



# Indiana Medicaid Drug Utilization Review Board Newsletter

Volume 12 Issue 3

August 2009

**Indiana Medicaid DUR  
Board  
Room W382  
Indiana State Government  
Center, South  
402 West Washington  
Street  
Indianapolis, Indiana 46204**

### DUR Board Members

Brian W. Musial, RPh (Chair)  
John J. Wernert, MD (Vice-chair)  
William J. Brown, MS, RPh  
Philip N. Eskew, Jr., MD  
Terry Lindstrom, PhD  
Kent Summers, RPh, PhD  
Patricia A. Treadwell, MD

### Inside this Issue

- **Highlight on Metabolic Syndrome**
- **Top 20 Drugs for 2Q2009**

### Highlight on Metabolic Syndrome Karen M. Powell, Pharm.D., Clinical Pharmacist

Approximately 34% of all U.S. adults (age  $\geq 20$  years) meet the criteria for metabolic syndrome. The prevalence of metabolic syndrome increases with age. While about 20% of men and 16% of women under the age of 40 meet criteria, 52% of men and 54% of women 60 years of age and older meet criteria.<sup>1</sup> Additionally, metabolic syndrome is twice as prevalent in women with polycystic ovary syndrome compared to controls matched for age and body mass index.<sup>9</sup> The most frequently occurring risk factors for metabolic syndrome are obesity (53%), hypertension (40%) and hyperglycemia (39%).<sup>1</sup>

#### Definition

In the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III Report (ATP III), metabolic syndrome is a constellation of factors that increase a person's risk of developing atherosclerotic cardiovascular disease (CVD). These risk factors include:

- Abdominal obesity
- Atherogenic dyslipidemia
- Elevated blood pressure
- Insulin resistance
- Prothrombotic state
- Pro-inflammatory state

Individuals with metabolic syndrome are not only at risk for developing heart disease and diabetes, but they also have higher incidences of cardiovascular and all cause mortality.<sup>2</sup> Early diagnosis and implementation of prevention strategies may decrease the risk of developing CVD and type 2 diabetes (T2DM) in those patients who have not yet developed it.<sup>3,7</sup>

Based upon a 24-month review of pharmacy and medical claims for Indiana Medicaid submitted from March 2007 through March 2009, an analysis of this data revealed the following:

### Underutilization of Preventive Interventions and Screenings (Indiana Fee-for-Service Population)

| Clinical Issue  | # Patients Meeting Criteria | # Total Metabolic Syndrome Patients | Incidence |
|---|-----------------------------|-------------------------------------|-----------|
| Underutilization of lipid lowering therapy in metabolic syndrome patients with hyperlipidemia, CHD or a CHD risk equivalent | 5,845                       | 11,388                              | 51.3%     |
| Underutilization of antihypertensive therapy in metabolic syndrome patients with HTN, CVD, or T2DM                          | 5,065                       | 11,388                              | 44.5%     |
| Underutilization of antiplatelet therapy in metabolic syndrome patients with CVD, T2DM, or a 10-year risk for CHD $>20\%$   | 5,789                       | 11,388                              | 50.8%     |
| Underutilization of antidiabetic therapy in metabolic syndrome patients with T2DM   | 5,289                       | 11,388                              | 46.4%     |

CHD = coronary heart disease; CVD = cardiovascular disease; HTN = hypertension; T2DM = type 2 diabetes

Continued on page 2

Continued from page 1

Several organizations have proposed definitions or diagnostic criteria for metabolic syndrome. The International Diabetes Foundation (IDF) and the American Heart Association in conjunction with the National Heart, Lung, and Blood Institute (AHA/NHLBI) each developed a set of criteria that offer the most practical use in the clinical setting. The Clinical Guidelines Subcommittee of the Endocrine Society suggest using the AHA/NHLBI criteria because they are easy to use and implement in the office setting.<sup>3,7</sup>

### Clinical Management

The primary goal of clinical management of metabolic syndrome is to reduce the risk of developing atherosclerotic CVD and T2DM by appropriately managing underlying risk factors through lifestyle changes and drug therapy when appropriate. The therapeutic targets and goals of therapy for each risk factor are listed below.

