The Role of Pharmaceuticals in Reducing Cardiometabolic Risk: Rethinking Pharmacy Benefit Design to Reduce the Burden on the Health Care System

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As the DHHS secretary, Thompson worked to modernize and add prescription drug coverage to Medicare. An advocate of welfare reform, he also focused on expanding services to seniors, people with disabilities, and low-income Americans. In addition, Thompson is recognized for his contributions to the U.S. response to the threat of bioterrorism and for his leadership in the fight against HIV/AIDS in the United States and abroad; he currently serves as the chairman of the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Thompson previously served in the state Assembly and was elected to four terms as governor of Wisconsin; he served in that position until his appointment as secretary of Health & Human Services in 2001. As governor of Wisconsin, Thompson worked on issues such as welfare reform and expanding health care access. He has received numerous awards for his public service. He is a former chairman of the National Governors’ Association, the Education Commission of the States, and the Midwestern Governors’ Conference. Thompson received both his bachelor of science and law degrees from the University of Wisconsin, Madison.
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Target Audience
Managed care pharmacists, clinical pharmacists, pharmacy directors, and medical directors

Learning Objectives
Upon completion of this program, participants will be better able to
1. discuss emerging trends in the assessment and management of metabolic syndrome;
2. discuss the value of pharmaceutical intervention in improving clinical and economic outcomes associated with metabolic syndrome, including obesity and cardiovascular risk reduction;
3. describe innovative benefit design strategies implemented by health plans to reduce cardiovascular and metabolic risk;
4. describe pharmacy benefit design strategies focused on increasing access, promoting appropriate use, and ensuring compliance, persistency, and adherence to medications used to manage metabolic syndrome; and
5. discuss strategies to accelerate the integration of innovative benefit design solutions with effective disease and health management initiatives to achieve and sustain improved cardiovascular and metabolic health.

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A Call to Action

TOMMY G. THOMPSON

ABSTRACT

OBJECTIVE: To summarize the challenges facing the U.S. health care system between now and 2013.

SUMMARY: Between now and 2013, the American health care system will need to make major changes to successfully address Medicare’s funding challenges. Making the patient a partner in care, developing systems that promote and reward prevention efforts, and ensuring that health care purchasers understand and pursue value will be key. The growing prevalence of diabetes and cardiometabolic conditions is one area in which concerted efforts are needed.

KEYWORDS: Medicare, Prevention programs, Employee participation, Diabetes, Cardiometabolic

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American health care has serious problems that, to solve, will require collaboration on many levels. Fewer companies offer health insurance; in the last 10 years, the proportion of companies offering health insurance has declined from 72% to approximately 59%. The number of uninsured individuals has increased from 43.6 to 45 million. The confluence of these trends—decreased health care coverage and greater numbers of uninsured—is costly. For example, when the uninsured need health care, they may be more likely to use an emergency department as a usual source of care. This is an expense that is ultimately absorbed by the average American. It is the purchasers of health care who have the greatest power to transform it because they influence direct health care costs.

To transform health care in a meaningful way, we have to increase every American’s involvement. Our current medical system is referred to as “curative.” It is geared toward treating people after they become ill, which is, again, a costly proposition. Spending money up front to keep people well is not the current, but clearly preferable, approach. Intuitively, we can see that this is backward. Our first step must be to emphasize prevention and wellness.

Next, we need to change the usual health benefit design and underscore the value of purchasing effective and practical health care. Only health care purchasers will be able to transform our system. A 2005 survey of 365 of the largest U.S. employers conducted by Deloitte & Touche Center for Health Solutions, which I chair, determined that almost 62% of these large employers have implemented healthy-lifestyle programs and 34% more are considering doing so. This has been an unfilled void for decades. We know that companies that have established disease prevention programs without offering incentives are experiencing employee participation rates of only about 25%. It is clear that we need to encourage their use of incentives. Companies might consider reducing premiums for those employees who actively engage in disease prevention programs. The Deloitte & Touche LLP 2005 Wellness Survey found that the use of incentives drives worker participation in the programs to as high as 80%. In these cases, employees begin taking care of themselves and also positively influence their family members and fellow employees. Productivity levels increase and have a positive impact on the workplace.

In addition, all health care stakeholders must understand the concept of “value purchases.” Consider diabetes and cardiovascular disease. The prevalence of diabetes in America is increasing to the point that many experts consider it a national epidemic. In 2002, America’s 18 million type 2 diabetics cost this country about $135 billion in direct and indirect costs. In addition, the growing prevalence of overweight and stressed individuals contributes to cardiovascular disease. Diabetes and cardiovascular health are ripe for comprehensive intervention and represent areas where drugs are a value purchase for cardiometabolic risk reduction. Although

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these drugs may seem too costly to a company's corporate financial officer and accounting department, they can often alter the course of these diseases, prevent decline of employees' health, boost worker productivity, and ultimately save the company money. Employees who are treated appropriately with drugs will be healthier, more productive, and incur fewer additional health care costs.

Promoting prevention, understanding value purchasing, reducing the numbers of uninsured individuals, and influencing benefit design represent our best opportunity to transform our curative system into the optimal system we need. By 2013, American will have to have a new, more efficient and more effective health care system in place. At that time, Medicare will no longer be able to sustain the federal health care programs because the government will have to start drawing down on the general treasury to finance the claims of a growing number of Medicare-eligible elderly. A crisis is looming. It will only be avoided if health care purchasers implement wellness programs that recognize value purchases, and educate their fellow Americans to be partners in prevention and health care long before they reach Medicare eligibility. All health care providers and purchasers can and should be part of this effort.

DISCLOSURES
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REFERENCES
Contemporary Strategies for Managing Cardiometabolic Risk Factors

STEVEN DAVIS, MD, FRCP

ABSTRACT

OBJECTIVE: To review the metabolic syndrome as defined by the 2001 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) and its modifiable risk factors and to review currently available treatment modalities.

