Management (IHPM) is a nonprofit research and development organization dedicated to establishing the value of employee health as a business asset and investment in corporate success. IHPM works with all major stakeholders in healthcare for this purpose—employers, providers, health plans, insurers and employees—to assemble and analyze databases, develop and refine key metrics and measurement tools, organize pilot projects to build the business case for health and productivity, and carry the message and the evidence to all stakeholders.

About NAMCP

NAMCP was founded in 1991 to serve the educational interests and needs of physicians working in any form of managed healthcare. NAMCP is a nonprofit association run by physicians for physicians. Since physicians affect 85% of the expense side in healthcare, they should take a proactive role in developing the best delivery system for patients in managed healthcare, thereby increasing quality, reducing costs and improving practice performance and clinical outcomes.

Additional Information

Confirmation letters will be sent to participants registering by April 1, 2004. Dress for the conference is business casual. For cancellations received by March 15, 2004, full credit will be applied toward any future

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