

JMCM

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A PEER-REVIEWED PUBLICATION

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

Vol. 9, No. 3, 2006

- **Managed Care and Disease Management:
Challenges and Opportunities**
- **New Treatments for Chronic Inflammatory Disease**
- **PLUS: Fall Managed Care Forum Preview**

SPECIAL SECTION



- **The Road to Value-based Healthcare:
Destination Apparent, Journey Uncertain**
- **New Treatments in Overactive Bladder and
Implications for Managed Care**
- **Highly Active Antiretroviral Therapy (HAART) in 2006**



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TABLE OF CONTENTS

Managed Care and Disease Management: Challenges and Opportunities

Tom Morrow, MD, and Dexter W. Shurney, MD, MPH, MBA 5

New Treatments for Chronic Inflammatory Disease

Arthur Kavanaugh, MD 11

FALL MANAGED CARE FORUM PREVIEW 19

SPECIAL SECTION: GENOMICS BIOTECH INSTITUTE

The Road to Value-based Healthcare:

Destination Apparent, Journey Uncertain

Eric C. Faulkner, MPH 27

New Treatments in Overactive Bladder and Implications for Managed Care

Michael Kennelly, MD, and Kenneth L. Schaecher, MD 34

Highly Active Antiretroviral Therapy (HAART) in 2006

Trevor Hawkins, MD 41

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Managed Care and Disease Management: Challenges and Opportunities

Tom Morrow, MD, and Dexter W. Shurney, MD, MPH, MBA

A continuing medical education activity sponsored by NAMCP

Summary

Several trends are affecting the disease management industry and managed care in general. Chief among these trends is the search for continuing value of disease management programs. In addition, the use of patient-centered programs is growing because healthy people produce fewer claims.

Key Points

- Healthcare payers are using new ways to define value of disease management programs.
- Disease management programs are focusing more on the whole patient rather than just a single disease.
- Patient-focused wellness/lifestyle programs are the newest type of disease management program.

THE DISEASE MANAGEMENT (DM) industry is a \$1.5 billion industry that is undergoing continual change. A major trend affecting the industry is healthcare payers searching for value in DM programs. One of the ways to search for value is a shift to “whole patient”-focused DM programs versus single-disease approaches to care. Among the lessons learned from single-disease DM programs is that few, if any, patients enter a program with only one chronic disease. On average, patients have five or more chronic illnesses. Disease management programs must be able to address all of a patient’s problems to achieve value. This move to whole-patient focused programs is blurring the lines between case management and disease management.

Requirements for proof of the return on investment (ROI) from DM programs is another trend that cannot be ignored. In the past, some companies claimed ROIs as high as 30 to one (i.e., \$30 saved for every dollar spent). Most published studies and current claims of ROI are between 1.5 to 8 percent.¹⁻³

Calculation methods for ROI are not standard and DM companies do not disclose publicly how they determine a client’s ROI. This makes it difficult for buyers to compare organizations. Most of the ROI that is publicized by the DM companies is not

determined in a randomized, controlled process. Medicare is currently running a three-year controlled program focusing on disease management for diabetes and heart failure to determine their ROI. Exhibit 1 illustrates many of the reasons DM program returns are elusive.

Payers are beginning to use a full-cost model to

Exhibit 1: Why Are Returns Elusive?

- Clinical Reasons
 - > Long-standing disease processes take time to reverse
 - > Behavioral changes are difficult
 - > Selection bias
- Data Issues
 - > Problems identifying the population
 - > Regression to the mean
- Health Plan Issues
 - > High turnover in MCO members
 - > Changes in benefit design; higher patient contribution
 - > Changes in networks
- Changes in the larger environment
 - > New technology effects
 - > Genetic drug available
- ROI may be soft dollars

determine the value of DM programs. This model says DM programs need to consider total cost, not just saved costs in one area such as medications. For example, in the past a pharmacy benefits management (PBM) company would have a disease-state management program that saved a health plan costs in terms of switching from one brand medication to another brand or generic. This would show a savings in medication costs, but perhaps inpatient days or some other component of the health spending might increase. Tracking costs in a single area does not capture everything happening with a patient. Exhibit 2 provides an example of a total cost model, dividing out sectors of care, in terms of the cost and expense, for year-to-year comparisons.

Another major area that health plans are examining and thus looking to DM companies for answers are ways to improve provider and/or patient behavior. Provider reimbursement increasingly will be based on performance and not upon activities. For the best outcomes, in a complex environment such as healthcare, there needs to be collaboration among all involved parties. Some have described healthcare as being an adaptive system. Using a

balloon as an example, if squeezed at one end, the other end will get larger. Unless there is control over the entire balloon—or healthcare system—the best value is not being achieved.

The most important link in the healthcare outcomes chain is the patient. In the past, DM programs concentrated on patterns of care. Few programs really looked at the patient or how the patient might be used as a team member for decision-making. Many companies are spending considerable time and research trying to understand the healthcare consumer. Techniques and tools that help the patient develop self-efficacy and discrepancy in their decision-making are very important and vital to patient-centered programs (see Exhibit 3). Discrepancy is bringing the patient to a decision-making conclusion based on what the patient believes is best for him or her. Instead of being told to stop smoking, the patient is stepped through a process where he or she can weigh the pros and cons of a decision. Patients are more likely to be motivated to take action if they make decisions rather than being told what to do.

Health IQ is an example of a cure-management

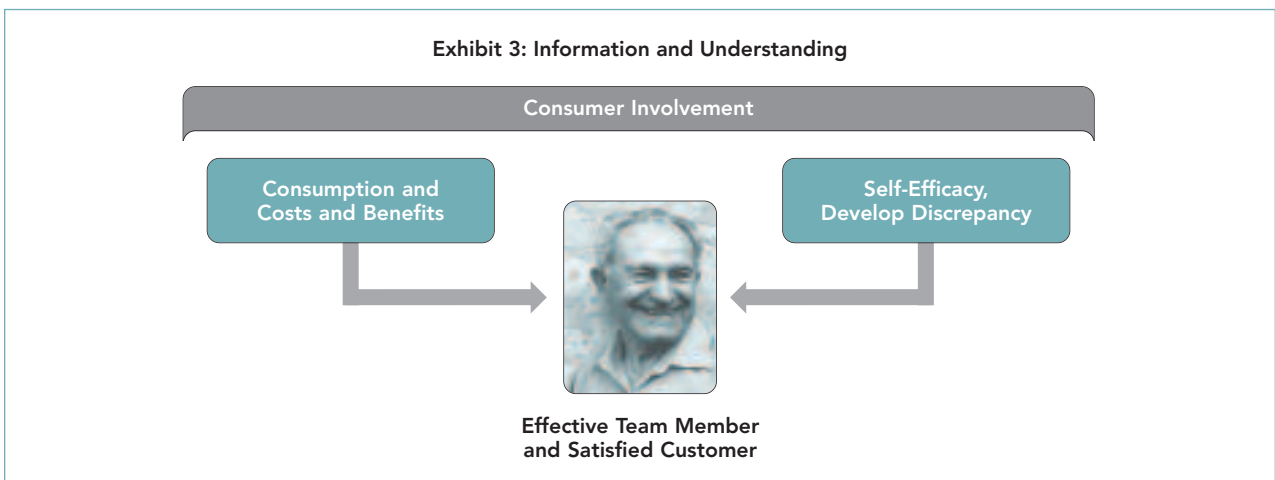
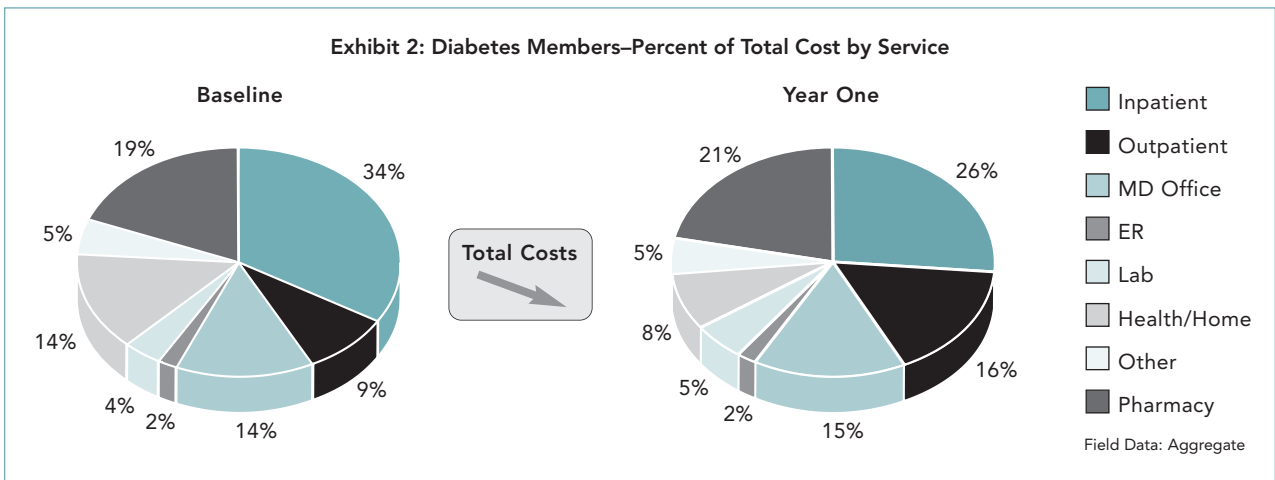
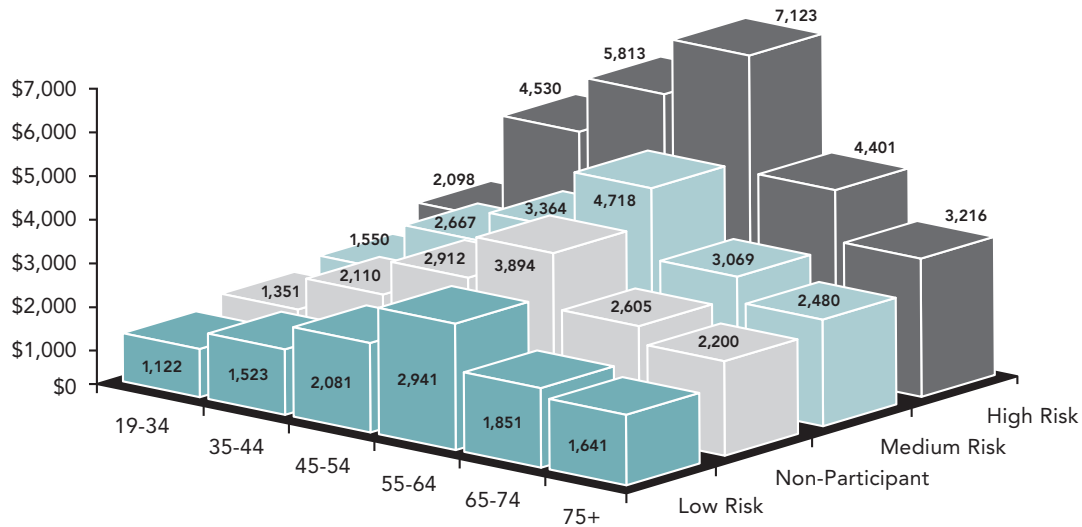


Exhibit 4: Costs Associated with Risks
Medical Paid Amount x Age x Risk⁴



program that is directed toward the consumer. But for this type of program to be truly effective, there must be incentives to motivate participants. With new patient-focused programs, there will be easy-to-achieve improvements in care early in the program. When DM programs first began, cost savings and care improvements were easy to achieve because of inconsistencies of guidelines and care. The same will be true for patient-centered DM programs. Small lifestyle changes can have a major impact in terms of a person's health and, subsequently, on the costs that he or she incurs. Most consumers do not have the right information or enough information to make appropriate healthcare decisions. Additionally, the majority of common diseases or the conditions that lead up to common illness are preventable. If people were better informed, exercised more, smoked less, and ate the right foods, there would be far fewer patients with chronic conditions.

Wellness or lifestyle programs have implications in terms of reducing healthcare cost. Exhibit 4 illustrates population health risk and the associated costs. As risk level increases from low to high, costs increase and the opposite is also true.⁴ As population health risk factors are reduced, true cost savings are possible. Those cost savings do not necessarily have to come in 10 or 20 years. They can be achieved in the short term.

Most employers are not aware of how much risk is present in their employee population, nor are the employees aware. Among 12,000 people who completed a health risk assessment (HRA) and work place medical examination, a significant number did not know their health risk factors (see Exhibit 5).

Exhibit 5: The Great UnKnown—Abundant Risk

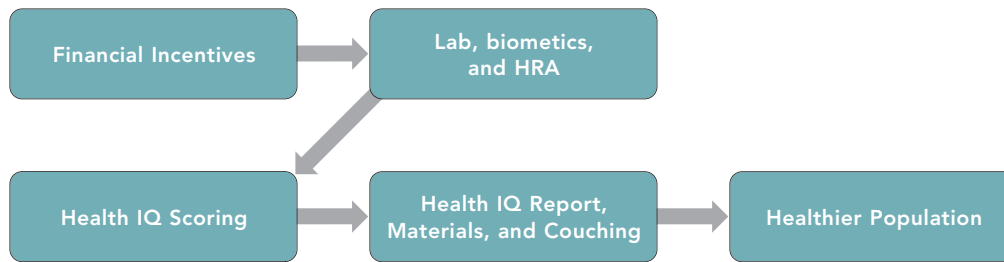
From a random sample of 12,000 participants who completed a HRA and Worksite Medical Exam:

- > 74% could not self-report their cholesterol, blood pressure or body fat
- > 60% reported not having a primary care doctor
- > 33% self-reported "good or excellent" self-perception of health but had 3+ clinical risk factors
- > 28% self-reported "good eating habits" but had dangerous blood cholesterol levels

Exhibit 6 illustrates how an example consumer-oriented wellness program might work. This program is driven by incentives. If employees participate in the program, they receive a discount on their healthcare benefits. Each participant has laboratory work and a health risk assessment completed. The participant is given a health risk score based on objective data (e.g., tobacco use, lipid profile, glucose, body mass index, and body fat). Based on the health risk score, the participant receives reports and educational materials and is given access to coaches to improve his or her score for the next round of testing. The first-year employees are offered incentives for participating. After the first year, employees are only allowed the incentives if they score at a specific risk level or if they are showing progress moving toward that risk level.

There are some definite benefits of a consumer-oriented wellness program. In addition to cost savings, these programs lead to a more educated, healthy consumer. Participants are aware of their

Exhibit 6: Basic Program Flow



health risks and feel better able to actually make changes. Other benefits include early detection of treatable conditions, improved primary care usage, more appropriate lifestyle/behavior choices, and improvement in modifiable risk factors.

In addition to looking for value and implementing consumer-oriented programs, more health plans are looking to implement or strengthen their specialty pharmacy disease management programs. The products, primarily biologics and injectables, handled by specialty pharmacies are the most costly of all medications. These medications can cost anywhere from \$10,000 per year to \$100,000 or more. A significant number of biologics are becoming available for more common, chronic diseases such as rheumatoid arthritis. As the number of specialty medications grows, this area is gaining more attention. In the past, these products were primarily for rare diseases and, although expensive, were a very small percentage of a health plan's spending.

Several miscellaneous trends are having an impact on not only DM but also all of managed care. These include the rise of consumer-driven health plans such as health savings accounts, the overwhelming burden of chronic diseases, and technology developments.

In response to rising healthcare costs, more employers are offering health savings accounts (HSAs). There are currently more than six million people with HSAs and this number is growing rapidly. This trend is going to have a significant impact on all of healthcare because it is pulling the healthiest people out of the insurance pool. By removing money from the insurance pool, there will be a shortfall of dollars to pay for the care of the sick. HSAs, being consumer-driven health plans, provide an opportunity for DM companies to provide education about wise healthcare dollar choices.

Another issue is primary care providers being overwhelmed with chronic care. A study from Duke University modeled the demographics of the average general practitioner in the United States' patients and their top 10 conditions. To follow the recommended guidelines for only those chronic diseases would take

every one of the primary care doctors in the United States 10.6 hours per day just to deal with those issues.⁵ Based on this model, chronic care cannot be successfully done in a physician's office. It has to be done somewhere else. Whether this will be within a disease management or case management program or other alternative site is unknown.