SUMMARY: Metabolic syndrome, although still controversial, is a growing concern. Most definitions include elevated blood pressure, smoking, inflammation, insulin resistance, abdominal adiposity, elevated blood glucose, and atherogenic dyslipidemia as modifiable risk factors. Some researchers believe that additional signs of inflammation such as plasminogen activator inhibitor-1 and C-reactive protein should be added to this list. Current treatment options include lifestyle changes (diet and exercise), pharmacotherapy, and bariatric surgery. The endocannabinoid system appears to play a key role in metabolism and weight gain. The investigational agent rimonabant is a cannabinoid receptor type 1 blocker that has been employed in numerous trials involving more than 6,500 patients. It has led to significant weight loss, reduced central fat, and improved glycemic and lipid profiles.

KEYWORDS: Metabolic syndrome, Adipose tissue, ATP III guidelines, C-reactive protein, Rimonabant

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Metabolic syndrome has several definitions, some of which remain controversial. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes have discussed doing away with this term. The controversy has plagued this symptom constellation for decades; in the 1980s, Gerald Reaven called it “Syndrome X,” prompting others to ask, “Is it real?” In the 1990s, we referred to “the insulin resistance syndrome,” or resistance to insulin-stimulated glucose uptake. A symptom constellation that transcends simple insulin resistance, however, occurs with great frequency around the world, and although some organizations question whether an actual syndrome exists, even they agree that these symptoms must be addressed aggressively and in concert. Addressing only one of the symptoms is a disservice to patients. Metabolic syndrome’s importance rests on a simple fact: it is associated with a 2- to 4-fold increase in cardiovascular morbidity and stroke.

Many Definitions

Two factors in cardiovascular risk are the underpinnings of the tremendous upsurge in diabetes and the metabolic syndrome: lack of exercise and ample, available, palatable food. The term “cardiometabolic risk” describes the increased risk of cardiovascular and/or metabolic morbidity resulting from a cluster of risk factors. The 2001 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III of the National Cholesterol Education Program [NCEP]) identified a cluster of modifiable risk factors predisposing individuals to cardiovascular and metabolic disease (and type 2 diabetes, which is related). The ATP III list includes elevated blood pressure, smoking, insulin resistance, abdominal adiposity, and elevated blood glucose. It also includes atherogenic dyslipidemia, which may include elevated triglycerides, and/or low high-density lipoprotein cholesterol (HDL-C). Together, these factors increase the risk for cardiovascular and metabolic conditions such as myocardial infarction (MI), stroke, and diabetes.

Risk factors alone are one issue, but when they occur in a pattern that is indicative of a disease, many experts begin to describe them as a syndrome. Recognizing that the presence of cardiometabolic risk factors increases morbidity and mortality, the World Health Organization, International Diabetes Federation, and the NCEPs ATP III have issued practical guidelines identifying this constellation of risk factors as “metabolic syndrome.” Their definitions differ, and there is currently no consensus, although most definitions are similar. Table 1 presents the ATP III guidelines for the clinical identification of metabolic syndrome. Note that they designate gender-specific cut-offs for low HDL and high waist circumference. A diagnosis of metabolic syndrome is made when 3 or more of these risk determinants are present.

Other Factors?

Insulin resistance is a driver of cardiometabolic risk. Insulin
resistance is not solely insulin’s inability to drive glucose into cells. It is a more fundamental problem that remains poorly understood. One might expect that 2 people who eat a candy bar would gain the same amount of weight. In the insulin-resistant individual, however, more energy may be stored as triglycerides in adipose tissue than will be metabolized. The net effect will be that the insulin-resistant individual will have a greater propensity to gain weight than the normal metabolizer.

Inflammation is an additional concern. One inflammatory marker, plasminogen activator inhibitor-1 (PAI-1), is involved in a major clotting mechanism. It is closely associated with cardiovascular disease, and, in fact, when added to other cardiometabolic risk factors, may work synergistically. Although, currently, the best predictor of type 2 diabetes is elevated fasting blood glucose or elevated glucose postchallenge, some researchers believe that, in the future, an elevated PAI-1 may also become an excellent tool to predict type 2 diabetes.6

Elevated blood glucose also represents a risk and may be a mechanism for cardiovascular disease.7 Two large multicenter studies are currently underway to determine the extent to which hyperglycemia is an independent risk factor for myocardial infarction and peripheral vascular disease in individuals with type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study is examining the possibility of preventing major cardiovascular events (heart attack, stroke, or cardiovascular death) in adults with type 2 diabetes mellitus using intensive glycemic control, intensive blood pressure control, and intensive lipid management. This study began enrollment in September 1999, and completion is expected in September 2010. The primary objective of the Veterans Affairs Diabetes Trial (VADT) is assessment of intensive glycemic treatment on cardiovascular events. Microangiopathy, quality of life, and cost-effectiveness are additional objectives being scrutinized. This study is of great interest because the participants come from an elderly population that has high rates of obesity and advanced complications. Enrolling since December 2000, 1,700 men and women with previously uncontrolled diabetes will be maintained on insulin or maximum doses of oral agents at 20 Veterans Affairs medical centers. Accrual is expected to take 2 years, with follow-up for 5 to 7 years.