#### Abdominal Obesity

- Weight reduction
  - Reduction of 5% to 10% of total body weight in the first year of therapy
- Decrease waist circumference
  - <120 cm in men and <88 cm in women of non-Asian origin
  - <90 cm in men and <80 cm in women of East or South Asian origin

Weight reduction should be a top priority in individuals with abdominal obesity and metabolic syndrome. Achieving the recommended amount of weight loss will reduce the severity of most or all of the other risk factors. Maintenance of a lower weight is just as important; this requires long-term follow-up and monitoring. Although reaching these targets is optimal, any lowering of body weight or waist circumference is beneficial.<sup>3,7</sup>

#### Atherogenic Dyslipidemia

- Lower apo B-containing lipoproteins (LDL-C and VLDL-C)
  - High-risk patients: LDL-C <100 mg/dl (very-high-risk optional <70 mg/dl); non-HDL-C <130 mg/dl (very-high-risk optional <100 mg/dl)
  - Moderately high-risk patients: LDL-C <130 mg/dl (optional <100 mg/dl); non-HDL-C <160 mg/dl (optional 130 mg/dl)
  - Moderate-risk patients: LDL-C < 130mg/dl; non-HDL < 160mg/dl

Consistent with NCEP ATP III treatment recommendations, LDL cholesterol (LDL-C) is the main target of therapy. After the LDL goal is reached, a non-HDL goal is targeted if triglyceride levels are  $\geq$  200 mg/dl. If triglyceride levels are  $\geq$  500 mg/dl, triglyceride lowering drug therapy should be used to decrease the risk of pancreatitis.<sup>2,3,7</sup>

#### Elevated Blood Pressure

- Lower blood pressure
  - <140/90 mmHg or <130/80 mmHg in individuals with diabetes or chronic kidney disease

Recommendations for hypertension follow the 7<sup>th</sup> Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).<sup>4,7</sup>

#### Insulin Resistance

- FPG <100 mg/dl
- 2-hour post glucose challenge <140 mg/dl
- HbA1C  $\leq$  7% in patients with diabetes

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are strong predictors of progression to T2DM and have been associated with increased CVD risk. Strategies to achieve normal levels of fasting plasma glucose (FPG) should be initiated.<sup>3,7,8</sup> For patients with diabetes, the recommended target for hemoglobin A1C (HbA1C) follows the American Diabetes Association (ADA) standard of care recommendations.<sup>3,6,7</sup>

#### Prothrombotic/Proinflammatory States

Currently, there are no specific treatment targets for the prothrombotic and proinflammatory states associated with metabolic syndrome. Lifestyle modifications can reduce coagulation factors (e.g., fibrinogen, plasminogen activator inhibitor-1) and inflammatory factors (e.g., tumor necrosis factor- $\alpha$ , interleukin-6, C-reactive protein).<sup>3,6,7</sup>

### Management of Underlying Risk Factors

#### Lifestyle Modifications

Lifestyle modifications are emphasized as primary therapy since they can reduce markers for all of the CVD risk factors. Reductions in LDL-C, blood pressure, plasma glucose, coagulation factors, antifibrinolytic factors, and CRP levels and increases in HDL cholesterol (HDL-C) have been achieved with lifestyle modifications. Lifestyle modifications include antiatherogenic dietary modification, a program of increased physical activity, weight reduction, and smoking cessation.<sup>3,7</sup>

#### Dietary Modifications

A diet low in saturated fat (<7% of total calories), *trans* fats (<1% of total calories), cholesterol (< 200 mg/day), and sodium (<2 g/day) should be prescribed. Additionally, patients should consume 2 grams per day of plant sterols (found in corn, wheat, soy, certain nuts and seeds, stanol ester dietary supplements, and fortified beverages, spreads, salad dressings and yogurt) and 5-10 grams per day of viscous fiber. Much controversy is involved with carbohydrates – whether a “low carb,” “no carb” or “40/30/30” diet is best. However, as a general rule, patients should increase the proportion of fiber and unprocessed grains and avoid foods with a high glycemic index (e.g., simple sugars).<sup>3,7</sup>

Continued from page 2

### Exercise

Increasing physical activity will have beneficial effects on all of the CVD risk factors and will help with both weight loss and maintenance. Patients should be encouraged to get 30-60 minutes of moderate-intensity aerobic activity, which can include brisk walking on most (and preferably all) days of the week. Increasing the duration to 60 minutes can further help to promote both weight loss and maintenance.<sup>3,7</sup>

### Weight Loss

Strategies for losing weight include decreasing caloric intake by 500 to 1,000 calories per day, increasing the consumption of nutrient-rich foods, increasing physical activity and formal behavior modification programs. FDA-approved weight-loss medications are available; however, their clinical utility is unknown since successful weight loss and maintenance requires a long-term commitment with lifestyle modifications.<sup>3,7</sup>

### Smoking Cessation

Smoking is a known risk factor for CVD. All patients with metabolic syndrome who smoke should be regularly encouraged to stop smoking. While there are drug therapies to assist with smoking cessation, the products are most successful when used in conjunction with behavior modification programs.<sup>7</sup>