Changing technology also is affecting the industry. There are many new tools to begin changing patient and provider behavior. Electronic medical records, web-based education and monitoring programs, and electronic practitioner report cards are just some of the technologies that are having an impact.

Conclusion

Several significant trends are affecting disease management program providers and those who contract with them. These trends present both opportunities and challenges. **JMCM**

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Thomas Morrow, MD, is president of the National Association of Managed Care Physicians (NAMCP) and has more than 20 years' experience as a managed care executive. He has also served as an NCQA surveyor overseeing disease management programs such as inflammatory arthritis, depression, chronic pain syndrome, and multiple sclerosis, as well as common chronic disease.

Dexter Shurney, MD, MPH, MBA, is vice president/national business medical director, Healthways Inc.

Disclosure

Dr. Morrow is president of NAMCP and serves as a consultant and/or is on the speakers' bureaus for Abbott Laboratories, Amgen, Aventis, Bristol-

Myers Squibb, Centocor, Genentech, Genzyme, Novartis, Teva, Wyeth, and several other pharmaceutical organizations. Dr. Shurney is an employee of Healthways Inc., which provides services on the presented topic.

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POST TEST

INSTRUCTIONS

Read the article, answer the post test questions, complete the evaluation form, and submit to Ann Patrick either by fax 804-747-5316 or mail: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

1. In the search for value, disease management programs need to shift from single disease state focus to a whole patient focus.

- a. True
- b. False

2. Due to the lack of a randomized, controlled process in determining ROI on a DM program, it is difficult to for the buyer to make quality comparisons.

- a. True
- b. False

3. In keeping the patient as an important link in the process, health plans are looking to DM companies to provide methods and changes in patient behaviors.

- a. True
- b. False

4. Disease management is a patient-centric, total cost model and should include incentives for improved behavior.

- a. True
- b. False

5. Measuring return on investment for disease management programs remains elusive due to:

- a. Clinical reasons
- b. Data issues
- c. Health plan issues
- d. All of the above

6. With wellness/lifestyle programs, healthcare cost savings can be achieved in the short term.

- a. True
- b. False

7. Health Risk Assessments can provide both the employee and employer with the degree of health risks present.

- a. True
- b. False

8. Consumer-oriented wellness programs can provide:

- a. Early detection of treatable conditions
- b. More appropriate lifestyle and behavior choices
- c. Improvement of modifiable risk factors
- d. Improved primary care usage
- e. All of the above

9. Health Savings Accounts will impact healthcare by pulling the healthiest people out of the insurance pool.

- a. True
- b. False

10. Other trends impacting managed care and disease management are:

- a. Consumer-driven health plans
- b. Overwhelming burden of chronic diseases
- c. Development of technology
- d. All of the above

11. New tools available now to begin changing patient and provider behavior include:

- a. Electronic Medical Records
- b. Practitioner report cards
- c. Web-based monitoring programs
- d. All of the above

DISEASE MANAGEMENT ANSWER SHEET

There is only one correct answer per question.
Circle your answers clearly.

1. a b

2. a b

3. a b

4. a b

5. a b c d

6. a b

7. a b

8. a b c d e

9. a b

10. a b c d

11. a b c d

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1. Please evaluate this activity based on the following scale:

4 Excellent 3 Good 2 Fair 1 Poor

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4 3 2 1

Activity was free of bias

4 3 2 1

Activity content was understandable

4 3 2 1

Presenters were free of bias

4 3 2 1

Method of learning was beneficial

4 3 2 1

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New Treatments for Chronic Inflammatory Disease

Arthur Kavanaugh, MD

A continuing medical education activity sponsored by NAMCP

Summary

Rheumatoid arthritis is an excellent model for discussing chronic inflammatory disease pathology and new treatments. A progressive disease, rheumatoid arthritis can cause significant disability that increases the costs related to the disease. New treatments such as tumor necrosis factor inhibitors, and T-cell modulators are proving to be valuable not only in symptomatic improvements but also in reducing progression of disease and preserving functional ability for many patients.

Key Points

- Rheumatoid arthritis is a progressive, disabling disease.
- Unlike older medications, new treatments are changing the treatment paradigm by being true disease modifiers.
- Although these agents are not yet a cure, with each new agent comes improved targeting of the underlying pathologic process.

RHEUMATOID ARTHRITIS (RA), which is the most common of the autoimmune diseases, can be used as a model when discussing chronic inflammatory diseases. Much of the information about the treatment of RA is applicable to other chronic inflammatory diseases, specifically Crohn's disease, psoriatic arthritis, and a number of others that are less common. Not only is the underlying pathophysiology similar, but also, and more importantly, the rationale for and development of new therapies is similar.

Three factors have been driving new pharmaceutical developments in the area of chronic inflammatory diseases. One is a better understanding of the underlying immunopathophysiology of these diseases. The second is an unmet clinical need; older treatments did not significantly alter the course of the diseases. The third factor is developments in biotechnology, primarily the ability to produce molecules that target the specific pathologic abnormalities.

Overview of Rheumatoid Arthritis

RA is relatively common, occurring in about 1 percent of the population. Women have RA more often than men, with the peak age of onset between 40 and 60 years of age.

The patient with RA has inflammation of synovial or diarthrodial joints. This usually presents in the small joints of the hands and feet. Untreated, joint inflammation can rapidly progress to joint destruction. One of the fundamental changes in RA treatment that has happened over the past couple of decades is a better understanding of what happens in the joint with this disease. Exhibit 1 illustrates what happens within a joint affected by RA in the early and late stages of the disease.¹

The natural history of rheumatoid arthritis is progression of damage (see Exhibit 2).² Joint pain, destruction, and dysfunction can lead to significant disability. As disability increases in the patient with RA, medical costs rise (see Exhibit 3).³

Although RA is a progressive disease, not every patient progresses at the same rate. Some patients have more severe disease and progress rapidly. There are surrogate markers that can help predict which patients should be treated more aggressively because of the possibility of rapid progression. These markers include such things as level of functional impairment, degree of joint damage at the time of diagnosis, and extra-articular disease (systemic manifestations). RA, like other chronic inflammatory diseases, is a systemic disease affecting more than just joints.

Exhibit 1: Rheumatoid Arthritis—Early and Late Progressive Changes¹

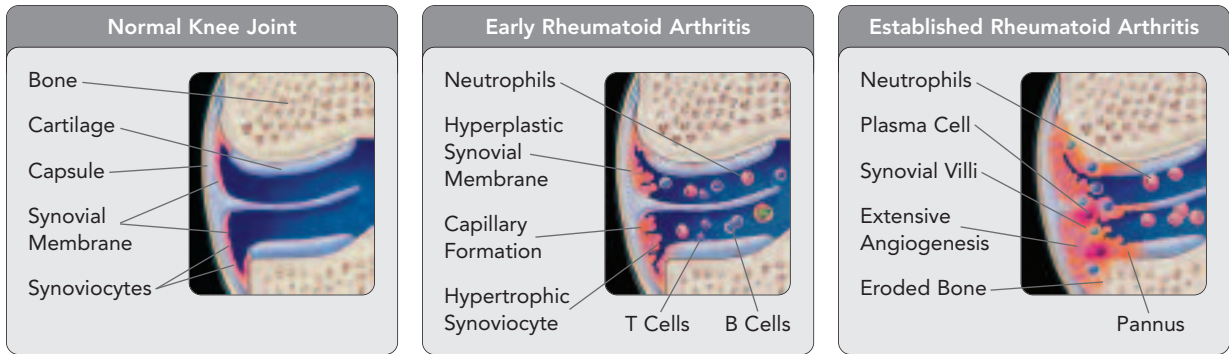


Exhibit 2: RA Is a Progressive Disease²

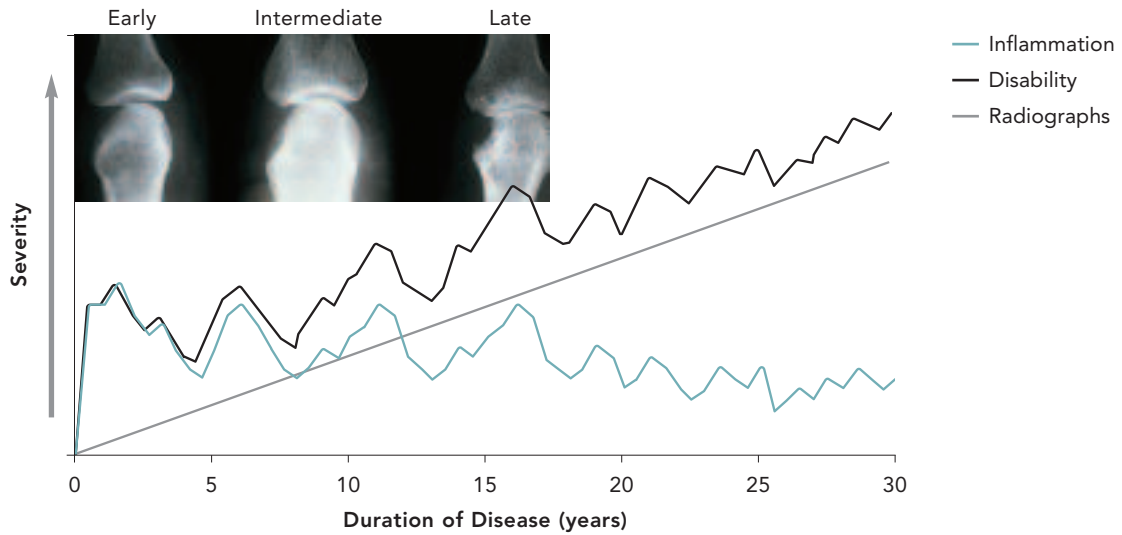
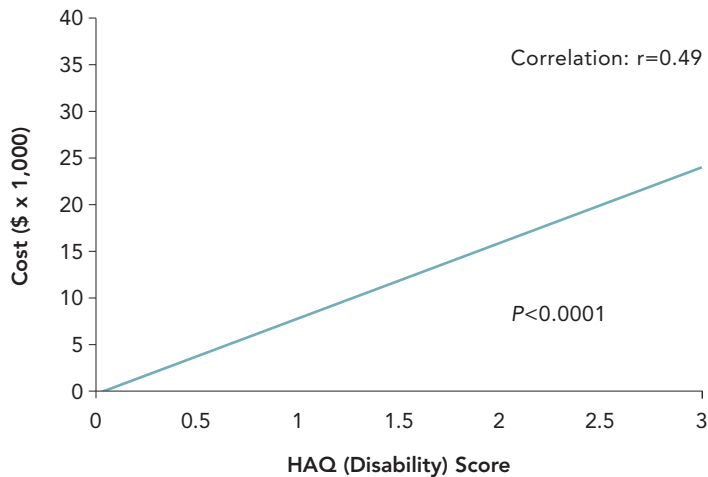


Photo: Copyright © American College of Rheumatology

Exhibit 3: Costs Rise with Increasing Disability³



Treatment

The goals of therapy in RA are:

- Prevent joint destruction, loss of joint function, deformity, disability, and early death
- Preserve quality of life
- Relieve symptoms, including fatigue, pain, swelling, and stiffness
- Achieve clinical remission.

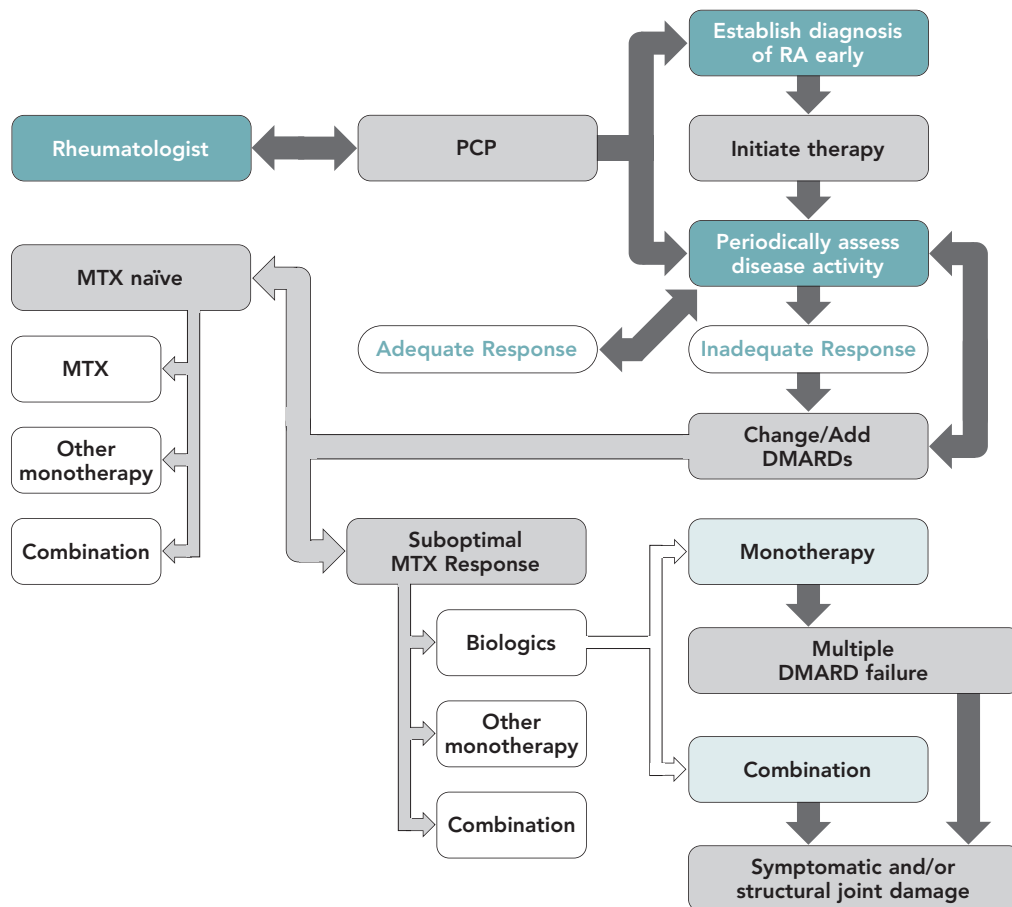
Traditionally, RA has been treated with many different classes of medications. Adjunctive therapy to manage pain includes nonsteroidal anti-inflammatory agents and corticosteroids but these agents do not change the course of the underlying disease. A mainstay of treatment for years has been disease-modifying anti-rheumatic drugs (DMARDs). Methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine are the most commonly used agents. Gold, azathioprine, minocycline, and cyclosporine are less frequently used. Although named disease-modifying agents, these medications do not directly target the immune abnormalities of RA or other chronic inflammatory diseases. They appear to have either anti-inflammatory

activity, nonspecific immune suppressant activity, or a combination of both. These agents can help improve disease symptoms and some can modestly impact progression of joint damage but very seldom put people into remission.

The treatment paradigm of RA changed with the introduction of biologic agents that are specially targeted to the immune system alterations. Three types of biologics are currently available: tumor necrosis factor (TNF) inhibitors (etanercept, infliximab, adalimumab); interleukin-1 (IL-1) inhibitors (anakinra); and T-cell modulators (abatacept). The available interleukin-1 inhibitor is not as effective as the TNF inhibitors, so it is not discussed here.