C-reactive proteins (CRP’s) contribution to disease development is unclear but appears to be tightly correlated with cardiovascular disease and diabetes. The statin drugs primarily used to lower low-density lipoprotein cholesterol (LDL-C) also lower CRP levels. In a study of 3,745 patients treated with either pravastatin or atorvastatin, researchers found that when statin therapy resulted in low CRP levels of <1 mg/L, patients had fewer cardiovascular events (2.4 events per 100 person-years) than with higher levels (3.1 events per 100 person-years). After 4 years of statin therapy, patients who had LDL-C levels of <70 mg/dL or CRP levels of <2 mg/L, patients had fewer cardiovascular events (2.4 events per 100 person-years) than with higher levels (3.1 events per 100 person-years). After 4 years of statin therapy, patients who had LDL-C levels of <70 mg/dL or CRP levels of <1 mg/L had the lowest rate of recurrent events (1.9 events per 100 person-years). They concluded that patients who have low CRP levels have better clinical outcomes than those with higher CRP levels, regardless of the resultant LDL-C levels.8

An elevated CRP level provides some prognostic information for the risk of metabolic syndrome. It is also a predictor for diabetes. Some experts have suggested adding elevated CRP to the list of components of the metabolic syndrome.

Prevalence

Ford et al. applied the ATP III criteria described in Table 1 to 8,814 participants in the Third National Health and Nutrition Examination Survey (1988-1994), a cross-sectional health survey of a nationally representative sample of the noninstitutionalized civilian U.S. population. They estimated the prevalence of metabolic syndrome to be approximately 24% of the total U.S. adult population of 196 million, or 47 million adults.9 The Centers for Disease Control and Prevention’s 2005 data indicate that around 21 million Americans (or 7% of the population) have diabetes, and an additional 41 million people have impaired fasting glucose (sometimes called prediabetes, or a fasting glucose between 100 mg/dL and 125 mg/dL).10

A recent National Institutes of Health (NIH) study reported that people in the United States with impaired glucose tolerance (IGT) may develop diabetes at a rate of about 11% annually.11 Given the prevalence of IGT, the prevalence of diabetes may double within 10 years. Roughly 42% of Americans have elevated fasting glucose levels. When diabetes begins, up to 25% of people have normal fasting glucose levels but elevated postprandial glucose levels.7

### Adipose Tissue as an Organ

Until just a few years ago, it was widely believed that adipose tissue was a fairly inert means of storing excess calories. Now, however, we have learned that adipose tissue is an active

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**TABLE 1**

<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
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<td>ATP III defines metabolic syndrome as consisting of any 3 or more of the following risk factors:</td>
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<tr>
<td>Triglycerides</td>
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<tr>
<td>HDL-C</td>
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<tr>
<td>Fasting glucose</td>
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<td>Blood pressure</td>
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*Note: The American Diabetes Association now defines fasting glucose levels of 100 to 125 mg/dL as impaired fasting glucose, and the American Heart Association has suggested lowering the cutoff to <100 mg/dL. ATP III=Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); HDL-C=high-density lipoprotein cholesterol.*
endocrine organ. Adipose tissue releases fatty acids, which can cause metabolic insulin resistance; it is also associated with higher levels of circulating CRP (a marker of chronic subclinical inflammation) and lower levels of adiponectin. Adiponectin, an adipose tissue-specific circulating protein, improves insulin sensitivity and reduces insulin resistance. Obese subjects and subjects with type 2 diabetes have decreased adiponectin plasma levels, reduced HDL-C, high triglycerides, and small dense LDL-C. (The size of LDL-C is important. Larger LDL-C particles, which appear fluffier (more buoyant) under the microscope, are less atherogenic than the highly oxidized small dense form of LDL-C.) Increased adiponectin levels are associated with a reduction in body weight and reduced levels of insulin, leading to improved insulin sensitivity. Drugs like metformin and the thiazolidinediones increase adiponectin.

Computed tomography (CT) scan or magnetic resonance imaging (MRI) can establish exact adipose tissue location and are considered the gold standards for doing so. Researchers observed in 1947 that women tend to gain weight in 2 separate places: in their hips and centrally (abdominally). Men tend to gain weight abdominally. For several decades, clinicians have embraced an easy description of the differences: “apples” versus “pears.” Apple-shaped people gain weight centrally, while pear-shaped people gain weight toward their hips. Growing circumstantial evidence indicates that visceral (central or apple) fat detected by CT or MRI correlates more closely with metabolic and cardiovascular complications of obesity, increasing diabetes risk up to 10-fold.

Studies have investigated whether removing fat using liposuction might lower cardiometabolic risk. Klein et al. removed 28% to 44% of subcutaneous adipose tissue in 15 obese women. Liposuction did not significantly alter muscle, liver, or adipose insulin sensitivity, nor did it significantly alter CRP, interleukin-6, tumor necrosis factor-alpha, or adiponectin plasma concentrations. Similarly, blood pressure, plasma glucose, insulin, and lipid concentrations did not change. Fat located in the visceral cavity (visceral adiposity), and especially fat located in the liver, is metabolically more active than subcutaneous adipose tissue. The role played by intrahepatic fat accumulation is a major research focus in the gastrointestinal, diabetes, and cardiovascular fields. Researchers postulate that hepatic adipose tissue (fatty liver) may drive increased glucose production, and be part of a gut-central nervous system (CNS) cycle that can regulate metabolism. Thus, the quick fix of simply removing fat surgically is not a solution.

Figure 1 demonstrates the importance of adipose tissue’s location either viscerally or subcutaneously. Abnormally obese individuals who lose body weight tend to experience preferential or selective mobilization of visceral adipose tissue. A reduction of 5% to 10% of body weight can lead to simultaneous improvement in all metabolic markers of coronary heart disease risk. As depicted in the figure, a weight loss of about 10% translates into a visceral adipose tissue loss approximating 30%, which elicits improvement in all metabolic parameters. Insulin resistance is reduced, insulin and blood glucose move downward toward normal levels, risk markers for thrombosis and inflammation improve, and endothelial function improves.