Treatment guidelines from the American College of Rheumatology (ACR) are given in Exhibit 4.⁴ Methotrexate is still considered a mainstay of RA therapy. This agent is usually the initial disease modifying therapy started but biologics are beginning to be used earlier in the treatment scheme. Early, aggressive treatment to get the disease under control appears to be the most important issue in preventing

Exhibit 4: ACR Treatment Algorithm⁴



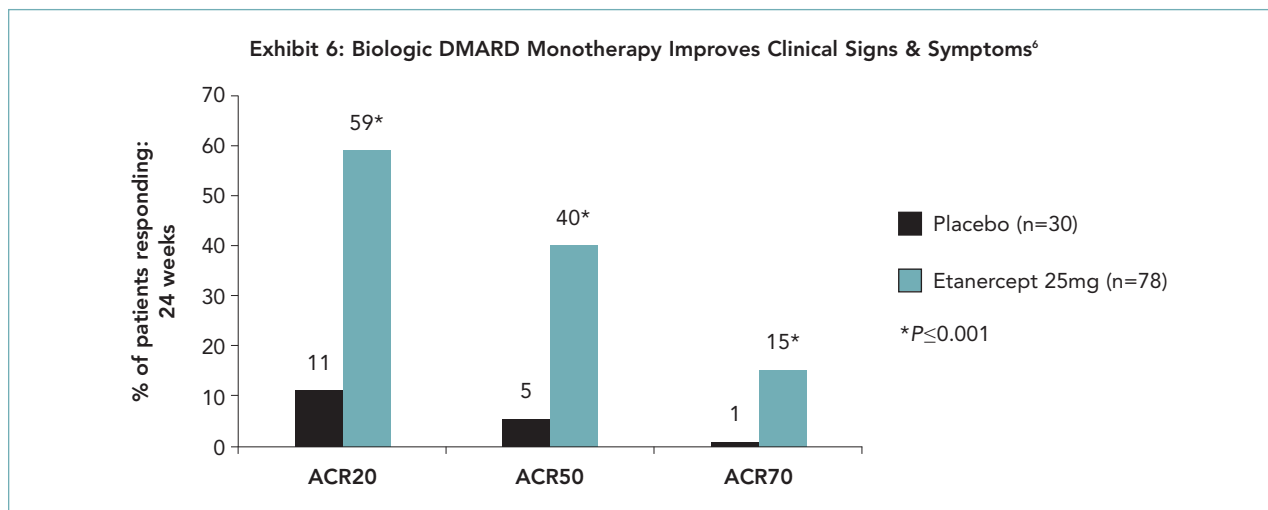
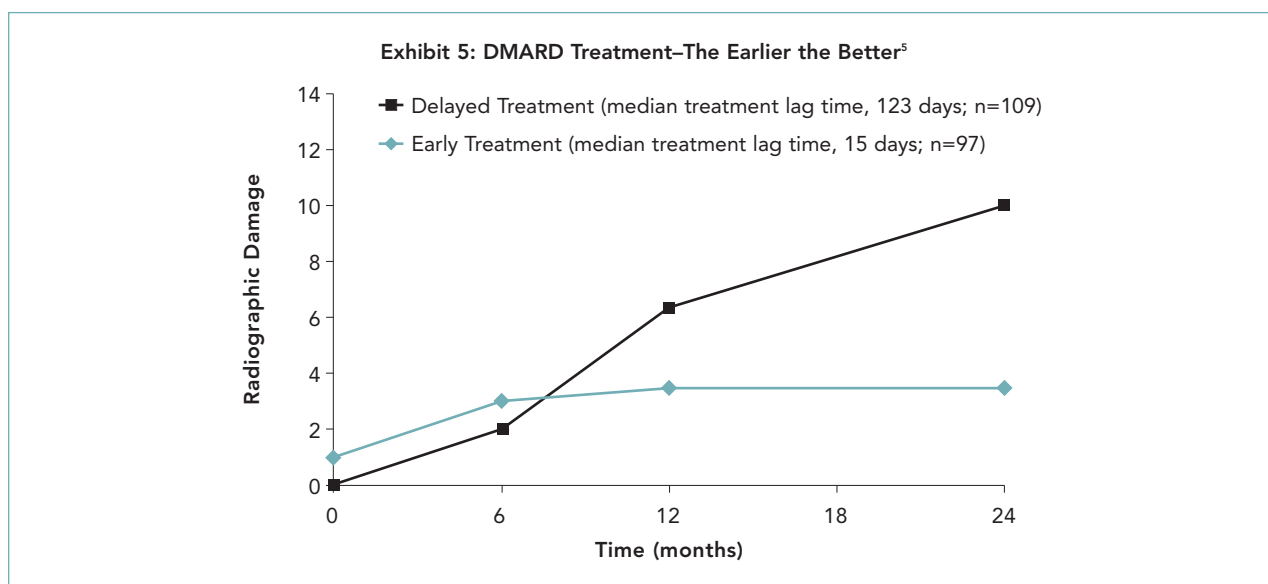
joint damage rather than which medication is used first (see Exhibit 5).⁵ The majority of the joint damage that occurs with RA happens in the first few years.

RA, psoriasis, and inflammatory bowel disease are thought to be caused by an imbalance in cytokines. Cytokines are small proteins that have myriad actions in the body. In patients without disease, there is a balance between opposing cytokines. For example, there is a balance between inflammatory and anti-inflammatory factors. In patients with disease, there is excess activity of inflammatory cytokines that is not compensated by the bodies naturally occurring down regulators. Biologics agents reestablish the balance.

TNF is thought to be a central cytokine, which directs the activity of other cytokines. Most patients respond to TNF inhibitors with a reduction in signs and symptoms and some achieve remission of their disease. Clinical efficacy with the TNF inhibitors requires continued therapy. These agents are not a

cure; when they are stopped, disease symptoms return because the imbalance returns.

Studies have shown that these agents have significant effects on slowing disease progression as evidenced by X-ray examination, improving quality of life, and preserving functional status. In an early study of etanercept versus placebo, 59 percent of the subjects achieved an ACR20 response, 40 percent an ACR50 response, and 15 percent an ACR70 response (see Exhibit 6).⁶ The efficacy of agents for RA is evaluated primarily using the American College of Rheumatology (ACR) core criteria for response (ACR20, ACR50, and ACR70), functional measures, and radiographic evidence of joint changes. The items measured in the ACR criteria include tender joint count (TJC), swollen joint count (SJC), patient's assessment of pain, patient's and physician's global assessment of disease activity, patient's assessment of physical function, and laboratory evaluation of one



measure of inflammation (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]). An ACR20 response is defined as a 20 percent improvement in TJC and SJC and 20 percent improvement in three of the five remaining ACR core set measures.⁷ The ACR50 and 70 responses are defined in the same manner as the ACR20, but with improvements in 50 percent and 70 percent, respectively.⁷ The goal of these measurements was to standardize outcome assessments in clinical trials. ATTRACT was the first study to demonstrate that a combination of a TNF inhibitor, infliximab, and methotrexate slowed radiographic progression of RA (see Exhibit 7).^{8,9} Patients on this combination had very little to no progression. Data

from a study of adalimumab in conjunction with methotrexate demonstrates the ability of TNF inhibitors to reduce disability (see Exhibit 8).¹⁰

A combination of a TNF-inhibitor with methotrexate is the current gold standard for RA treatment because this combination is synergistic. In cases where one TNF inhibitor is not effective, a growing body of data suggests switching from one to another is a reasonable strategy. TNF inhibitors are also effective in ankylosing spondylitis, psoriasis, psoriatic arthritis, and Crohn's disease. They are being tested for treatment of other chronic inflammatory diseases.

Studies have found TNF inhibitors ineffective in

Exhibit 7: Biologic DMARD + MTX Combination Slows Radiographic Progression^{8,9}

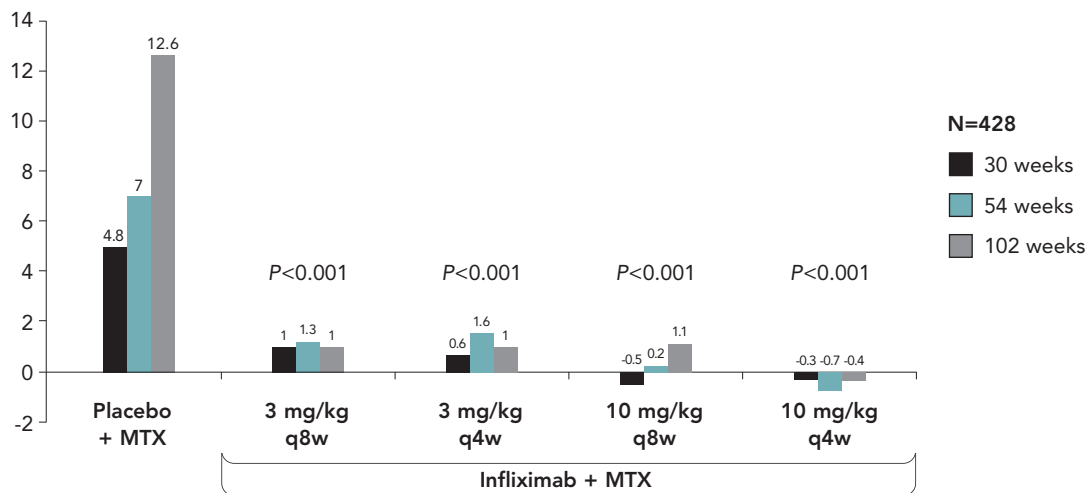
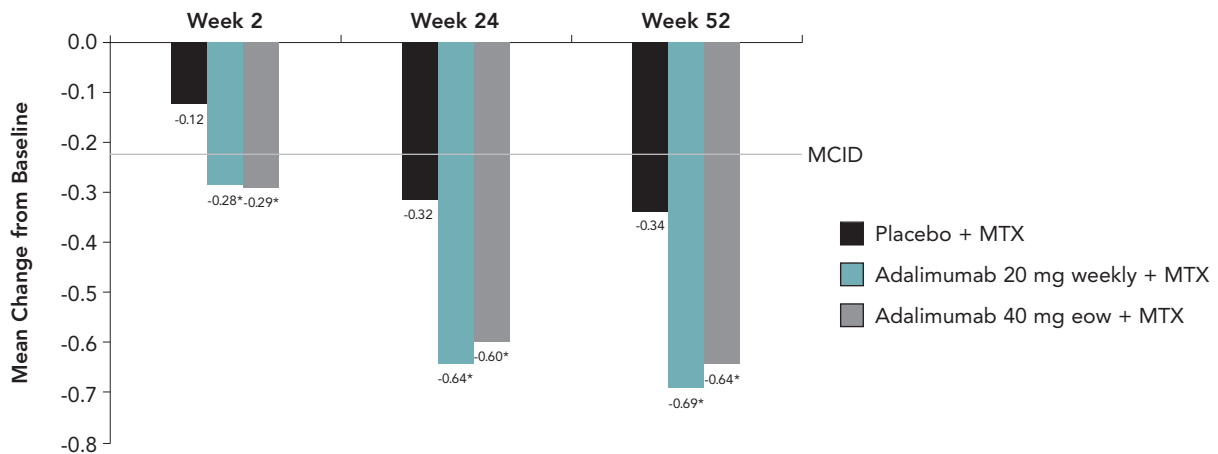


Exhibit 8: Biologic DMARD + MTX Combination Reduces Disability¹⁰



heart failure, Wegener's granulomatosis, polymyalgia rheumatica, and temporal arteritis.

TNF inhibitors do have some significant adverse effects. Some agent-related effects are injection site or infusion reactions. The majority of serious adverse effects are related to blocking TNF. TNF, being important in inflammation, has some beneficial aspects. One of these is protecting the body from invading organisms. Opportunistic infections (e.g., tuberculosis) are of particular concern. The patients selected for treatment with biologic agents tend to have the most severe disease and have a higher risk of infection irrespective of the treatment chosen. Data suggests that this prior risk is increased by treatment with TNF inhibitors.¹¹ Patients treated with biologics need to be closely monitored for infection development.

Additionally, demyelinating conditions, hematologic abnormalities, congestive heart failure, possible increased risk of lymphomas, and autoantibodies can all result from blocking TNF. Autoantibodies are antibodies against the patient's DNA. Although greater than 40 percent of patients treated with TNF inhibitors will develop some type of autoantibodies, these do not seem to be relevant clinically. A few people do get lupus-like syndromes, but this is rare.

Obstacles to Curing RA

Despite the availability of new, highly effective, targeted therapies that provide unprecedented opportunities to treat rheumatoid arthritis, major obstacles still stand in the way of a cure. These include 1) a lack of knowledge of the etiology of the disease, 2) a lack of means to intervene in the most relevant disease processes, 3) the inability to make an early diagnosis, and 4) limited ability to recognize those at risk for significant disability. Although data have long hinted that bacteria, viruses, nonspecific inflammation, and autoantibodies might be pathogenic factors in at least some cases of RA, the basic mechanisms that initiate and sustain this disease remain elusive. Even the most advanced therapies currently available appear to suppress relatively peripheral pathways of inflammation and not central abnormalities of cell function that underlie the disease. The considerable clinical, pathological, and immunological heterogeneity of RA may also influence the capacity to induce remission. By the time physicians are able to spot clinical signs of the disease, it is probably too late to bring tissues back to normal. One of the most important obstacles is an inability to detect the earliest events that lead to the development of persistent, destructive synovitis.

The Newest Agent

One promising agent that reached the market in 2006 for RA is abatacept (Orencia). This agent selectively modulates antigen-specific autoimmune T-cell activation. Existing autoimmune T-cells are induced by this agent to quit working. A decrease in autoimmune T-cell activation reduces amounts of inflammatory cytokines, such as TNF and IL-1. Abatacept appears to interrupt the autoimmune response underlying RA, both at initiation and at the established stage. This agent has been shown to slow progression of structural damage and to significantly improve symptoms and quality of life even in patients who did not respond to TNF inhibitors.¹²

Conclusion

RA, along with other chronic inflammatory diseases, has a significant impact on patients' lives. New treatments currently available are revolutionizing the treatment of chronic inflammatory diseases by better targeting the underlying pathologic processes. **JMCM**

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Faculty

Arthur Kavanaugh, MD, is director of the Center for Innovative Therapy and a professor of medicine in the Department of Rheumatology, Allergy, and Immunology at the University of California-San Diego.

Disclosure

Dr. Kavanaugh has no real or perceived financial relationships that present a conflict of interest.

Accreditation

The National Association of Managed Care Physicians (NAMCP) is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. NAMCP designates this activity for a maximum of 1 AMA PRA Category I credits™. Each physician should claim credit commensurate with the extent of their participation in the activity.

The American Association of Managed Care Nurses (AAMCN) has been approved as a provider of continuing education by the Virginia Nurses

Association (VNA) for the period of Jan. 1, 2004, to Dec. 31, 2006. VNA is accredited as an approver of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation. Nurses who complete this activity will be awarded 1.2 contact hours.

This activity has been approved by the American Board of Managed Care Nursing for 1.2 contact hours toward CMCN recertification requirements.

This activity was held live at the NAMCP Spring Managed Care Forum. This activity is valid from Sept. 1 to Dec. 31, 2006.

POST TEST

INSTRUCTIONS

Read the article, answer the post test questions, complete the evaluation form, and submit to Ann Patrick either by fax 804-747-5316 or mail: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

1. The factors driving new developments in chronic inflammatory disease are:

- a. Understanding the immunopathophysiology of these diseases
- b. Ability to produce molecules that target specific abnormalities
- c. Requests from patients
- d. Unmet needs by older treatments
- e. A, B, D
- f. A, C, D

2. In the natural progression of RA, joint pain, destruction, and dysfunction can lead to significant disability.

- a. True
- b. False

3. Surrogate markers can help clinicians predict which patients to treat more aggressively.

- a. True
- b. False

4. Therapy goals for RA include:

- a. Prevention of joint destruction
- b. Achieve clinical remission
- c. Preserve quality of life
- d. Relieve symptoms
- e. All of the above

5. DMARDs impact the progression of joint damage, improve symptoms, and some can place patients in remission.

- a. True
- b. False

6. An imbalance of cytokines is the cause of RA, psoriasis and inflammatory bowel disease.

- a. True
- b. False

7. Health Risk Assessments can provide both the employee and employer with the degree of health risks present.

- a. True
- b. False

8. Through continued therapy of TNF inhibitors most patients have a decrease in symptoms and achieve remission.

- a. True
- b. False

9. Combination therapy of TNF inhibitor and methotrexate demonstrates a reduction in disability and is considered the gold standard for RA.

- a. True
- b. False

10. Obstacles to a cure for RA include:

- a. Inability to recognize patients at risk for RA
- b. No means to intervene in the relevant disease processes
- c. Inability to make early diagnosis
- d. Lack of knowledge of the etiology of RA
- e. All of the above

CID ANSWER SHEET

There is only one correct answer per question.
Circle your answers clearly.