Steps to Improved Care

Patients with metabolic syndrome present with a complicated set of needs. Different practitioners will address cardiometabolic risk factors differently. Endocrinologists tend to treat blood glucose, blood pressure, and lipids together. Busy general practitioners sometimes have to split risk-factor treatment, addressing blood pressure, glucose, and lipids at separate visits. Generally, the steps in a good plan include identifying at-risk patients (as discussed above), encouraging behavior modification, and then using pharmacotherapy.
NIH has published guidelines to help clinicians identify appropriate steps when patients with metabolic syndrome (see Table 2) present for care. Certain lifestyle changes are always appropriate. When body mass index (BMI) is above 27, pharmacologic agents may be indicated if comorbidities are present; if patients are morbidly obese (>100 pounds overweight or have a BMI >35 and at least 2 comorbidities), bariatric surgery is an option. This latter option is used more frequently; the number of gastric bypass surgeries climbed more than 600% from 1993 to 2003, when 103,000 Americans underwent this procedure. Its complications include infection, hernia, gall stones, and malabsorption syndromes.

Exercise continues to be a highly recommended and very effective intervention. In recent years, recommendations are more likely to refer to “physical activity” than exercise, stressing that the benefits of repeated brief periods of as little as 10 minutes of activity during the day are cumulative. In 1996, the U.S. Surgeon General recommended that most American adults need a minimum of 30 minutes of physical activity most days of the week. Yet, approximately 25% of the population does not exercise at all. A September 2002 Institute of Medicine (IOM) report more than doubled the time recommended to at least 60 minutes of moderately intense physical activity—such as brisk walking—every day. It recommends twice that amount if the goal is weight loss.

The 1996 recommendation was based on research showing that 30 minutes of physical activity most days of the week could reduce the risk of many chronic diseases. The IOM based its recommendation on evidence showing that 30 minutes of activity most days of the week may be insufficient for most people to maintain an ideal weight and achieve maximum health benefits. These recommendations acknowledge that Americans consume more calories than ever before, and are becoming heavier. Clearly, public health and public opinion must change, and the best place to initiate the change and establish exercise as a habit is among children.

Numerous drug therapies are available for the constellation of risk factors described herein. These would include

- the antiobesity agents: sibutramine (an anorexiant that may cause hypertension and increased sympathetic activity) and orlistat (a lipase inhibitor that often causes a gastrointestinal malabsorption syndrome); use of either agent usually results in a moderate weight loss of approximately 4% to 8.5% of body weight at 2 years of treatment; the antihypertensive agents, noting that some of the newer antihypertensive agents have pleotropic effects (simultaneous effects on multiple systems);
- the oral antidiabetic agents, many of which have dose- and compliance-limiting side effects;
- insulin and the new injectable antidiabetic agents: exenatide and pramlintide acetate;
- lipid modifiers;
- and antiplatelet agents.

No specific “metabolic” anti-inflammatory agent has been developed or approved by the U.S. Food and Drug Administration yet. These therapies and interventions are not completely effective against metabolic syndrome nor are they always easy to comply with—with or without side effects. Something new is needed.

**Something New**

Since dietary changes and exercise appear to be insufficient to blunt the increase in obesity, another intervention is needed, perhaps one that would address the problem at both the CNS and peripheral target organ level. The endocannabinoid system (ECS) is a very important neuromodulatory signaling system. ECS plays a major role in many important physiologic processes, including energy homeostasis, regulation of body weight and metabolic processes, and motivational behaviors. Unfortunately, excessive food, especially palatable food, increases ECS activity and subsequently increases fat accumulation.

Cannabinoid receptors are distributed throughout the brain and body, with 2 types of G-protein-coupled cannabinoid receptors. Cannabinoid receptor type 1 (CB1) is expressed predominantly in the central and peripheral nervous system, while cannabinoid receptor type 2 (CB2) is present almost exclusively in immune cells. Besides the well-known exogenous phytocannabinoids of the cannabis plant, endogenous cannabinoid ligands work very actively at these receptors and are cleared almost instantaneously. These endocannabinoids, derivatives of arachidonic acid, are produced as needed by cleavage of membrane lipid precursors (much like prostaglandin is). They play an important part in everyday physiology. The effects of ECS overactivity are presented in Figure 2. A CB1 blockade produces a lean phenotype in animals, with resistance to diet-induced obesity and associated dyslipidemia.
Rimonabant is a new selective CB1 blocker. It has been studied in more than 6,500 patients in multicenter international studies in the United States and Europe. The Rimonabant in Obesity (RIO)-Europe study assessed rimonabant’s effect on body weight and cardiovascular risk factors in 1,509 overweight or obese patients. Participants had BMIs of ≥30 kg/m² or BMIs >27 kg/m² with treated or untreated dyslipidemia, hypertension, or both. They were randomized to receive double-blind treatment with placebo, 5 mg rimonabant, or 20 mg rimonabant once daily. They followed a mild hypocaloric diet (600 kcal/day deficit) for 1 year. Weight loss was significantly greater in patients treated with rimonabant 5 mg (mean loss of 3.4 kg [SD 5.7]; P = 0.002 vs. placebo) and 20 mg (mean loss of 6.6 kg [SD 7.2]; P<0.001 vs. placebo) compared with placebo (mean loss of 1.8 kg [SD 6.4]). Patients treated with rimonabant 20 mg were significantly more likely to lose 5% of their body weight than those treated with placebo. Compared with placebo, rimonabant 20 mg was associated with significantly greater improvements in waist circumference, HDL-C (increases of approximately 25%), triglycerides (decreases of 18%), insulin resistance, and prevalence of metabolic syndrome.  

Study participants in the rimonabant 20 mg group were more likely to experience adverse events leading to discontinuation than those in the rimonabant 5 mg and placebo groups. Common adverse events included nausea, dizziness, arthralgia and diarrhea, events that were generally mild to moderate in intensity. They also tended to be transient, occurring primarily during the first months of treatment. Although there were concerns that this centrally acting drug may cause psychiatric or nervous system adverse events, the incidence of these was generally low; however, discontinuation rates due to anxiety, depression, and nausea were slightly higher than placebo.  

Clearly, weight loss alone improves cardiovascular risk factors, and it would be important to tease out effects of treatment unrelated to weight loss. In the rimonabant trials, researchers were able to elucidate effects in excess of those related to weight loss because active treatment was compared with control. This allowed covariance analysis to test whether rimonabant treatment affected insulin resistance beyond the effect of greater weight loss produced by rimonabant. After adjustment for the differences between groups in weight loss, rimonabant’s effect on both fasting insulin and estimated insulin resistance was found to be significant. Roughly half of the change in both variables could be attributed to weight loss and half of the improvement in insulin resistance was independent of rimonabant-induced weight loss. Rimonabant’s peripheral and central effects seemed to influence risk factors positively.

With each 1 mg/dL increase in HDL-C, cardiovascular risk and mortality falls 2%. Thus, rimonabant’s effect on HDL-C is an important finding, considering that the prevalence of cardiovascular risk has increased 30% in dyslipidemic patients in the last 10 years. Diabetes-related death from cardiovascular disease is increasing and expected to continue increasing unless effective interventions are found. Other modalities, such as exercise, can improve HDL-C, but this lifestyle change is a challenge for patients. Some treatment modalities may actually aggravate metabolic syndrome. Niacin has been used as a lipid modifier, for example, but at dosages exceeding 2 grams per day, insulin resistance increases.

Another recently published RIO study, RIO-Lipids, examined changes in leptin and adiponectin. Study investigators found that if fat mass diminishes pursuant to treatment with rimonabant, leptin levels will fall and adiponectin levels, which improve insulin sensitivity, will rise. CRP, an important surrogate marker for inflammation, also tends to fall, reflecting a reduction in inflammation. Based on the results of the RIO-North America study, nondiabetic individuals with metabolic syndrome who were treated with rimonabant for 2 years experienced a 35% reduction in metabolic syndrome while, among diabetics, the reduction was 19%.

The latest RIO study to report was the RIO-Diabetes study, which found that patients who received 20 mg of rimonabant had a reduction of glycosylated hemoglobin (A1c) of 0.6% from baseline levels of 7.3%, and weight and waist circumference were reduced 11.7 pounds and 2 inches, respectively, compared with those taking placebo. The mean difference between rimonabant and placebo was that rimonabant-treated patients lost a mean difference of 8.6 pounds more than those treated with placebo, with each 2.2 pounds corresponding to 0.4 inches of waist circumference loss. HDL-C and triglyceride levels were also similarly significantly improved compared with those found in RIO-Europe. Future studies may support use of rimonabant for the spectrum problems related to diabetes, or possibly to delay its onset.

**Summary**

Despite extensive medical advances in risk management, patients still experience cardiovascular events and develop type 2 diabetes. Current treatment paradigms tend to treat only a single element of the constellation of risk factors, for example, dyslipidemia, or glucose, or abdominal adiposity, or hypertension, but new therapeutic advances including the CB1 receptor blocker, rimonabant, combined with a hypocaloric diet, may reduce cardiometabolic risk and may sustain health benefits. If rimonabant in combination with other weight-loss interventions is shown to produce significant weight loss, it may eliminate the need for many bariatric surgeries.

**DISCLOSURES**

This article is based on the proceedings of a symposium held on October 7, 2005, at the Academy of Managed Care Pharmacy’s 2005 Educational Conference in Nashville, Tennessee, which was sponsored by the Benefit Design Institute and was supported through an educational grant from sanofi-aventis. The author received an honorarium from sanofi-aventis for participation in the symposium. He has received grants from sanofi-aventis, Bayer, and Eli Lilly and Company. He discloses no potential bias or conflict of interest relating to this article.
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ABSTRACT

OBJECTIVE: To review managed care’s current cost management trends and the consumerism movement; to elucidate the pros and cons of key issues; and to describe the philosophy of focusing on the patient, also called patient-centric care, while improving the patient’s care through value-based purchasing and plan design.

SUMMARY: Managed care is sometimes practiced using a silo approach with little concern for the consumer. In this model, medical and pharmaceutical issues are addressed in silos, and value is narrowly defined. Increasingly, cost and responsibility is shared with or shifted to the patients. Patients may be unable or unwilling to assume these costs or responsibilities. Several studies have demonstrated that they may react with noncompliance. Managed care’s definition of value must expand and integrate across silos to consider the needs and interests of the patient’s overall care, in particular, addressing key cost drivers in terms of diseases that cause recurring costs. Using predictive modeling can result in cost savings. A case study (Pitney Bowes) is included in this article.

KEYWORDS: Cost management, Silos, Pharmaceuticals, Consumers, Consumerism, Predictive modeling, Key cost drivers

A discussion of managing cost is necessary and appropriate because managed care was market-driven to manage cost. Managing cost has 3 components: lowering unit price, reducing the number of units used (utilization), and examining the product/service mix. In terms of lowering the unit price, managed care plans frequently use volume purchasing as a strategy. In the medical management area, they often restrict networks or hospital physicians to increase leverage for discounts. To address utilization via medical management, they implement plan designs with disincentives that target physicians and patients to decrease service utilization and unnecessary service use. Some systems require patients to schedule care through an advice nurse. The strategy employed to address the mix of services is often cost-based substitution. Plans may prefer that patients see primary care physicians who are reimbursed at a lower rate than specialists. When gatekeepers increasingly assume more responsibility, point-of-care providers are leveraged and rewarded to reduce overall costs.