1. a b c d e f

2. a b

3. a b

4. a b c d e

5. a b

6. a b

7. a b

8. a b

9. a b

10. a b c d e

ACTIVITY EVALUATION

1. Please evaluate this activity based on the following scale:

4 Excellent 3 Good 2 Fair 1 Poor

Activity met my expectations

4 3 2 1

Activity was free of bias

4 3 2 1

Activity content was understandable

4 3 2 1

Presenters were free of bias

4 3 2 1

Method of learning was beneficial

4 3 2 1

I will change my practice patterns by (please specify):

My practice patterns will not change.

Name: _____

MD DO Other _____

Mailing Address: _____

City: _____

State: _____ ZIP: _____

Phone: _____

Fax: _____

E-mail: _____

Send my certificate by:

U.S Mail E-mail

I heard about this activity from:

Colleague Internet e-News Journal

FALL MANAGED CARE FORUM

The Future of Healthcare Delivery

ATTENTION MEDICAL DIRECTORS!

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You can bring your team: Medical Directors, Nurses and others
at these special group rates!

This year's Fall Managed Care Forum will be held at:

**The Venetian Hotel
Las Vegas, NV
November 16-17, 2006**

The National Association of Managed Care Physicians (NAMCP)
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The American Association of Integrated Healthcare Delivery Systems (AAIHDS)
is dedicated to PHO's, IPA's, Health Systems, and Integrated Delivery
Systems in Managed Care

The American Association of Managed Care Nurses (AAMCN) is dedicated to
Nurses, Case Managers, and Care Managers in Managed Care

Please visit namcp.org, aaihds.org, and aamcn.org to join!

FALL MANAGED CARE FORUM 2006

Conference Program

WEDNESDAY, NOVEMBER 15

8:00 am - 12:00 noon

American Board of Managed Care Nursing (ABMCN) Examination

Ensure you are on the leading edge of success in the nursing profession. Become a Certified Managed Care Nurse (CMCN)! Applications must be received and eligibility requirements met by October 1, 2006. For more information go to www.abmcn.org.

12:00 noon - 2:00 pm

Registration Information Desk Open

1:30 pm - 2:30 pm

American Association of Managed Care Nurses (AAMCN) Pre-Conference Workshop: Facilitating and Mentoring During Transitional Change

LaNita Knoke, RN, BS, CMCN, Director, AAMCN Leadership Institute; Director of Clinical Operations, Ancillary Care Management

Are you and your staff facing challenges from organizational changes and/or mergers? This presentation will provide you with the tools and information you need to succeed. Discover how organizational change can impact employee productivity and patient outcomes. You will learn to recognize that change is a good motivator. Also, you will learn to determine the best method to mentor and to be mentored.

2:30 pm - 2:45 pm

Break

2:45 pm - 3:45 pm

AAMCN Pre-Conference Workshop

Integrated Case Management for Medicare and Medicaid Programs

Mary Krentzman, MS, RN, Vice President Clinical Operations, Enhanced Care Initiatives

A focus on the combination of hands on and call center care coordination for this difficult population. The presenter will also discuss how all of this needs to be coordinated with the managed care organization and/or health plan.

3:45 pm - 4:45 pm

AAMCN Pre-Conference Workshop

Integration of Hospital Case Management with Hospitalist Programs

Michelle Martin, BSN, MHSA, CPHQ, CMCN, CCM, President, AAMCN; Director of Operations, Nevada Market, TriCity Medical Associates, Director of Case Management, North Vista Hospital

Why do hospitals decide to implement hospitalist programs? Discover five reasons why a hospital medical management program improves patient outcomes and physician satisfaction. Gain insight into appropriate communication and evaluation techniques to integrate case management into hospitalist programs.

5:30 pm - 7:00 pm

Registration Information Desk Open

THURSDAY, NOVEMBER 16

7:00 am - 4:30 pm

Registration Information Desk Open

7:00 am - 8:00 am

Continental Breakfast

8:00 am - 8:15 am

Opening Remarks and Welcome

Doug Chaet, FACHE, Chairman, AAIHDS, Vice President, Managed Care, Shands Healthcare

KEYNOTE ADDRESS

8:15 am - 9:30 am

The Future of Managed Care and Healthcare Delivery

Jacque Sokolov, MD, Chairman and Senior Partner, SSB Solutions

Maximize this opportunity to discover what the future of healthcare holds from one of the nation's leading healthcare consultants. Be there to get the latest information on lessons learned, the current market trends, and strategies for your success.

9:30 am - 10:00 am

Break and Networking

GENERAL SESSIONS

10:00 am - 11:00 am

CMS Issues and Updates

David Sayen, Associate Regional Administrator, CMS

Mr. Sayen will deliver a comprehensive overview of what providers can expect from CMS over the coming year. Areas to be addressed include the Center's organizational goals, initiatives affecting provider reimbursement and pertinent upcoming demonstration projects.

11:00 am - 12:00 noon

Healthcare Antitrust: Policy Enforcement Actions and Trends for Physician Integration and Managed Care Contracting Strategies

Jeffrey Spigel, Partner, King & Spalding, LLP

This presentation will cover recent policy and enforcement decisions made by the Federal Trade Commission and the Department of Justice. Discover the effect those actions have had on strategies for dealing with commercial payors. Learn future trends, the steps that commercial payors are taking to place downward pressure on providers' reimbursement rates and how to increase your negotiating leverage with commercial payors in a lawful manner.

12:00 noon - 1:00 pm

Lunch and Networking

12:00 noon - 1:00 pm

PHO/IPA Roundtable and Lunch

PHO and IPA leaders are invited to participate in a facilitated discussion covering best practices, challenges and opportunities facing PHOs and IPAs today. Topics include chronic disease registries, partnering with pharmaceutical companies, the changing marketplace and clinical integration. Enjoy your lunch and share your ideas. Facilitated by John M. Harris, MBA, Partner, DGA Partners

CONCURRENT TRACK SESSIONS

1:00 pm - 2:00 pm

Internal Revenue Cycle Yields Collections Improvements

Gary Lewins, FHFMA, CPA, Manager, Wipfli, LLP

During this session you will learn how to implement internal revenue cycle improvements. Internal processes are defined as being completely within the control of the practice. The simple steps described

are in five "high potential areas" that many practices struggle to manage effectively. In addition, this session will provide details of how to get started and sustain improvement.

Metastatic Colorectal Cancer and New Therapies

Alan P. Venook, MD, Professor of Clinical Medicine, University of California - San Francisco

Discover how new therapies can affect patient outcomes during the natural progression of metastatic colorectal cancer.

2:00 pm - 2:30 pm

Break and Networking

2:30 pm - 3:30 pm

Margin Alert: Time to Revisit Your Outpatient Strategy

Steven M. Abramson, Senior Manager, Ernst & Young, LLP

Are you prepared for a drop in managed care outpatient rates? The competition is heating up and that may drive your profit margins down. Find out how to prevent a decrease in your margin.

Integrating Advanced Wound Care Therapy as a Key Component of Diabetes Disease Management

Peter Sheehan, MD, Glamoria Powell, RN, Diabetes Center of Greater New York and Glenn Donovan, DPM, Medical Director, GHI New York

The incidence of diabetic ulcers is reportedly increasing 14% per year and the lifetime risk of diabetic foot ulcers may be as high as 25% and lead to lower extremity amputations. Annual costs for limb amputation related to diabetic wounds exceed \$350 million. Accordingly, this presentation will provide clinician and payer perspective on the methods and benefits of effective management of diabetic patients with wound-related complications.

3:30 pm - 4:30 pm

Physician Integration Strategies: How to Successfully Recruit and Retain Your Most Expensive Asset

Arthur W. Saunders, Partner, Wipfli LLP

This session will review keys to successfully recruit physicians with a focus on how to appropriately compensate them initially and long term. The most commonly used compensation formulas and models will be discussed and analyzed. You will learn what works and what does not work when negotiating compensation with physicians, and how to develop physician alignment to organizational goals through compensation.

Leveraging Data to Strengthen Your PHO/IPA

John Harris, MBA, Partner, DGA Partners

Successful PHOs and IPAs are using data to provide real value and establish a strong market position. Everyone agrees that data is critical to improving quality and maintaining cost. But sometimes we assume that we cannot obtain and use data effectively. Big or small, every PHO or IPA can capture and use data to its advantage. Possible data strategies include electronic medical record initiatives, chronic disease registries, claims data warehouses and pharmacy data. Learn how to choose the right data strategy to provide critical strength to your PHO or IPA.

Diagnosis and Management of HBV in Managed Care

Steven Flamm, MD, Associate Professor of Medicine, Medical Director, Liver Transplantation, Feinberg School of Medicine, Northwestern University

More than 2 billion people worldwide have been infected with the Hepatitis B virus. This presentation will review the importance of identifying and managing patients at risk of Hepatitis B. Treatment modal-

ities will be highlighted and the impact of anti-viral therapy will be discussed. The presentation will review the latest diagnosis and treatment guidelines and will emphasize the importance of screening persons at high risk for infection.

4:30 pm - 6:00 pm

Reception and Networking

FRIDAY, NOVEMBER 17

7:00 am - 4:00 pm

Registration Information Desk Open

7:00 am - 8:00 am

Continental Breakfast

GENERAL SESSION

8:00 am - 9:30 am

Leveraging Health Risk Assessments for Maximum Effect

Dexter W. Shurney, MD, MBA, MPH, Chief Medical Officer, Healthways

Discover the role of Health Risk Assessments (HRAs) as part of an effective patient wellness and prevention program. Learn the positive effect of incentives and health risk reduction and new designs on benefits to drive patient outcomes.

9:30 am - 10:00 am

Break and Networking

CONCURRENT TRACK SESSIONS

10:00 am - 11:00 am

Creating a Partnership Model of Health Plan Contracting - Part One

Mike Bond, MBA, Chief Executive Officer, PrimeCare

Pinpoint your organization's strengths and weaknesses as they influence the negotiating process. Learn how to create "win-win" relationships through mutual benefit. Discover how to establish successful contract relationships by understanding the influence of non-traditional risk models, high deductible or self-directed health plans, discounted



FFS and pay-for-performance.

Acute Coronary Syndrome: Improving Outcomes

A presentation on how to improve outcomes based on when and how treatment is provided.

11:00 am - 12:00 noon

Creating a Partnership Model of Health Plan Contracting - Part Two

Mike Bond, MBA, Chief Executive Officer, PrimeCare

A continuation of the previous hour with a more in-depth look at contracting within a partnership model. This session will provide you with details and tools to accomplish advanced contracting.

Case Study - The Changing Role of a Physician-Hospital Organization: From Risk Sharing to Clinical Improvement and Integration

Peter W. Wood, MBA, Executive Director, MMC Physician-Hospital Organization

This presentation will cover the transformation of a PHO from risk sharing to P4P and CLIP (structure, process, outcomes), the critical players in support of the transition, the challenges, the financing, what worked and what didn't; the market environment; lessons learned; what's ahead and what other PHOs can do.

New Opportunities in the Treatment of Parkinson's Disease

An update on the treatment and implications of Parkinson's Disease.

12:00 noon - 1:00 pm

Lunch and Networking

GENERAL SESSIONS

1:00 pm - 2:00 pm

Benefit Design and How it Affects Medication Adherence

Michael C. Sokol, MD, MS, Medical Director, Health Management Innovations, Managed Markets Division, GlaxoSmithKline

Many factors affect patients' adherence to medications which in turn has an impact on outcomes. This presentation will examine those factors, including patient behavior and drug benefit design, and will explore the relationship between medication adherence and clinical and economic outcomes, such as medical resource utilization and total healthcare costs.

2:00 pm - 3:00 pm

Managing the Injectable Market: Barriers and Issues

Gregory Bell, Group Vice President, CRA International

This presentation will cover specialty pharmaceuticals, population, total cost vs. drug cost and other related issues including billing and coding. The presenter will discuss how to overcome barriers by looking at the big picture in this specialized market.

3:00 pm - 4:00 pm

Formulary Considerations, Beyond Acquisition Cost to Optimally Manage a Dyslipidemic Patient Population

Reducing cardiac risks through the medical management of dyslipidemia and other cardiovascular risk factors requires a major commitment of time and effort. The implications of recent trials for patient management and guideline development will be discussed targeting dyslipidemic patients with multiple cardiovascular risk factors. This presentation will provide attendees with the existing body of evidence-based literature specific to the management of dyslipidemic patient populations and provide practical recommendations to balance cost pressures with clinical outcomes.

4:00 pm

Adjourn

You Cannot Afford to Miss This Conference!

You won't want to miss this enticing program featuring dynamic speakers, thought provoking topics and a location sure to be envied by all. Whether you are interested in learning about the latest managed care trends or simply gaining fresh ideas to boost your ROI, the possibilities at the Fall Managed Care Forum are endless. Attend this conference and gain expert insight that will directly impact the success of your organization!

About the Sponsoring Organizations

AAIHDS

Established in 1993, the American Association of Integrated Healthcare Delivery Systems (AAIHDS) is a non-profit organization dedicated to the educational advancement of provider-based managed care professionals involved in integrated healthcare delivery.

AAMCN

The American Association of Managed Care Nurses (AAMCN) was established in 1994 in response to an identified need to educate nurses about managed healthcare. The AAMCN is a non-profit membership association of Registered Nurses, Nurse Practitioners and Licensed Practical Nurses including top level administrators, managers, directors and consultants associated with a variety of managed healthcare organizations.

NAMCP

The National Association of Managed Care Physicians (NAMCP) is a non-profit membership association founded in 1991 to serve the educational interests and needs of physicians working in managed care. Since physicians affect 85% of healthcare expenditures, we believe they should take a proactive role in developing the best delivery system for patients, thereby increasing quality, reducing costs and improving practice performance and clinical outcomes.

Who Should Attend

Attendees include Vice Presidents and Directors of Managed Care, Contracting and Provider Relations Managers, Medical Directors, Hospital and Health System Chief Executive Officers, Senior Management Teams, and Governing Board Members of Managed Care Organizations, and Integrated Delivery Systems such as Physician Hospital Organizations and Independent Practice Associations. Also, Executive Directors, Administrators, Case Managers, Utilization Managers, Quality Managers, Medical Management Directors and Clinical Managers associated with a variety of Managed Care Organizations.

Accommodations

The Fall Managed Care Forum will be held at The Venetian Resort, 3355 Las Vegas Boulevard South, Las Vegas, NV. To make your hotel reservations, please call 877-283-6423 prior to October 23, 2006. A special conference rate of \$199 per night has been secured. To reserve this rate, mention the Fall Managed Care Forum.

Additional Information

Email confirmation notifications will be sent to participants registering by November 1, 2006. Dress for the conference is business casual. Meeting room temperatures vary and sometimes are uncontrollable, please keep this in mind when packing. **Cancellations must be received in writing by November 1, 2006, for full credit will be applied toward any future program of equal or greater value. Registration is also transferable to an alternate attendee. We are unable to refund any registration fees.**

FALL MANAGED CARE FORUM 2006

Registration

Form can be duplicated for additional participants. One form per participant. Please print exactly as you wish your name to appear on your name badge.

First Name _____ Last Name _____

Title _____ Organization _____

Address _____ City _____ State _____ Zip _____

Phone _____ Fax _____ Email _____

Value Code _____ RN MD Other _____

Registration Fees

Registration fee includes all conference materials, pre-conference workshops, concurrent track sessions, continental breakfasts, refreshment breaks, opening night reception and lunches.