Pharmacy has sometimes evolved in a silo that is completely separate from the medical model, but its strategies and tactics used to address unit pricing, utilization, and therapeutic mix are exactly the same. Pharmacy networks are akin to hospital networks, and formularies provide leverage and reduce unit cost. Mandating generic substitution is akin to using prior authorization; it simply reduces accessibility to more-costly brand-name drugs.

These cost-management strategies have been effective in reducing cost trends. In the early stages of their evolution, between 1992 and 1994, premiums did fall each year. However, after remaining flat for 2 years, and during the last few years, premiums have increased steadily (See Figure 1). Medical directors and health benefits managers have had to justify double-digit increases that exceed inflation rates of only 2% or 3%. Managed care’s business people want to control costs, however.

As cost continues to rise and the focus on pharmacy costs, in particular, increases, the trend has been to increase the carve-out (specialty health services obtained by contracting with a company that specializes in that service) to leverage unit prices down further, make prior-authorization criteria stricter, and implement...
automated processes to limit utilization. Market and regulatory pressures are driving increased consumer involvement through pricing transparency (allowing consumers to see the cost strategy, disclosure of rebates and future drug purchase credits, acknowledgment of fees received from networks or pharmacies, and disclosure of real and potential conflicts of interest) and shifting more cost to consumers. Increasingly, the philosophy is if consumers want something, they should pay for it. At the same time, under the mantra of consumer advocacy, regulators have imposed more restrictions on prior-authorization regulations, defined fraud and abuse much more broadly, and created different kinds of pricing transparency regulations, thereby relegating the decision making to the ultimate consumer.

As cost pressures increase, there is increased focus on carve-outs to intensify cost management, thereby making overall care management difficult. Even specialty pharmacy is being carved out by therapeutic class and by disease state. Increasingly, carve-outs like pharmacy and mental health are riders on basic catastrophic plans to reduce premium trends. Shifting cost and responsibility to the consumer makes sense in a market economy since consumers are the ultimate beneficiaries of health care choices. They can help control costs through demand management and demand for market pricing. However, merely shifting cost and responsibility without appropriate consideration for access can marginalize the patient’s overall cost, care, and outcome.

Cost shifting is not a new concept. Examples include the 3-tier copay and new consumer-directed health plans. California now allows $5,000 deductibles, making it the first state to allow the first $5,000 of health care costs to come completely from the patient’s pocket.

So what is wrong with this? The vast majority of consumers do not have the skills necessary to manage their own health care, and many have no interest.

### Need Versus Choice

Blatant examples confirm that consumers may make poor choices and are not always accountable. Despite decades of campaigns to educate Americans about the dangers of smoking, almost 25% of women and 33% of men still smoke. Similarly, people are well aware of the dangers of being overweight and the benefits of exercise, but many sustain unhealthy, irresponsible lifestyles. Thirty percent of U.S. adults aged 20 years and older—more than 60 million people—are obese. Ultimately, someone else is financially responsible for the risks smokers and obese individuals assume because, in catastrophic cases, the individual will be unable to afford medical costs. In fact, health care expenses are now the number one reason for personal bankruptcy in the United States.

Each patient is different, not only clinically but also in his or her ability to pay, and, historically, plan designs have been “one size fits all.” All patients, regardless of income, have paid the same copayment. Further, consumers are unclear about available choices; they receive information from multiple carve-outs that is not always aligned or consistent. Considering that consumers receive information from pharmacists, physicians, their utilization management component, compliance and disease management departments, and direct-to-consumers advertisements, their inability to make sense of cost and quality is understandable. Then, payers implement plan designs that make it harder and harder for consumers to access the products that they want or need.

Payers continue to increase funding for compliance programs while increasing copayment amounts. What kind of message is that sending? When tracking compliance, or noncompliance, the copayment amount is quite relevant in terms of income level. Coincidentally, the population with the lowest income often tends to be the population with the highest health risk in this country, for a number of different reasons.

Taylor and Leitman conducted an interactive telephone survey to determine if out-of-pocket copayments required to fill prescriptions were a compliance barrier. They asked respondents to report if they had (1) not filled a prescription in the previous year because of cost, or (2) taken medication in doses smaller than prescribed to save money, or (3) taken medicine less frequently than prescribed as a cost-savings mechanism. They also gathered household income information, recognizing that the average household income in the United States approaches $40,000. They found that 79% of patients earning less than $25,000 annually had failed to fill prescriptions because of out-of-pocket cost. In patients from households at or above the national income average, approximately 18% of respondents reported not filling prescriptions because of cost. Among all adults, regardless of income, 22% did not fill a prescription, 14% took less medication than prescribed, and 16% took medication less often than prescribed because of cost. Rates were significantly higher in all...
3 types of noncompliance among people with disabilities (35%, 27%, and 28%, respectively). Thus, unaffordable copayments represent a compliance barrier. Patients may take no medication rather than switch to a generic medication or pursue a less-costly alternative.

Discontinuation rates also increase, sometimes dramatically, when payers switch preferred products. Huskamp et al. examined the repercussions of implemental changes in formulary administration for angiotensin-converting enzyme (ACE) inhibitors, proton pump inhibitors (PPI), and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in 2 employer-sponsored health plans. They compared groups of enrollees covered by the same insurers. One plan switched from a 1-tier to a 3-tier formulary and increased all enrollee medication copayments simultaneously. The second switched from a 2-tier to a 3-tier formulary but changed only the tier-3 copayment amount.

More dramatic formulary changes reduced the probability that enrollees used ACE inhibitors, PPIs, or statins and markedly shifted spending from the plan to the enrollee. Among the enrollees who were initially taking tier-3 statins, 21% stopped taking statins entirely compared with 11% in the comparison group. Similar patterns were observed for ACE inhibitors and PPIs. Enrollees covered by the employer who implemented more moderate changes were more likely to switch to tier-1 or tier-2 medications but not to discontinue these medications altogether than were the comparison enrollees. Copayment changes can alter enrollees’ out-of-pocket spending considerably, cause unauthorized medication discontinuation, and possibly alter the quality of care.

In any employer or health plan population risk pool, a small percentage of patients tend to account for the overwhelming amounts of cost. Approximately 20% to 25% of patients tend to account for 85% of costs, and, in the Medicare population, the statistics are more dramatic. Clinically, this means that if, as the previous studies suggest, 15% to 16% of patients may stop taking medication pursuant to cost-shifting strategies implemented by plans, if they happen to be the sickest 15% or 16%, the outcomes in terms of morbidity and mortality might be disastrous. In the context of metabolic syndrome for diabetes, experts estimate that the global economic burden of illness for diabetes is 2.7 to 3 times greater than that for healthy individuals. They also estimate that the burden of illness for metabolic syndrome is higher (from 3 to 4 times greater) because of its comorbidities: it may consumes 21% to 40% of the U.S. health care budget.

### Silo Disconnects

Managing medical care separate from managing pharmacy cost can result in a significant disconnect. Unfortunately, Medicare legislation further intensifies the silo cost management by shifting risks to the pharmacy benefits manager (PBM) by therapeutic class. However, we need to be concerned about the overall cost of health care to the payer. As such, “value” needs to be redefined. It needs to encompass overall cost, including total medical costs, disability costs, lost productivity, and liability costs. It also needs to address quality outcomes: clinical improvement, increased productivity, decreased population risk, and patient satisfaction.

To do so, the paradigm much shift from a “pharmaco-centric” model to a “payer-centric” model. A pharmaco-centric model assesses the value of a product within therapeutic classes in silos. A payer-centric model assesses a product based on its contribution to the payer’s goals—decreasing overall cost, improving overall outcomes, and increasing productivity. Value-based purchasing and plan designs may vary based on specific populations’ needs in terms of their demographics and health risks. But in order to meet specific population needs, a patient-centric model is necessary. Our goal in managed care is ultimately to improve overall outcomes and overall satisfaction, not specific silos, trade-offs, different products, and carve-outs.

In this context, pharmaceuticals should not be considered as a separate silo but as a part of the value-added chain of health care benefits that include prevention, primary, secondary, and tertiary health care; mental health, and overall health care (see Figure 2).

### Case Study

In 2001, Pitney Bowes faced numerous threats to its health care benefit. Chronic disease was pushing unit cost and utilization upwards, and its members had an unexpected number of recurring medical problems and changing diagnoses. The company developed an innovative plan design and has tracked outcomes since its implementation. Using a predictive modeling tool (technology employing rules-based algorithms or artificial intelligence to predict future expenses), the company identified the key cost drivers in its population in terms of medical costs: asthma, diabetes, and cardiovascular disease, primarily hypertension. It found a strong association between chronic condition progression and a lack of screening or prevention and also low possession rates for medications necessary to treat the condition. Thus, it concluded that poor medication compliance was a key
driver of increasing costs. Pitney Bowes changed its overall plan to incorporate more disease management and to approach pharmaceuticals differently. It used a coinsurance as opposed to a strict copayment, so although there was a small differential between brand and generic medications, it was not cost prohibitive. Generic medications were not mandatory. They made all first-tier medications accessible and made all medications to treat asthma, diabetes, and hypertension first tier. They also limited prior authorizations.

Since these allowances designed to benefit patients have been made, there has been an interesting migration to combination products. (This is unlike general trends among PBMs, wherein combination products tend to migrate to the top tier. Rebate contracting for combination products is difficult; it reduces the number of claims and, thus, reimbursement.) Patients were more likely to adopt new drugs early, and tier-1 generic drug users were more likely to discontinue medication than others.

Drug possession among patients, a compliance indicator, improved significantly, particularly for patients with asthma and diabetes who switched to brand products.

Compliance with combination oral hypoglycemics increased significantly. Preliminary data indicated that the annual cost of chronic disease care decreased 6% for diabetes and 15% for asthma during fiscal years 2002 and 2003, although the prevalence of these conditions increased. (The savings are not adjusted for this trend.) These savings were sustained in 2004. Pharmacy costs decreased 7% for asthma and 19% for diabetes, probably because of decreased reliance on medications to treat complications and exacerbations. “Controller” drugs became more important than “rescue” drugs. Savings in short-term disability and absenteeism were also posted. It took approximately 3 years to see a return on investment for hypertension, in keeping with its longer lag time to impact medical cost.

Summary

The overall picture for plan design is one of conflicting messages and ample challenge. Business incentives and management incentives have rewarded short-term reduction of cost trends within silos. At the same time, high copays are strong disincentives for consumers to access and adhere to therapies. Change will require a fundamental shift in managed care.

The issues are not insignificant, but they must be addressed if we are to attain affordable cost and quality outcomes. The process must begin with a recognition of and appreciation for value. This country struggles with some health care reform issues like integrated financial quality accountability, pay for performance, consumer physician decision support with information technology systems, and physician reimbursement and documentation. Rewarding and promoting access to value are driven through benefit design. It is central to driving consumer access, using lower out-of-pocket expense and, ultimately, improving the consumer’s behavior and compliance.