Physician/Nurse		Healthcare Executive		ABMCN Examination	
<input type="checkbox"/> Member Rate	\$495	<input type="checkbox"/> Member Rate	\$695	<input type="checkbox"/> \$295	
<input type="checkbox"/> Join and Attend	\$595	<input type="checkbox"/> Join and Attend	\$795		
<input type="checkbox"/> Non-Member Rate	\$695	<input type="checkbox"/> Non-Member Rate	\$895		

AAMCN Pre-Conference Workshops

1:30 pm - 2:30 pm

Facilitating and Mentoring During Transitional Change

2:45 pm - 3:45 pm

Integrated Case Management for Medicare and Medicaid Programs

3:45 pm - 4:45 pm

Integration of Hospital Case Management with Hospitalist Programs

Concurrent Track Sessions Thursday, November 16

1:00 pm - 2:00 pm

Internal Revenue Cycle Yields Collections Improvements
 Metastatic Colorectal Cancer and New Therapies

2:30 pm - 3:30 pm

Margin Alert: Time to Revisit Your Outpatient Strategy
 Integrating Advanced Wound Care Therapy

3:30 pm - 4:30 pm

Physician Integration Strategies
 Leveraging Data to Strengthen Your PHO/IPA
 Diagnosis and Management of Hepatitis B Virus

Concurrent Track Sessions Friday, November 17

10:00 am - 11:00 am

Creating a Partnership Model of Health Plan Contracting
 Acute Coronary Syndrome: Improving Outcomes

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- Describe methods to increase your market share for outpatient services.
- Discuss clinician and payer perspective on the methods and benefits of effective management of diabetic patients with wound-related complications.
- Evaluate linking of provider compensation to overall system profitability.
- Discuss the value of data for PHOs and IPAs.
- Demonstrate the relationship between plan design and medication adherence.
- Establish effective mechanisms for resolving problems in the ongoing management of contract relationships.
- Discover the role of the professional in developing and implementing the business development strategies as part of the organizational approach.
- Inspect the use of technology and recognition to change behavior and close the quality gap.
- Describe how HRAs impact the health of a pre-determined population.
- Describe appropriate management approached for HBV patients.

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TABLE OF CONTENTS

The Road to Value-based Healthcare:

Destination Apparent, Journey Uncertain

Eric C. Faulkner, MPH 27

New Treatments in Overactive Bladder and Implications for Managed Care

Michael Kennelly, MD, and Kenneth L. Schaecher, MD 34

Highly Active Antiretroviral Therapy (HAART) in 2006

Trevor Hawkins, MD 41

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The Road to Value-based Healthcare: Destination Apparent, Journey Uncertain

Eric Faulkner, MPH

In healthcare, the destination is apparent: improve quality and control costs. But it is the journey to that point that remains uncertain. Many stakeholders are intensely focused on identifying solutions that address the double-digit annual spending growth that has launched healthcare to the forefront of our nation's priority list. Of equal concern is that we do not have a good handle on what we truly obtain for our investment.

In the words of Tom Scully, former administrator of the Centers for Medicare and Medicaid Services (CMS): "In an era of change in which the annual healthcare budget in the U.S. exceeds the Department of Defense budget by a factor of four, it is imperative that the American public receives the greatest value for its hard-earned dollars."¹ Although the overall costs of healthcare are unlikely to go down, we can hope to improve quality and use resources more efficiently. To accomplish these goals and maintain a sustainable healthcare system, it will be necessary to develop better means of measuring *value* and aligning system incentives to reward it.

To fill this "value gap," we have embarked on restructuring efforts that will fundamentally alter systems of care. Evidence-based medicine (EBM), economic and outcomes research, and other tools are being

integrated into health reimbursement processes.² A variety of pay-for-performance approaches have emerged, offering incentives for physicians and hospitals to standardize use of technologies and services with well-established value. Health plan benefit designs are encouraging consumer selection of high-quality, cost-effective services. Evolving databases, registries, and information networks will significantly influence the way that we evaluate, monitor, and direct the use of health services in the future.

Although value is the common thread among these approaches, in reality they are a patchwork of disparate efforts—not a systematic approach to value integration. Certainly providers, payers, manufacturers, and others are moving toward collaboration, transparency, and common standards—establishing the "rules of the road" for value-based healthcare—but we are only at the beginning stages of this journey. As the vanguard advances to usher in this new value-based world, a variety of factors will influence the success and overall impact of these efforts.

A number of key issues relate to value-based healthcare, including considerations for emerging genomic and biotechnology products.

What Is Value?

For purposes of this discussion, we will consider value in the academic sense, as understood by healthcare purchasers and policy makers, as well as in the broader applied context of healthcare purchasing strategies (see Exhibit 1).

As it pertains to a particular technology or service, most purchasers of healthcare would define value as quality/outcomes divided by the cost required to obtain those outcomes. Some might think that conventional EBM enables comparative assessment of the value associated with a particular intervention, but this is not technically true. EBM can

be considered a component of "value," but it does not fully reflect value because it mainly emphasizes the clinical/outcomes portion of the value equation. Value measurement most often involves econometric methods, such as cost-effectiveness or cost-utility analysis that integrate both outcomes and cost information. Although these methods have been around for a long time, methodological and policy concerns have historically delayed broader adoption of such techniques in health decision-making. Others would argue that even these measures fall short of informing real value-based medicine because they do not adequately incorporate patient perceptions of quality or quality-of-life factors.²

Value-based purchasing (VBP) is a relatively new term. VBP emphasizes activities that aim to improve both the quality and cost of care by a) purchasing/use of health technologies or services with demonstrated value and b) applying "system controls" that encourage the desired purchasing behavior or other changes.³ In other words, VBP uses value information to influence the decision making of consumers, plans, and providers. System controls, defined broadly, can include pay-for-performance, health benefit and reimbursement restructuring, total quality improvement, and knowledge transfer. Whether VBP actually results in quality or cost benefits will largely depend on how we define and apply value in practice—beyond the academic definition above—and the capacity of our health system and system controls to truly deliver value.

Exhibit 1: What Is Value?

$$\text{Value} = \frac{\text{Quality (Outcome)}}{\text{Cost}}$$

$$\text{Value-based Purchasing} = \frac{\text{Quality (Outcome)}}{\text{Cost}} + \text{System Controls}$$

Destination Value: Uncertain Implications for New Health Technologies

It's no secret that we frequently deliver costly services of marginal value, while other more cost-effective services are grossly underutilized.⁴ Development of methods to better estimate and compare the value of health services will narrow this gap in the future. However, efforts to advance value-based healthcare have exposed potential challenges for new health technologies—including those that promise to usher in new paradigms of health delivery—warranting careful implementation of tomorrow's health solutions today. Though not a comprehensive list, some of these challenges are as follows.

What Is the Right Measuring Stick?

Finding a common measure to compare similar technologies has long been debated in economics and outcomes research. Scholars have considered various economic measures that blend quality and cost information, including whether they are comprehensible and useful in health decision-making. In the quest for an adequate measure of value, a single standard would be ideal. However, the one-size-fits-all approaches to value estimation that have largely been applied to drugs may not be practicable for all technologies, particularly emerging medical devices and diagnostics.

Devices and diagnostics generally have shorter realized patent lives and greater technology turnover than drugs, which can diminish incentives to conduct the extensive randomized controlled trials (RCTs) and economic studies often required for drugs. Many technical challenges also exist. For example, recent discussions on estimating the value of pharmacogenomics cite significant barriers to assessment, such as lack of causal and comparative effectiveness data and the multi-factorial complexities

of evaluating diagnostic/drug combinations.⁵ Likewise, it is often difficult for diagnostic studies to generate direct evidence of impacts on health outcomes. This is because the link between treatment use and outcomes is more straightforward than for diagnostics. One renders a treatment and can then measure the short- and long-term outcomes. A diagnostic study geared to measure health outcomes, on the other hand, is subject to a wider variety of confounding effects, including multiple treatment options and variation in care delivery.

For which technologies do we need more or different evidence than others? What standards will we adopt in value measurement? When should we adopt other approaches such as patient registries or patient-reported outcomes? When is data modeling more efficient than direct evidence collection and how can we best use these results in practice? Many questions remain unanswered. As we refine our approach to measuring value, it remains important to consider both the need to readily compare value among similar services and the need to adopt methods that account for variability among technology types and applications.

When Is the Right Time to Assess Value?

Once we agree on a means to measure value, when should we evaluate it? Payers and technology assessment organizations (e.g., BCBS TEC, Hayes, ECRI) are now considering new technologies much earlier in the product life cycle. Some payers also employ "horizon scanning" approaches that identify technologies anticipated to have a significant impact on beneficiary care—even before they emerge on the market. It is essential that the potential of these technologies be reasonably tested in practice, without prematurely rendering a decision about value.

In scenarios where early technology assessment is necessary, but evidence of value is incomplete, what options exist to explore promising but unproven technologies?

The "coverage with evidence development" (CED) guidance recently released by the Center for Medicare and Medicaid Services (CMS) appears to be one option. Although it is anticipated that CED will be limited to only a few applications per year, eligible technologies engaged in the National Coverage Determination (NCD) process will be temporarily covered and reimbursed while additional data are collected. CED also reflects an approach where the manufacturer and payer share the financial burden associated with data collection to better field-test the value of new technologies post-FDA approval.

In an environment where the consumer will increasingly drive purchasing decisions, CMS and other payers are beginning to view these types of investments in new technology assessment as good business for their beneficiaries. Such approaches also support innovation for high-potential services, help decision makers gain answers to questions on value not covered by studies for market clearance, and ensure that patients can access those technologies that truly improve quality and costs of care.

How Much Evidence of Value Is Enough?

Most clinical practice guidelines and health quality measures integrate technologies with supporting evidence developed through years of clinical study and application. New health technologies such as pharmacogenomics, molecular imaging, and targeted biotechnologies do not yet have the same deep evidentiary support. Nevertheless, they offer opportunities to improve the quality and precision of healthcare—to personalize medicine—in ways that we are only beginning to understand.

As health decision makers struggle with quality and cost constraints, evidentiary expectations for new health technologies appear to be expanding. How do we best align our “need to know” with the timing and resource constraints inherent to new technology development?

The value dossier, of the type often developed under the Academy of Managed Care Pharmacy (AMCP), is one example of an approach to conveying the value of new drugs and biologics. These dossiers, familiar to the managed care community, communicate clinical and economic outcomes associated with a particular intervention. Evidence of value is presented in a manner that enables payers to assess implications for their beneficiary populations and make real time health decisions without unnecessarily delaying patient access. This approach also integrates modeling to account for lack of direct evidence at the time of product launch. Although this approach would likely need to be altered for medical devices and diagnostics, it does represent a standardized means of communicating value that most stakeholders accept.

In our efforts to assess value, we must continually ask ourselves how much information do we need to render a decision and how accurate do we need to be? When setting new thresholds for value, against which we will measure new health technologies and services, we must not create unnecessary barriers to innovation or access or “break the bank.” This means setting value expectations for new technologies in a manner that is sensitive to level of maturity and technological change. It also means requiring sufficient value information to inform rational selection among available healthcare alternatives and integration into systems of care.

How Do We Reward Value?

When it comes to rewarding value in the health system, we find

ourselves at the earliest stages of trial and error versus other U.S. industries. Once we have defined and measured value, how do we align incentives to drive desired results? What type and level of incentives are required to alter consumer, practitioner, and hospital behavior? These and other questions loom large over initial attempts to focus on value. But it is where the rubber truly meets the road if we are to succeed in value-based healthcare.

Recent pay-for-performance (P4P) and other quality initiatives are forerunners of the broader approaches to value integration yet to come. These efforts have been driven by a variety of payers, large employers, and consumer coalitions and largely operationalize quality and performance measures aimed at improving various aspects of care (e.g., safety, effectiveness, efficiency). Perhaps the most widely accepted set of such measures is the Health Plan Employer Data and Information Set (HEDIS), used by 90 percent of managed care organizations today. Although current P4P models generally focus at the hospital level, the Medicare Payment Advisory Commission (MedPAC) and other influential groups are now exploring ways to encourage individual physicians to select care options with established value.² Additionally, consumer-directed methods will continue to shift responsibility and financial burden to the patient in an attempt to balance value and choice. In this evolving system, it may be possible to choose technologies that do not offer proven value, but this will increasingly occur at a cost.

Despite the tremendous potential of such performance- and value-based purchasing strategies, it is currently uncertain whether or how such mechanisms will address emerging technologies. Presumably new technologies, such as genomic testing and targeted therapies, will offer value through improved

outcomes and efficiencies in care delivery. However, if the role of such technologies in meeting performance goals is unclear, it is conceivable that evolving systems may create unanticipated disincentives for their use. Incentive structures will influence whether providers offer certain services or decline others—it is hoped in ways that improve patient care and outcomes. It will be important for the new value infrastructure to anticipate potential care gaps and build in safeguards that foster prudent provider and patient choices without precluding advancement of emerging technologies and services.

Conclusion

As Steven Teutsch and Marc Berger have pointed out: “balancing our investment in the promise of tomorrow versus the needs of the present is a tricky business.”⁵ On the road to value in U.S. healthcare, we are finding that there are just as many questions as answers. The journey is far from over and far from certain. Identifying the solutions will require collaborative communication and the will to address the formidable healthcare challenges that affect all stakeholders, including payers, providers, purchasers, and manufacturers. **JMCM**

Eric Faulkner, MPH, is associate editor of the Genomics Biotech Institute Special Section and a senior associate at Littell Group Inc.

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IMPORTANT SAFETY INFORMATION

TUBERCULOSIS (TB), INVASIVE FUNGAL AND OTHER OPPORTUNISTIC INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING HUMIRA. SOME INFECTIONS HAVE BEEN FATAL. ANTI-TB TREATMENT OF PATIENTS WITH LATENT TB INFECTION REDUCES THE RISK OF REACTIVATION IN PATIENTS RECEIVING HUMIRA. HOWEVER, ACTIVE TB HAS DEVELOPED IN PATIENTS RECEIVING HUMIRA WHOSE SCREENING FOR LATENT TB INFECTION WAS NEGATIVE. PATIENTS SHOULD BE EVALUATED FOR LATENT TB WITH A TUBERCULIN SKIN TEST. TREATMENT OF LATENT TB SHOULD BE INITIATED PRIOR TO THERAPY WITH HUMIRA. PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING HUMIRA FOR SIGNS AND SYMPTOMS OF ACTIVE TB, INCLUDING PATIENTS WHO ARE TB SKIN TEST NEGATIVE.

SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF-BLOCKING AGENTS, INCLUDING HUMIRA. MANY OF THESE INFECTIONS OCCURRED IN PATIENTS PREDISPOSED TO INFECTIONS BECAUSE OF CONCOMITANT IMMUNOSUPPRESSIVE THERAPY IN ADDITION TO THEIR UNDERLYING DISEASE. PATIENTS WHO DEVELOP A NEW INFECTION WHILE USING HUMIRA SHOULD BE MONITORED CLOSELY. TREATMENT SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. DO NOT START HUMIRA IN PATIENTS WITH ACTIVE INFECTION (INCLUDING CHRONIC OR LOCALIZED), OR ALLERGY TO HUMIRA OR ITS COMPONENTS. EXERCISE CAUTION IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR WITH UNDERLYING CONDITIONS, WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS, OR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TB AND HISTOPLASMOSIS ARE ENDEMIC.

The combination of HUMIRA and anakinra is not recommended. TNF-blocking agents, including HUMIRA, have been associated with reactivation of hepatitis B (HBV) in patients who are chronic carriers. Some cases have been fatal. Patients at risk for HBV infections should be evaluated for prior evidence of HBV infections before initiating TNF blocker therapy. For patients identified as carriers of HBV, exercise caution when prescribing HUMIRA, with careful evaluation and monitoring prior to and during treatment. HUMIRA should be stopped and antiviral therapy should be initiated in patients who develop hepatitis B reactivation. TNF-blocking agents, including HUMIRA, have been associated in rare cases with new onset or exacerbation of demyelinating disease. Exercise caution when considering HUMIRA for patients with these disorders. More cases of malignancies have been observed among patients receiving TNF blockers, including HUMIRA, compared to control patients in clinical trials. These malignancies, other than lymphoma and non-melanoma skin cancer, were similar in type and number to what would be expected in the general population. In the controlled and open-label portions of HUMIRA clinical trials, there was an approximately four fold higher rate of lymphoma than expected in the general population. The potential role of TNF-blocking therapy in the development of malignancies is not known.

Anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration. Rare reports of pancytopenia including aplastic anemia have been reported with TNF-blocking agents. Medically significant cytopenia (e.g. thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Worsening congestive heart failure (CHF) has been observed with TNF-blocking agents, including HUMIRA, and new onset CHF has been reported with TNF-blocking agents.

Most frequent adverse events vs placebo from rheumatoid arthritis placebo-controlled studies were injection site reactions (20% vs 14%), upper respiratory infection (17% vs 13%), injection site pain (12% vs 12%), headache (12% vs 8%), rash (12% vs 6%), and sinusitis (11% vs 9%). Discontinuations due to adverse events were 7% for HUMIRA vs 4% for placebo.