DISCLOSURES

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REFERENCES

The Role of Pharmaceuticals in Reducing Cardiometabolic Risk: Rethinking Pharmacy Benefit Design to Reduce the Burden on the Health Care System

Managed Market Resources is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. A total of 0.20 CEUs (2.0 contact hours) will be awarded and a continuing education statement will be sent to pharmacists for successful completion of this continuing education program, which is defined as receiving a minimum score of 70% on the posttest and completion of the Program Evaluation form. ACPE Universal Program No. 788-000-05-002-C01. (Release date: January 1, 2006; Expiration date: December 31, 2006)
5. The ADA now defines fasting glucose levels of ____ as prediabetes.
   a. 90 to 115 mg/dL
   b. 100 to 140 mg/dL
   c. 100 to 125 mg/dL
   d. 118 to 125 mg/dL

6. Plasminogen activator inhibitor-1 (PAI-1) is
   a. involved in a major clotting mechanism.
   b. loosely associated with cardiovascular disease.
   c. a poor predictor of type 2 diabetes.
   d. of no interest to endocrinology researchers.

7. According to a study conducted by Ford et al. using the Third National Health and Nutrition Examination Survey, what is the prevalence of metabolic syndrome in the United States?
   a. 11%
   b. 24%
   c. 34%
   d. 47%

8. Which of the following is false?
   a. Adipose tissue releases triglycerides and fatty acids, which can cause insulin resistance; it also releases the inflammatory marker CRP and adiponectin.
   b. Adiponectin, an adipose tissue-specific circulating protein, improves insulin sensitivity and reduces insulin resistance.
   c. Obese subjects and subjects with type 2 diabetes have decreased adiponectin plasma levels.
   d. Increasing serum adiponectin levels are associated with an increased body weight.

9. Select the answer that best describes what the statin drugs do.
   a. Elevate LDL, elevate CRP levels
   b. Elevate LDL, lower CRP levels
   c. Lower LDL, elevate CRP levels
   d. Lower LDL, lower CRP levels

10. Select the statement that is true concerning adipose tissue:
    a. CT scan or MRI cannot establish exact adipose tissue location.
    b. Researchers have known since 1947 that men tend to gain weight in 2 separate places: in their hips and centrally (abdominally).
    c. Women tend to gain weight abdominally only.
    d. Growing circumstantial evidence indicates that visceral fat detected by CT or MRI correlates more closely with metabolic and cardiovascular complications of obesity, increasing diabetes risk 10-fold.

11. Fat located in the visceral cavity (visceral adiposity), and especially if it is located in the _______, is metabolically more active than subcutaneous adipose tissue.
    a. liver
    b. kidney
    c. subcutaneous layer
    d. GI areas

12. Abdominally obese individuals who lose 10% of their body weight will experience preferential or selective mobilization of visceral adipose tissue. This leads to
    a. slight improvement in selected metabolic markers of coronary heart disease risk.
    b. a visceral adipose tissue loss approximating 30%.
    c. stable insulin resistance, insulin, and blood glucose.
    d. thrombosis and inflammation.

13. According to the National Institutes of Health guidelines, which of the following interventions would be best for an individual who is more than 100 pounds overweight?
    a. Dietary changes
    b. Dietary changes and exercise
    c. Dietary changes, exercise, and pharmacologic agents
    d. Dietary changes, exercise, and pharmacologic agents or bariatric surgery if the patient is a good candidate for drugs or surgery

14. Select the sentence that is false.
    a. The endocannabinoid system (ECS) plays a major role in energy homeostasis, regulating body weight and metabolic processes, and motivational behaviors.
    b. Starvation, especially that associated with binge dieting, increases ECS activity and subsequently increases fat accumulation.
    c. Cannabinoid receptor type 1 (CB1) is expressed predominantly in the central and peripheral nervous system, while cannabinoid receptor type 2 (CB2) is present almost exclusively in immune cells.
    d. CB1 blockade produces a lean phenotype in animals, with resistance to diet-induced obesity and associated dyslipidemia.

15. The CB1 blocker rimonabant
    a. was associated with mild-to-moderate nausea, dizziness, arthralgia, and diarrhea at a dose of 20 mg daily.
    b. was associated with mild-to-moderate headache fatigue and respiratory infection at a dose of 20 mg daily.
    c. was associated with mild-to-moderate headache fatigue and respiratory infection at a dose of 5 mg daily.
    d. was associated with dose-limiting nausea, dizziness, arthralgia, and diarrhea at a dose of 5 mg daily.
16. The effect of rimonabant treatment on insulin resistance after adjustment for the differences between treated and control groups in weight loss was
a. slight.
b. encouraging.
c. significant.
d. centrally mediated.

17. Which of the following is not a cost-management component?
a. Lowering unit price
b. Reducing the number of units used (utilization)
c. Examining the product/service mix
d. Soliciting customer input

18. Which of the following statements is true about greater consumer involvement in health care decisions?
a. All consumers embrace the idea of paying more, but having more decision-making ability.
b. Shifting costs to consumers never affects their compliance rates.
c. Teaching consumers to make informed choices and helping them manage their own care could lead to the dismantling of infrastructure developed over the last 20 years to manage costs.
d. The large majority of consumers are able to sort through and assimilate information that they receive from various representatives of the health care system.

19. Taylor and Leitman’s telephone interactive survey to determine if out-of-pocket copayments required to fill prescriptions were a compliance barrier found that
a. 79% of patients earning less than $25,000 annually had failed to fill prescriptions because of out-of-pocket cost.
b. in patients from households at or above the national average, approximately 79% of respondents reported not filling prescriptions because of cost.
c. among all adults regardless of income, 79% did not fill a prescription, and 5% took less medication than prescribed because of cost.
d. out-of-pocket expense only affects compliance in the highest income categories.

20. Which of the following statements describes the Pitney Bowes system initiated in 2001?
a. It was implemented to address increasing costs despite few recurring medical problems among its members.
b. It was based on predictive modeling that found that the number of prescriptions filled, good compliance with antidepressants, and health expenditures less than $781 annually were associated with increased cost in the next year.
c. It moved all combination products into the third tier.
d. It led to significantly improved drug possession among patients, particularly for patients with asthma and diabetes who switched to brand products.

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