The safety profile for patients with psoriatic arthritis treated with HUMIRA was similar to the safety profile seen in patients with rheumatoid arthritis.

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PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST. TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH HUMIRA. PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING HUMIRA FOR SIGNS AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE TUBERCULIN SKIN TEST NEGATIVE.

INDICATIONS AND USAGE

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with MTX or other DMARDs.

HUMIRA is indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis. HUMIRA can be used alone or in combination with DMARDs.

CONTRAINDICATIONS

HUMIRA should not be administered to patients with known hypersensitivity to HUMIRA or any of its components.

WARNINGS

Serious Infections

SERIOUS INFECTIONS, SEPSIS, TUBERCULOSIS AND RARE CASES OF OPPORTUNISTIC INFECTIONS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF BLOCKING AGENTS INCLUDING HUMIRA. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS.

TREATMENT WITH HUMIRA SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH HUMIRA SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF HUMIRA SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF HUMIRA IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR UNDERLYING CONDITIONS WHICH MAY PREDISPOSE THEM TO INFECTIONS, OR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TUBERCULOSIS AND HISTOPLASMOSIS ARE ENDEMIC (see PRECAUTIONS- Tuberculosis and ADVERSE REACTIONS - Infections). THE BENEFITS AND RISKS OF HUMIRA TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF HUMIRA THERAPY.

Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blocking agents. Therefore, the combination of HUMIRA and anakinra is not recommended (see PRECAUTIONS - Drug Interactions).

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated

for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, HUMIRA should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

Neurologic Events

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central nervous system demyelinating disorders.

Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents, including HUMIRA, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with moderately to severely active RA, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.4, 1.3)/100 patient-years among 1922 HUMIRA-treated patients versus a rate of 0.4 (0.1, 1.2)/100 patient-years among 947 control patients (median duration of treatment of 5.6 months for HUMIRA-treated patients and 5.2 months for control-treated patients). The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. In the controlled and uncontrolled open-label portions of the clinical trials of HUMIRA, the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung and uterine. These malignancies in HUMIRA-treated and control-treated patients were similar in type and number to what would be expected in the general population. During the controlled portions of HUMIRA rheumatoid arthritis trials, the rate (95% confidence interval) of non-melanoma skin cancers was 0.9 (0.56, 1.55)/100 patient-years among HUMIRA-treated patients and 0.3 (0.07, 1.07)/100 patient-years among control patients. The potential role of TNF blocking therapy in the development of malignancies is not known.

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled trials in patients with rheumatoid arthritis, 2 lymphomas were observed among 1922 HUMIRA-treated patients versus 1 among 947 control patients. In combining the controlled and uncontrolled open-label portions of these clinical trials with a median duration of approximately 3 years, including 3042 patients and over 8500 patient-years of therapy, the observed rate of lymphomas is approximately 0.15/100 patient-years. This is approximately 4-fold higher than expected in the general population. Rates in clinical trials for HUMIRA cannot be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

Hypersensitivity Reactions

In postmarketing experience, anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy instituted. In clinical trials of HUMIRA, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

Hematologic Events

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA (see ADVERSE REACTIONS, Other Adverse Reactions). The causal relationship of these reports to HUMIRA remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g. persistent fever, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

PRECAUTIONS

Information to Patients

The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of HUMIRA (see HUMIRA, PATIENT INFORMATION LEAFLET). A puncture-resistant container for disposal of needles

and syringes should be used. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

Tuberculosis

As observed with other TNF blocking agents, tuberculosis associated with the administration of HUMIRA in clinical trials has been reported (see **WARNINGS**). While cases were observed at all doses, the incidence of tuberculosis reactivations was particularly increased at doses of HUMIRA that were higher than the recommended dose.

Before initiation of therapy with HUMIRA, patients should be evaluated for active or latent tuberculosis infection with a tuberculin skin test. If latent infection is diagnosed, appropriate prophylaxis in accordance with the Centers for Disease Control and Prevention guidelines should be instituted. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur.

Patients with Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse events was observed. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Immunosuppression

The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with HUMIRA, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with HUMIRA on the development and course of malignancies, as well as active and/or chronic infections is not fully understood (see **WARNINGS, ADVERSE REACTIONS - Infections and Malignancies**). The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

Immunizations

No data are available on the effects of vaccination in patients receiving HUMIRA. Live vaccines should not be given concurrently with HUMIRA. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, treatment should be discontinued (see **ADVERSE REACTIONS, Autoantibodies**).

Drug Interactions

Methotrexate

HUMIRA has been studied in rheumatoid arthritis patients taking concomitant MTX (see **CLINICAL PHARMACOLOGY, Drug Interactions**). The data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF-blocking agents, including HUMIRA, may also result in similar toxicities (see **WARNINGS, Serious Infections**).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

Pregnancy

Pregnancy Category B

An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneous with MTX every week or 373 times human AUC when given 40 mg subcutaneous without MTX) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.

Pregnancy Registry

To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

Nursing Mothers

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of HUMIRA in pediatric patients have not been established.

Geriatric Use

A total of 519 patients 65 years of age and older, including 107 patients 75 years and older, received HUMIRA in clinical studies. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

ADVERSE REACTIONS

General

The most serious adverse reactions were (see **WARNINGS**):

- Serious Infections
- Neurologic Events
- Malignancies

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of Studies I, II, III and IV was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse events leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Infections

In placebo-controlled rheumatoid arthritis trials, the rate of infection was 1 per patient-year in the HUMIRA-treated patients and 0.9 per patient-year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on HUMIRA after the infection resolved. The incidence of serious infections was 0.04 per patient-year in HUMIRA treated patients and 0.02 per patient-year in placebo-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis (see **WARNINGS**).

In completed and ongoing global clinical studies that include over 13000 patients, the overall rate of tuberculosis is approximately 0.26 per 100 patient-years. In over 4500 patients in the US and Canada, the rate is approximately 0.07 per 100 patient-years. These studies include reports of miliary, lymphatic, peritoneal, as well as pulmonary tuberculosis. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Cases of opportunistic infections have also been reported in these clinical trials at an overall rate of approximately 0.075/100 patient-years. Some cases of opportunistic infections and tuberculosis have been fatal (see **WARNINGS**). In postmarketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving HUMIRA alone or in combination with immunosuppressive agents.

Malignancies

More cases of malignancy have been observed in HUMIRA-treated patients compared to control-treated patients in clinical trials (see **WARNINGS**).

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at Week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Immunogenicity

Patients in Studies I, II, and III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies

to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant MTX had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse events was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies I, II, III, and IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes events reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. Adverse event rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week. In Study III, the types and frequencies of adverse events in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Events Reported by ≥ 5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

Adverse Event (Preferred Term)	HUMIRA	Placebo
	40 mg subcutaneous Every Other Week (N=705)	(N=690)
	Percentage	Percentage
Respiratory		
Upper respiratory infection	17	13
Sinusitis	11	9
Flu syndrome	7	6
Gastrointestinal		
Nausea	9	8
Abdominal pain	7	4
Laboratory Tests*		
Laboratory test abnormal	8	7
Hypercholesterolemia	6	4
Hyperlipidemia	7	5
Hematuria	5	4
Alkaline phosphatase increased	5	3
Other		
Injection site pain	12	12
Headache	12	8
Rash	12	6
Accidental injury	10	8
Injection site reaction**	8	1
Back pain	6	4
Urinary tract infection	8	5
Hypertension	5	3

* Laboratory test abnormalities were reported as adverse events in European trials

** Does not include erythema and/or itching, hemorrhage, pain or swelling

Other Adverse Events

Other infrequent serious adverse events occurring at an incidence of less than 5% in rheumatoid arthritis patients treated with HUMIRA were:

Body As A Whole: Fever, infection, pain in extremity, pelvic pain, sepsis, surgery, thorax pain, tuberculosis reactivated

Cardiovascular System: Arrhythmia, atrial fibrillation, cardiovascular disorder, chest pain, congestive heart failure, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, vascular disorder

Collagen Disorder: Lupus erythematosus syndrome

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, granulocytopenia, leukopenia, lymphoma like reaction, pancytopenia, polycythemia (see **WARNINGS - Hematologic Events**).

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma, carcinomas such as breast, gastrointestinal, skin, urogenital, and others; lymphoma and melanoma.

Nervous System: Confusion, multiple sclerosis, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung disorder, lung function decreased, pleural effusion, pneumonia

Skin And Appendages: Cellulitis, erysipelas, herpes zoster

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder, pyelonephritis

HUMIRA has been studied in 395 patients with psoriatic arthritis in two placebo-controlled studies and in an open-label extension study. The safety profile for patients with psoriatic arthritis treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with rheumatoid arthritis.

Adverse Reaction Information from Spontaneous Reports

Adverse events have been reported during post-approval use of HUMIRA. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure

Hematologic Events

Thrombocytopenia (see **WARNINGS , Hematologic Events**).

Hypersensitivity Reactions

Anaphylaxis, angioneurotic edema (see **WARNINGS , Hypersensitivity Reactions**).

Respiratory disorders

Interstitial lung disease, including pulmonary fibrosis.

Skin Reactions

cutaneous vasculitis.

OVERDOSAGE

The maximum tolerated dose of HUMIRA has not been established in humans. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

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New Treatments in Overactive Bladder and Implications for Managed Care

Michael Kennelly, MD, and Kenneth L. Schaecher, MD

A continuing medical education activity sponsored by NAMCP

Summary

Overactive bladder (OAB) is a significant social, medical, and cost issue for a large percentage of the population and these problems only increase as one ages. Current treatment with behavior management and anticholinergic medications does not significantly improve bladder capacity, or improve continence. Newer treatments, such as neurostimulation with implanted devices and injection of the bladder muscles with botulinum toxin, indicate that such interventions improve these parameters to a greater extent.

Key Points

- OAB is a significant problem both from a quality-of-life and a cost perspective.
- Oral medications and behavior therapies that are currently available do not optimally control the disease.
- The ultimate goal with OAB is to improve quality of life by decreasing symptoms and achieving continence.
- Neurostimulation with implanted devices or injected botulinum toxin appears to result in improvements in continence rates and bladder capacity.

ACCORDING TO THE International Continence Society, overactive bladder is a symptom syndrome of urgency, with or without urge incontinence, usually with frequency and nocturia.¹ Overactive bladder really incorporates a variety of issues including frequency, nocturia, urgency, and incontinence. Frequency is defined as voiding more than eight times a day. Nocturia is having to get up more than two times at night. Urgency is a sudden, compelling desire to urinate. Incontinence is often the result of urgency. Incontinence causes much of the patient distress and difficulty related to OAB.

In differentiating the type of urinary incontinence (UI), there is overlap of the symptoms between urge UI and stress UI. Stress incontinence is urine leakage during some type of activity, such as coughing or sneezing. Stress incontinence is a structural problem with the urethra. Any type of increased abdominal exertion, whether a cough or strain or sneeze, puts increased abdominal pressure on top of the bladder, which overcomes the resistance of the urethra. The patient will leak a defined amount of urine at a defined

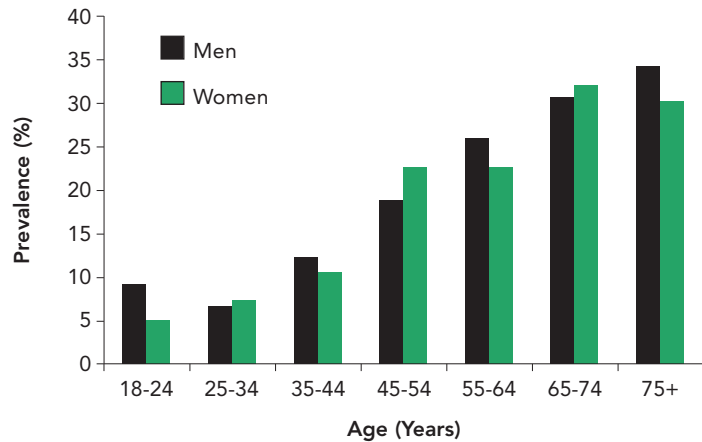
moment. In differentiating stress incontinence from urge incontinence secondary to OAB, the issue with OAB is a spasticity of the bladder muscle that will suddenly cause a contraction and leakage of urine. Typically, the leakage of urine that occurs is a large volume loss. The key component in OAB is dealing with the bladder hypersensitivity and spasticity to decrease symptoms and prevent incontinence. OAB can occur with pelvic prolapse, urinary tract infection, and benign prostatic hyperplasia. The bottom line is that stress incontinence is a urethral problem, whereas OAB is a bladder problem.

Almost 16 percent of the U.S. population, approximately 33 million Americans, will have symptoms of OAB (see Exhibit 1).² One third of people with OAB symptoms will have accompanying urge incontinence. Prevalence of OAB increases with age. Interestingly, men have nearly equal prevalence as women. Roughly 10 percent of people in their 30s will have symptoms of OAB, whereas 30 percent of people in their 60s will have symptoms of OAB.

OAB has a significant impact on a person's lifestyle

Exhibit 1: Prevalence Increases with Age²

- Overall, 16.6% had symptoms of OAB
- Prevalence of OAB increases with age
- Prevalence similar in men and women
- Other risk factors
 - > neurological disease
 - > bladder outlet obstruction
 - > stress incontinence



(see Exhibit 2).³ It affects all quality-of-life domains including social, sexual, work environment, and others. Patients with OAB can also become withdrawn from society and depressed.⁴

Pathophysiology

The bladder is a simple organ for urine storage and elimination, but it has a complex neuroanatomy. The control center for the bladder is at the base of the brain. Parasympathetic, sympathetic, and somatic nerves innervate the bladder, the stem of the bladder and the pelvic floor. With normal micturition, as the bladder starts filling, stress receptors are triggered within the bladder. The stress receptors will then signal the sacral micturition center, causing the bladder to contract reflexively, the urethra to relax, and urination to occur. As children mature, they gain cognitive control of urination. Parasympathetic input from the central nervous system inhibits bladder contraction and tightens the urethral area.

The neurogenic theory of OAB proposes that several things can disrupt normal bladder activity and lead to OAB. Decreased central inhibitory control that stems from brain injury, stroke, multiple sclerosis, and spinal cord injury can lead to OAB. Additionally, the receptors that are within the bladder can have hypersensitivity. The nerve impulses that come from the bladder as it is stretching can be hypersensitive and actually cause more afferent stimulation.

Treatment

The traditional approach to OAB treatment includes a combination of behavioral therapy and pharmacologic therapy. Currently, surgical therapy is rarely done.

Behavioral therapy is the foundation for OAB treatment. This entails bladder training, dietary modification, patient education, scheduled voiding,

Exhibit 2: OAB—Personal and Societal Burden^{3,4}

- Increased hospitalization costs (\$49.1 million/year)³
- Increased nursing home stays (\$1.47 billion/year)³
- Frequent occurrence of urinary tract infections (\$1.19 billion/year)³
- Increased risk for falls and fractures (\$306.9 million/year)³
- Frequent occurrence of skin irritation (\$38.4 million/year)³
- 60% of OAB patients suffer from depression²

and positive reinforcement. Additional behavior interventions include pelvic floor exercises, biofeedback, and electric stimulation therapy. For behavioral therapy to be successful, an extremely motivated and dedicated patient is required. On the positive side, with behavioral therapy, continence rates of up to 30 percent can be achieved and most people will have some improvement in symptoms. The negative issues include difficulty in sustaining patient motivation and a lack of reimbursement to the health professional providing training.

The most common aspect of treatment is pharmacotherapy, with numerous medications recently marketed for OAB. However, medications have not significantly improved continence rates over behavior therapy alone. The medications result in about a 30 percent continence rate. Additionally, the side effects of dry mouth, constipation, blurred vision, and confusion are a limiting factor for these medications. When prescription claims data are examined, about 80 percent of people are discontinuing medication management

Exhibit 3: Neuromodulation for OAB

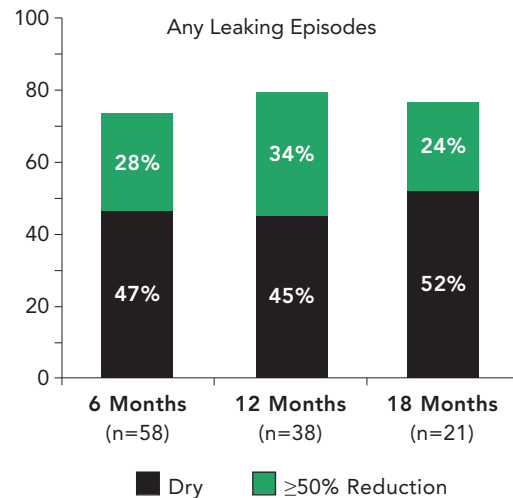


within three months primarily due to lack of efficacy, in addition to intolerable side effects, or a combination of both. Therefore, OAB is not ideally managed with currently available pharmacologic therapy.

New treatments for OAB are in the realm of neuromodulation. Neuromodulation is trying to alter the natural pathways of the nervous system. There are three main neuromodulation systems available or under study: sacral nerve root stimulation, posterior tibial stimulation, and pudendal nerve stimulation (see Exhibit 3). All of these therapies are targeting the spinal cord and altering the natural nerve reflex pathways to the bladder. The first therapy approved was InterStim, which is sacral nerve modulation. InterStim is FDA approved for urinary urgency frequency, urge incontinence, and urinary retention. This therapy requires a test phase to determine if the therapy will work and, if it will, surgical implantation of the stimulation device. To move on to the implant phase, the patient should have at least a 50 percent improvement in urge incontinence. The benefit to sacral neuromodulation therapy is longstanding results of 47 to 50 percent continence rate compared with a 30 percent rate with behavioral or medication therapy (see Exhibit 4).⁵

Another neuromodulation device that is being tested is tibial nerve stimulation. This is an office-based therapy that stimulates the tibial nerve for about 20 to 25 minutes once a week for three months. A small acupuncture needle is placed into the tibial nerve. The needle is connected to an external battery generator and a grounding pad. When a therapy session is complete, the acupuncture needle is removed. In a small sample of 53 patients treated over a 12-week period, there was a 25 percent reduction in urinary frequency, a 21 percent reduction in nocturia, and a 35 percent reduction in incontinence.⁶ To achieve continence, tibial nerve stimulation may not be significantly better than pharmacotherapy or behavior management. It may be an option for patients who do not want to proceed to the implantable therapies. A

Exhibit 4: Urge Incontinence Sustained Clinical Efficacy



future improvement of tibial nerve neuromodulation will be a small implantable device so patients will have the ability to do the therapy at home.

A third neuromodulation device under study stimulates the pudendal nerve. The theoretical basis of this device is that stimulation of the pudendal nerve results in increased afferent sensation to the sacral two, three, and four nerve roots. Stimulation of the third sacral nerve has been shown to be effective in treating voiding dysfunction. The stimulation device is known as a bion, which is a small single-channel, self-powered, implantable pulse generator with integrated electrode. It is implanted next to the pudendal nerve (see Exhibit 3). To determine if the device is likely to work, a test phase must be conducted. In the physician's office under local anesthesia, a small stimulating electrode is placed at the patient's pudendal nerve to stimulate the nerve for 15 minutes. Bladder volume is tested before and after the stimulation. If the patient has a greater than 50 percent increase in bladder volume, a greater than 50 percent increase in first sensation to void, or an

increase of 50 percent from the first involuntary bladder contraction, he or she would be a candidate to have the small device implanted. Unlike the InterStim device, the bion has to be recharged using a base station in a chair pad. The patient sits on this chair pad for 15 minutes a day for recharging.

In one published study of 14 subjects treated with pudendal stimulation, only six subjects passed the stimulation test.⁷ Of six patients who proceeded to the implant, there were some reductions in urge incontinence, and bladder volume increased by 120 to 130 cubic centimeters. Bladder capacity is a key component that drives frequency. The available pharmacologic agents only increase bladder capacity by 30 cubic centimeters.

Another area of research is biological neuromodulation, which uses botulinum toxin. Botulinum toxin, derived from *Clostridium botulinum*, inhibits the release of acetylcholine from the nerve terminal and blocks smooth muscle contraction. Although other types are available, botulinum toxin A (Botox) is the type primarily under investigation for OAB. For OAB, the botulinum toxin is injected into the detrusor muscle of the bladder via a cystoscope. The procedure can be office or hospital based, depending on the practitioner.

A benefit of botulinum toxin in treating OAB is that it is not permanent. Its effects are temporary, typically lasting six to nine months for smooth muscles like the detrusor. Although not FDA approved for the indication, botulinum toxin has been used for several years for bladder and urinary tract issues. It has been used for neurogenic overactivity, bladder pain of interstitial cystitis, non-neurogenic overactivity, outflow obstruction secondary to BPH, and detrusor-sphincter dyssynergia.

Several peer-reviewed studies of botulinum toxin in the treatment of OAB have been published. The

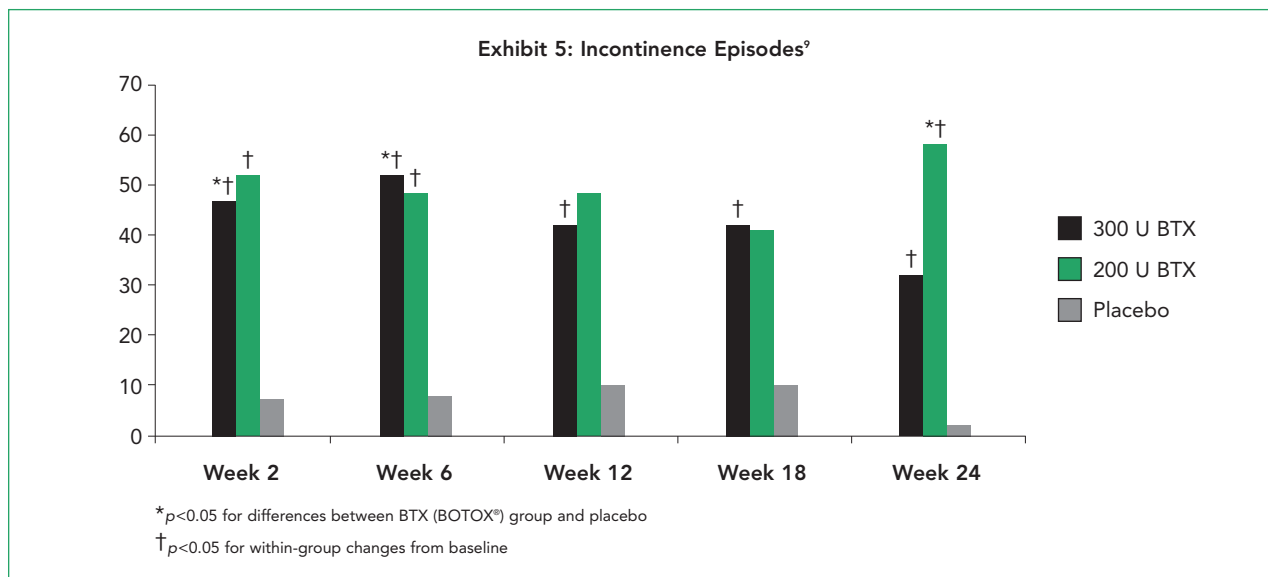
majority of published studies have been for neurogenic OAB. One multi-center trial of 200 patients showed a greater than 50 percent improvement in bladder capacity.⁸ A multi-center trial of patients with multiple sclerosis or spinal cord injury who had leaking of urine between intermittent catheterization treated with botulinum toxin A was published in the *Journal of Urology* in 2005.⁹ The injections resulted in a 45 to 50 percent reduction in incontinence two weeks after injection (see Exhibit 5). Bladder capacity improved significantly (see Exhibit 6). Statistical improvements in quality of life measures were seen as early as two weeks after the injections. Quality of life continued to improve all the way to week 24. There were no adverse events that were attributed to the botulinum toxin therapy.

In rare instances, injection of botulinum toxin B into the bladder has been reported to cause transient generalized weakness, but this has not been reported with the type A toxin.¹⁰ Urinary retention also is a possible side effect. At this time, there has been no evidence of long-term structural bladder change caused by toxin injections.¹¹

More study is needed to determine the ideal dose, number of injections, and injection technique. Another issue to be addressed is pharmacoeconomics analyses comparing botulinum toxin to other therapies.

Managed Care Issues

In addition to being a quality-of-life issue, OAB is also a cost issue. An example of these costs comes from SelectHealth, formerly InterMountain Health. SelectHealth is a commercial health plan covering a young population of 480,000 in Utah and Idaho. The group examined its claims data for OAB costs for 2005 (see Exhibit 7). Overall, its costs for OAB medications were 18 cents per member per month. The health plan



also found that patients were not regularly filling their OAB medication prescriptions and frequently were switched from one medication to another. When medical claims costs were considered, the health plan spent \$3.2 million for people with OAB, or 58 cents per member per month. Neurostimulation, while infrequently used in this health plan, was expensive. Ten claims for seven members resulted in \$8,500 in costs. Although these costs are only \$0.01 per member per month, it's important to note that the costs were generated by only 10 claims. The plan's estimated total per member per month cost for all care related to OAB was \$0.79, which was significant. In managed care finances, 25 cents per member per month attracts attention. Thus, OAB is not an insignificant problem for a commercial HMO. Health plans with a large elderly population would have even higher costs.

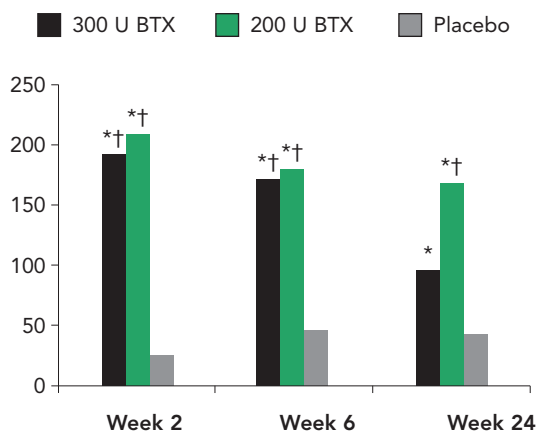
Conclusion

Because behavior and medication therapies are not meeting the needs of many patients, neuromodulation and botulinum toxin are likely future therapies for OAB. These therapies do not require patient motivation to be effective and avoid the typical adverse effects of oral medications. Overall, therapy most likely will employ a combination of approaches to significantly improve patients' quality of life. **JMCM**

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Exhibit 6: Maximum Cystometric Capacity⁹



* $p < 0.05$ for within-group changes from baseline

† $p < 0.05$ for pairwise contrasts between BTX (BOTOX®) groups versus placebo

Exhibit 7: Cost Implications of OAB for MCOs SelectHealth Example

Claims for OAB

- 476,000 total members in 2005
- 5,033 members with claims for OAB
- 4,173 members with physician claims
- 1,511 members with outpatient facility claims
- 316 members with OAB and claims for UTIs
- 195 members underwent surgery for OAB
- 7 members underwent sacral nerve stimulation

Cost to the Health Plan

- Total medication costs (including patient co-pays): \$1,025,795.69 (\$0.18 PMPM)
- Total procedure/physician fee/ancillary costs: \$3,296,263.34 (\$0.58 PMPM)
- Total neurostimulation procedure costs: \$85,927.99 (\$0.015 PMPM)
- Total office/lab costs related to treating infections secondary to OAB: \$92,131.02 (\$0.16 PMPM)*
- Overall PMPM Costs: \$0.79

OAB = over active bladder; UTI = urinary tract infection; PMPM = per member per month

*Antibiotic costs specifically for treating infections secondary to OAB not available.

Faculty

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Disclosure

Dr. Kennelly receives research support from Allergan, Watson, Pfizer, Ortho-McNeil, Astellas, AstraZeneca, Medtronic and Eli Lilly. He serves on the speakers' bureaus for Pfizer, Ortho-McNeil, GlaxoSmithKline, Novartis, and Esprit.

Dr. Schaecher has no real or perceived financial relationships that present a conflict of interest.

Accreditation

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This activity has been approved by the American Board of Managed Care Nursing for 1.2 contact hours toward CMCN recertification requirements.

This activity was held live at the NAMCP Spring Managed Care Forum. This activity is valid from Sept. 1 to Dec. 31, 2006.

POST TEST

INSTRUCTIONS

Read the article, answer the post test questions, complete the evaluation form, and submit to Ann Patrick either by fax 804-747-5316 or mail: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

1. OAB is a symptom syndrome of urgency, with or without urge incontinence, usually with frequency and nocturia.

- a. True
- b. False

2. Today, 33 million adults have OAB, and this number includes men and women.

- a. True
- b. False

3. The burden of OAB includes:

- a. Requirement for specialized underwear and bedding
- b. Avoidance of sexual contact and intimacy
- c. Limitation or cessation of physical activities
- d. Reduction in social interaction
- e. Fear of being a burden and urine odor
- f. All of the above

4. The treatment cascade for OAB includes behavioral therapy, pharmacotherapy, and neuromodulation treatment.

- a. True
- b. False

5. Sacral nerve stimulation has indications for

- a. Urge incontinence
- b. Urgency and frequency
- c. Urinary retention
- d. All of the above

6. Tibial Nerve Stimulation reduces urge incontinence 35 percent.

- a. True
- b. False

7. In one trial, treatment with botulinum toxin showed a 50 percent increase in bladder capacity

- a. True
- b. False

8. Future direction for OAB treatment with botulinum toxin includes:

- a. Pharmacoeconomics of therapies
- b. Standardization of dosing
- c. Standardization of injection technique and number of injections
- d. All of the above

9. A managed care organization can spend up to \$0.79 per member per month on OAB claims.

- a. True
- b. False

10. New therapies for OAB most likely will be a combination of approaches to improve the patient's quality of life.

- a. True
- b. False

OAB ANSWER SHEET

There is only one correct answer per question.
Circle your answers clearly.

1. a b

2. a b

3. a b c d e f

4. a b

5. a b c d

6. a b

7. a b

8. a b c d

9. a b

10. a b

ACTIVITY EVALUATION

1. Please evaluate this activity based on the following scale:

4 Excellent 3 Good 2 Fair 1 Poor

Activity met my expectations

4 3 2 1

Activity was free of bias

4 3 2 1

Activity content was understandable

4 3 2 1

Presenters were free of bias

4 3 2 1

Method of learning was beneficial

4 3 2 1

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Highly Active Antiretroviral Therapy (HAART) in 2006

Trevor Hawkins, MD

A continuing medical education activity sponsored by NAMCP

Summary

The human immunodeficiency virus (HIV) epidemic continues to be a significant public health issue around the world. Highly active antiretroviral therapy (HAART), the use of various medication combinations, has transformed HIV infection from a death sentence into a chronic manageable disease. To best manage patients, minimize costs, and prevent drug resistance, patients need assistance with adhering to their complicated therapeutic regimens.

Key Points

- HIV infection remains a significant worldwide problem with 5 million new cases yearly.
- With HAART, the death rate from HIV has declined significantly.
- With HAART, HIV infection has become a chronic, manageable disease.
- Patient adherence to therapy is one of the key determinants in preventing drug-resistant HIV virus.
- Medical costs for patients with HIV infection increase when drug resistance occurs.
- Assisting patients with adherence to prevent resistance can be a significant role for managed care.

HUMAN IMMUNODEFICIENCY VIRUS was introduced into the human population when hunters became exposed to infected blood of the African Green chimpanzee.¹ The majority of virus found in the United States is type 1 group M and subtype B.² There is much more diversity in the virus in other countries.

Worldwide, 40 million people are estimated to have HIV and 5 million new cases occur each year (see Exhibits 1 and 2).³ About 20 million people have died from the virus. The biggest epidemic is in Africa, but the fastest growth of cases is in Eastern Europe and the former Soviet Union.

The HIV epidemic in the U.S. started off as an epidemic in the homosexual community and it is now slowly shifting into a people-of-color epidemic. People of color are disproportionately representative in terms of people with HIV.² For example, one out of five black men between the ages of 40 and 49 in New York is HIV positive. Thirty four percent of new cases are in black women. Mortality is six times higher in black men than it is in white men, and that is partly because of access to care.⁴ Overall, even though African

Americans make up only approximately 13 percent of the U.S. population, one half of the estimated new numbers of HIV/AIDS diagnoses in the U.S. in 2004 were for African Americans.² Another part of the epidemic is continued high-risk sexual behaviors among young homosexual men.²

One success story with HIV is the reduction in mother-to-child transmission in many countries. Pediatric HIV in the developed world is rapidly becoming a thing of the past. The vast majority of women with HIV can have uninfected babies as long as the mother is getting treatment.

Although progress has been made in preventing the spread of the virus, there needs to be more political recognition and willingness to assist in halting the continuing spread of HIV infections. The U.S. needs more public health infrastructure and better public education on this issue.

The long-term outlook on HIV infection changed in 1995 with the introduction of the protease inhibitor, the first highly active antiretroviral. Since the highly active antiretroviral therapy era began, HIV infection is no

Exhibit 1: Adults and Children Living with HIV/AIDS³

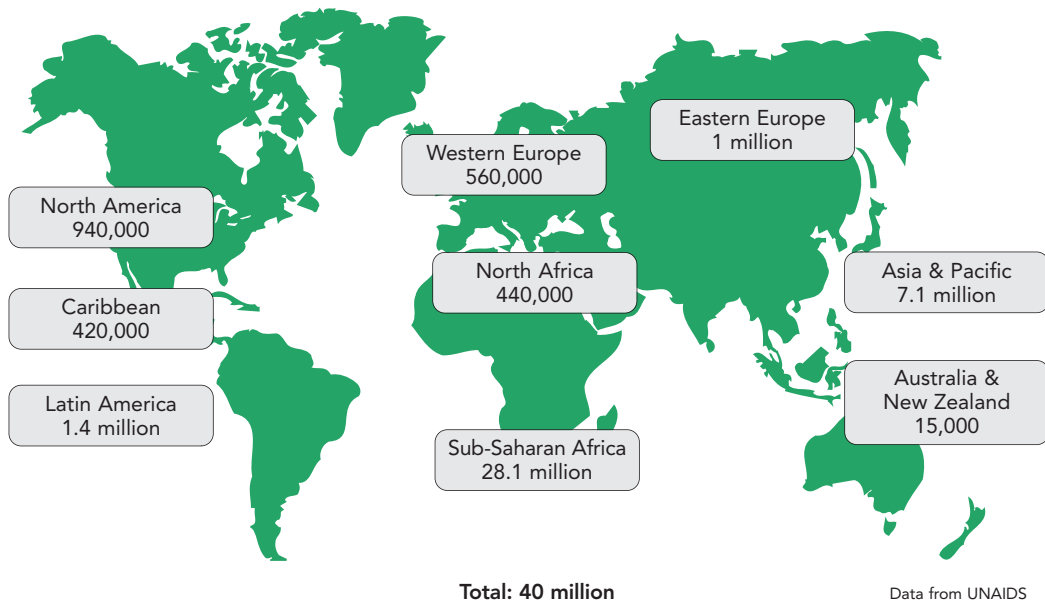
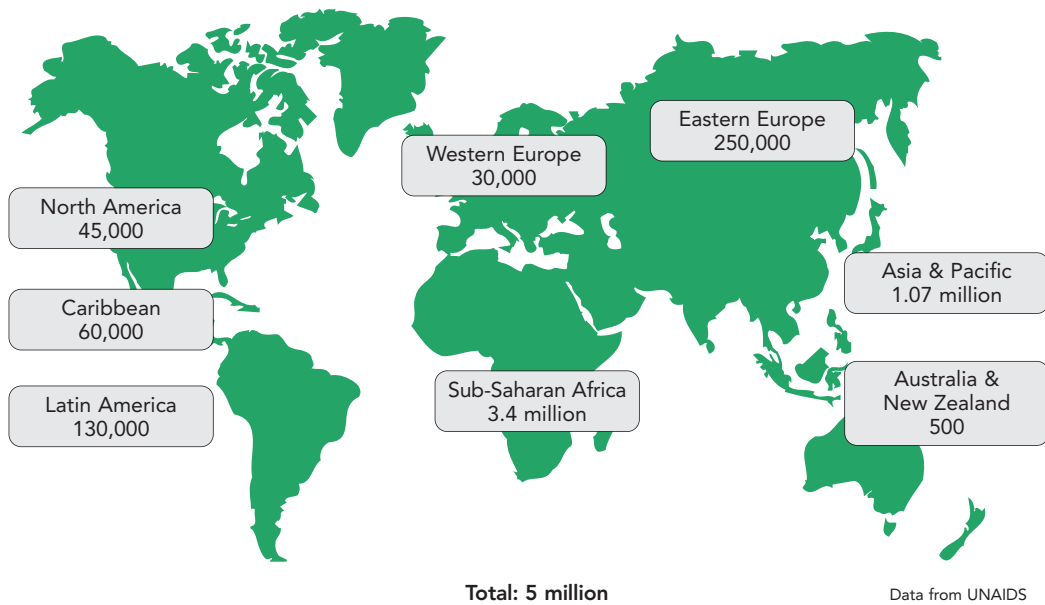


Exhibit 2: Annual New Infections of HIV in Adults and Children³



longer a death sentence. Use of these therapies has been associated with substantial declines in HIV-associated morbidity and mortality in recent years (see Exhibit 3).⁵ HAART has significantly reduced the incidence of opportunistic infections including *Pneumocystis carinii* pneumonia (PCP), *Cytomegalovirus* (CMV), and *Mycobacterium avium* complex (MAC). See Exhibit 4.⁵

With the success of HAART in suppressing the HIV virus, hepatitis C virus infection is now of great

concern in the HIV-infected population. Because each infection has many of the same risk factors, hepatitis C and HIV commonly occur in combination. Hepatitis C is rapidly becoming the leading cause of death for people with HIV because these patients are now living long enough to sustain significant liver damage. Unfortunately the medications currently available to treat hepatitis C are not particularly effective.

Exhibit 5 details the current guidelines for when to

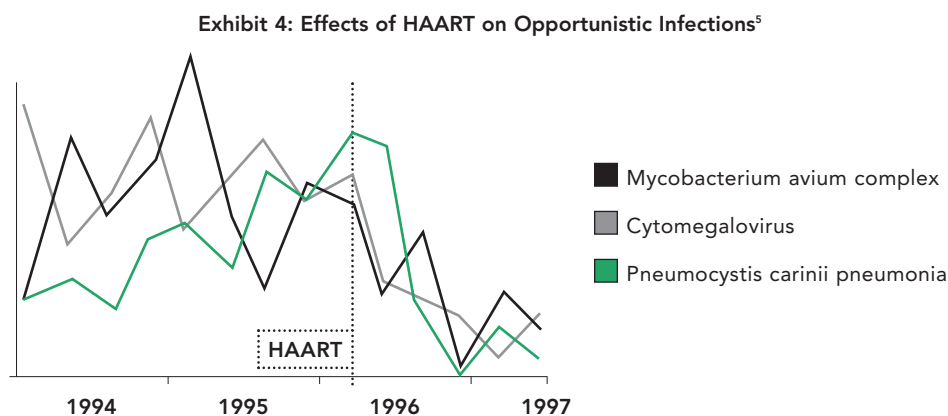
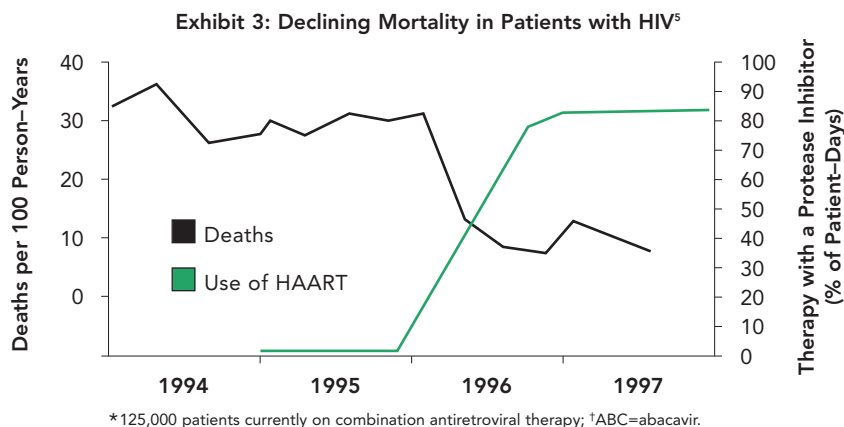


Exhibit 5: Updated DHHS Guidelines—When to Start Treatment⁶

Clinical Category	CD4+ Cell Count	Plasma HIV-1 RNA	General Guidelines
AIDS-defining illness or severe symptoms	Any Value	Any Value	Treat
Asymptomatic	<200	Any Value	Treat
Asymptomatic	200-350	Any Value	Treatment should be offered following full discussion of pros and cons of treatment
Asymptomatic	>350	≥100,000	Most clinicians recommend deferring therapy, but some clinicians will treat
Asymptomatic	>350	<100,000	Defer therapy

treat patients with HIV infection.⁶ Guidelines for HIV are constantly changing because of new evidence. Recent evidence suggests that treatment should begin before the CD4 count falls below 350.

Exhibit 6 lists the currently available antiretroviral

medications. Many different combinations of these agents are used. Usually three different antiretrovirals are used. Which combination is chosen will depend on whether a patient is treatment naïve or if resistance is present. Other factors in selecting the combination

Exhibit 6: Current Antiretroviral Medications

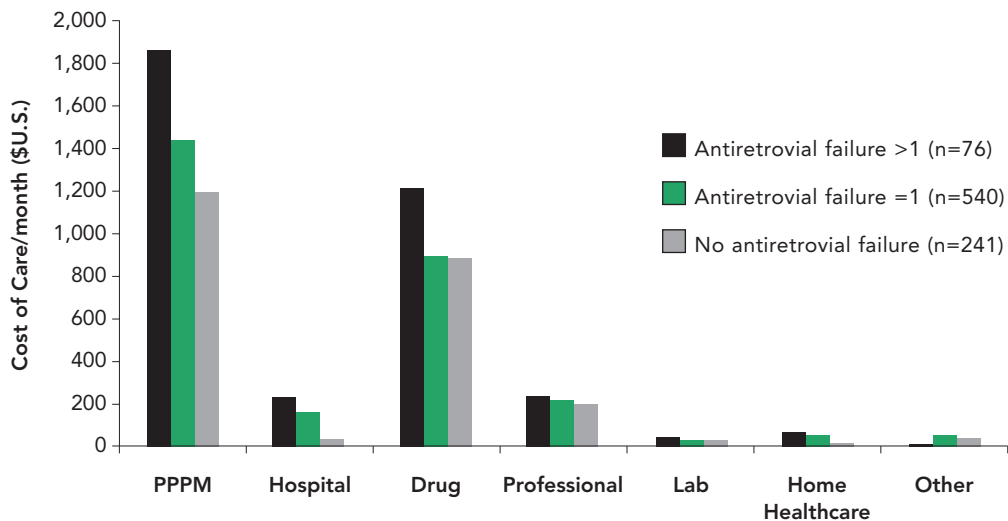
Nucleoside Reverse Transcriptase Inhibitor (NRTI)	
Abacavir	ABC
Didanosine	DDI
Emtricitabine	FTC
Lamivudine	3TC
Stavudine	D4T
Zidovudine	ZDV, AZT
Zalcitabine	DDC
Tenofovir	TDF

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	
Delavirdine	DLV
Efavirenz	EFV
Nevirapine	NVP

Protease Inhibitors	
Amprenavir	APV
Atazanavir	ATV
Fosamprenavir	FPV
Indinavir	IDV
Lopinavir	LPV
Nelfinavir	NFV
Ritonavir	RTV
Saquinavir	SQV

Fusion Inhibitor	
Enfuvirtide	T-20

Exhibit 7: Comparative Cost of Care for All Patients⁹



include potential adverse effects, current treatment guidelines, and possible drug interactions. For example, the preferred regimen for treatment naïve patients includes a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse transcriptase inhibitors (NRTI).⁶

In recent years, HAART regimens have improved because of better medication efficacy and easier regimens. Previously, patients had to take large numbers of tablets or capsules multiple times daily.

More combination products as well as products that require fewer tablets and fewer daily doses have been introduced. Various trials have been conducted and are ongoing to determine the best treatment regimens and whether therapy can be safely stopped periodically based on viral suppression. So far, continuous treatment appears to be the best solution for most patients in order to continue viral suppression and prevent medication resistance.

Antiviral drug resistance can be one of the causes for

HIV therapy failure. Recent data suggest that the prevalence of drug resistance is about 14.5 percent.⁶ Resistance testing is becoming more common. The most common use is to test newly infected patients to determine if they have a resistant virus, making it possible to better plan therapy. Testing also is done when a patient fails antiviral therapy. Viral phenotyping is done when a patient is multi-drug resistant. With viral phenotyping, the virus is tested against different antivirals.

Adherence to HAART therapy is a significant factor in reducing the development of drug-resistant virus and in reducing therapy failure. Patients who miss enough doses of HAART therapy rapidly develop drug-resistant virus. At less than 95 percent adherence, 50 percent of patients develop drug-resistant virus.⁷ Resistance and antiretroviral therapy failure are not random or inevitable, but they are predictable outcomes with a number of controllable factors. The incidence of good adherence and full viral suppression depends on the expertise of the people taking care of the patients. Patient factors clearly associated with the risk of decreased adherence—such as active substance abuse, depression, and lack of social support—need to be addressed with patients before initiation of antiretroviral therapy.⁸

Exhibit 7 compares the treatment costs for patients who fail therapy and those who have success.⁹ Patients who fail therapy have much higher costs because they are more likely to be sicker, be hospitalized, and require more expensive combinations of HAART. Good care in HIV to prevent medication failure means patients must be very adherent to their medication. Some strategies to enhance adherence to HAART are outlined in Exhibit 8.⁸ Promoting adherence to therapy is a significant role for managed care in the cost-effective management of HIV-infected patients.

The future of treatment and control of HIV infection is exciting. Significant work is ongoing on vaccines, improved single-pill combination therapy, long-acting medications for once-weekly administration, and better treatments for hepatitis C. **JMCM**

Exhibit 8: Improving Adherence to HAART⁸

- Support and reinforcement
- Simplified dosing strategies
- Reminders, alarms, timers, and pill boxes
- Ongoing patient education
- Trust in healthcare provider

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Faculty

Trevor Hawkins is associate clinical professor at the University of New Mexico and medical director at Southwest CARE Center in Santa Fe, N.M.

Disclosure

Dr. Hawkins receives research funding from Pfizer, Gilead, Tibotec, and GlaxoSmithKline. He also serves on the speakers' bureaus for Gilead, GlaxoSmithKline, Abbott, Bristol Myers-Squibb, and Boehringer-Ingelheim. Dr. Hawkins serves on advisory boards for Gilead and Cytodyn.

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1. HIV affects all genders, race, or sexual orientation the same.
 - a. True
 - b. False

2. Mother-to-child transmission is becoming a thing of the past.
 - a. True
 - b. False

3. HAART has made a significant impact on the incidence of opportunistic infections in HIV patients.
 - a. True
 - b. False

4. HIV patients are now at risk for death from Hepatitis C not HIV.
 - a. True
 - b. False

5. In addition to many other factors, the combination of antiretroviral therapy should be based on:
 - a. Whether the patient is treatment naive
 - b. The presence of resistance
 - c. Current treatment guidelines
 - d. Potential side effects and drug interactions
 - e. All of the above

6. The development of resistance and therapy failure is dependant on adherence.
 - a. True
 - b. False

7. Patients with active substance abuse, depression, and a lack of social support should be counseled about therapy adherence prior to the initiation of HAART.
 - a. True
 - b. False

8. Therapy failure requires more hospitalizations and more expensive combinations of HAART resulting in higher costs during the continuum.
 - a. True
 - b. False

9. Managed care's role in treating HIV should be promoting therapy adherence.
 - a. True
 - b. False

HAART ANSWER SHEET

There is only one correct answer per question.
Circle your answers clearly.

1. a b
2. a b
3. a b
4. a b
5. a b c d e

6. a b
7. a b
8. a b
9. a b

ACTIVITY EVALUATION

1. Please evaluate this activity based on the following scale:

4 Excellent 3 Good 2 Fair 1 Poor

Activity met my expectations

4 3 2 1

Activity was free of bias

4 3 2 1

Activity content was understandable

4 3 2 1

Presenters were free of bias

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