### **Drug Therapy**

Currently, no medications are approved specifically to treat metabolic syndrome; however, effective therapies are available to treat the individual components of the syndrome. If weight loss and lifestyle modifications are not successful or if a patient's absolute risk of developing CVD is very high, consideration should be given to incorporating drug therapy with lifestyle modifications. Drug therapy should be directed towards any of the metabolic risk factors present, especially if therapy is recommended based on current treatment guidelines for hyperlipidemia, hypertension, or diabetes. The appropriate antilipemic, antihypertensive, antidiabetic or antiplatelet therapy should be instituted and dose adjusted to treat to target.<sup>3,7</sup>

The HMG-CoA reductase inhibitors, or statins, can significantly lower both LDL-C and triglycerides and increase HDL-C. Additionally, statin therapy has decreased the risk of morbidity and mortality in patients with or without established heart disease in numerous trials. If further triglyceride lowering is needed, a fibrate or nicotinic acid can be added to statin therapy. However, extra monitoring for signs and symptoms of myopathy is needed with this combination.<sup>2,7</sup>

Several different drug classes are FDA-approved for the treatment of hypertension. While no specific antihypertensives are recommended for use in patients with metabolic syndrome, patients with established heart disease, diabetes, or stroke may benefit from the use of certain antihypertensives such as beta-blockers, ACE-inhibitors or angiotensin receptor blockers.<sup>4</sup>

The concept that patients with overt diabetes should receive antidiabetic therapy is well-accepted. In fact, the consensus algorithm for the management of T2DM developed by the ADA

and the European Association for the Study of Diabetes recommends initiating metformin therapy in conjunction with lifestyle modifications at diagnosis.<sup>7</sup> However, controversy surrounds whether patients with IFG and/or IGT should be treated with drugs.<sup>7,8</sup> While metformin, thiazolidinediones (TZDs), and acarbose have decreased the risk of developing diabetes in some trials, neither of the current treatment guidelines recommend drug therapy in these patients due to three reasons:

1. Lifestyle therapies appear to be as effective as drug therapies in preventing the development of T2DM.
2. Data is limited on the long-term safety of drug therapy for the treatment of IFG and/or IGT.
3. The cost-effectiveness and long-term risks of drug therapy in the treatment of IFG and/or IGT have not been adequately assessed.<sup>6,7</sup>

While levels of coagulation factors are not routinely tested in clinical practice, their negative effects can be treated with antiplatelet agents such as aspirin. Aspirin is currently recommended for secondary prevention in patients with CVD unless contraindications exist. Aspirin is also recommended as primary prevention in patients with either type 1 or type 2 diabetes with concomitant cardiovascular disease risk factors and in individuals at metabolic risk who are over age 40 and whose 10-year risk is more than 10%.<sup>3,6,7</sup>

### **Conclusions**

Metabolic syndrome is a constellation of interrelated risk factors that appear to promote the development of CVD. The possibility of one single cause has not been determined yet; however, obesity and many underlying risk factors precipitate this syndrome. Emphasis should be placed on management of the underlying risk factors through lifestyle changes as these changes can produce a reduction in all of the metabolic risk factors. If applicable, drug therapy should be directed toward the presence of major risk factors including: hypertension, diabetes, and LDL-C above goal as defined by their specific treatment guidelines.

For more information on metabolic syndrome, management of risk factors, and patient education materials please visit the following websites:

American Academy of Family Physicians [www.familydoctor.org](http://www.familydoctor.org)

American Diabetes Association [www.diabetes.org](http://www.diabetes.org)

American Dietetic Association [www.eatright.org](http://www.eatright.org)

American Heart Association [www.americanheart.org](http://www.americanheart.org)

National Heart Lung and Blood Institute [www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)

Continued from page 3

**Table 1. Criteria for Clinical Diagnosis of Metabolic Syndrome<sup>3</sup>**

| Measure (any 3 of 5 constitute diagnosis of Metabolic) | Categorical Cutpoints  |
|--|--|
| Elevated waist circumference*†                         | ≥ 102 cm (≥ 40 inches) in men<br>≥ 88 cm (≥ 35 inches) in women  |
| Elevated triglycerides                                 | ≥ 150 mg/dl (1.7mmol/L) <b>or</b> on drug treatment for elevated triglycerides‡  |
| Reduced HDL-C  | < 40 mg/dl (1.03 mmol/L) in men <b>or</b> on drug treatment for reduced HDL-C‡<br>< 50 mg/dl (1.3 mmol/L) in women <b>or</b> on drug treatment for reduced HDL-C‡        |
| Elevated blood pressure                                | ≥ 130 mmHg systolic blood pressure <b>or</b> ≥ 85 mmHg diastolic blood pressure <b>or</b> on antihypertensive drug treatment in a patient with a history of hypertension |
| Elevated fasting glucose                               | ≥ 100 mg/dl <b>or</b> on drug treatment for elevated glucose   |

\* To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to the floor. Measurement is made at the end of a normal expiration.

† Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94-101 cm [37-39 inches] in men and 80-87 cm [31-34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cutpoint (eg, ≥ 90 cm [35 inches] in men and ≥ 80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡ Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and HDL-C. Patients taking one of these drugs are presumed to have high TG and low HDL.

**References:**

1. Ervin RB. Prevalence of Metabolic Syndrome among Adults 20 Years of Age and Over, by Sex, Age, Race and Ethnicity, and Body Mass Index: United States 2003-2006. *National Health Statistics Report* 2009;13:1-8.
2. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
3. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and Management of the Metabolic Syndrome. An American Heart Association/National Heart, Lung, Blood Institute Scientific Statement. *Circulation* 2005;112:2735-2752.
4. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003 Dec;42(6):1206-52.
5. Knowler WC, Barrett-Conner E, Fowler SE, et al. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. *NEJM* 2002;346:393-403.
6. American Diabetes Association. Standard of Medical Care in Diabetes-2009. *Diabetes Care* 2009;32:S13-S61.
7. The Endocrine Society. Primary Prevention of Cardiovascular Disease and Type 2 Diabetes in Patients at Metabolic Risk: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2008;93:3671-3689.
8. Garber AJ, et al. Diagnosis and Management of Prediabetes in the Continuum of Hyperglycemia - When Do the Risks of Diabetes Begin? A Consensus Statement American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocr Pract* 2008;14(No.7).
9. Nelson AL. Metabolic Syndrome in Women with Polycystic Ovary Syndrome. *The Female Patient* 2009;34:15-21.

Diabetes Management will be the topic for the next quarterly newsletter topic.

Continued from page 4

**Program Assistance**

All prior authorization requests or questions regarding the PDL should be directed to the ACS Clinical Call Center at 1-866-879-0106.

**PDL Listing**

The fee-for-service PDL listing may be found at the following Web site:  
<http://www.indianapbm.com/>

**Top 20 Drugs for 2Q 2009**

| Top 20 Drugs 2 <sup>nd</sup> Quarter 2009<br>Ranked by Total Amount Paid |              |                |
|--|--------------|----------------|
| Drug   | Total Claims | Total Paid     |
| Aripiprazole   | 9,239        | \$3,773,393.77 |
| Quetiapine Fumarate  | 10,411       | \$3,120,244.14 |
| Antihemoph. FVIII Plas/<br>Alb Free                                      | 98           | \$2,948,404.56 |
| Olanzapine   | 5,313        | \$2,764,157.55 |
| Antihemoph. Factor,<br>Hum. Rec.   | 71           | \$2,074,759.75 |
| Risperidone  | 12,393       | \$1,589,559.46 |
| Insulin  | 8,963        | \$1,473,487.38 |
| Topiramate   | 5,500        | \$1,346,128.80 |
| Oxycodone HCL  | 4,666        | \$1,301,031.13 |
| Ziprasidone HCL  | 3,942        | \$1,265,101.97 |
| Fluticasone/Salmeterol   | 5,049        | \$1,052,054.70 |
| Divalproex Sodium  | 9,283        | \$1,022,135.42 |
| Levetiracetam  | 4,625        | \$951,324.64   |
| Duloxetine HCL   | 6,223        | \$891,218.00   |
| Lamotrigine  | 6,392        | \$883,273.58   |
| Atorvastatin Calcium   | 6,925        | \$829,756.42   |
| Clopidogrel Bisulfate  | 5,161        | \$793,211.32   |
| Methylphenidate HCL  | 7,397        | \$779,581.17   |
| Paliperidone   | 1,914        | \$759,555.79   |
| Amphet. Asp/Amphet./<br>D-Amphet.  | 6,297        | \$752,028.61   |

| Top 20 Drugs 2 <sup>nd</sup> Quarter 2009<br>Ranked by Total Number of Claims Paid |              |                |
|--|--------------|----------------|
| Drug   | Total Claims | Total Paid     |
| Hydrocodone/APAP   | 40,656       | \$317,207.60   |
| Aspirin  | 34,161       | \$31,146.16    |
| Docusate Sodium  | 30,860       | \$67,688.36    |
| Alprazolam   | 29,399       | \$163,829.45   |
| Calcium Carb/Vit D   | 28,263       | 61,073.45      |
| Acetaminophen  | 26,058       | \$71,925.61    |
| Multivitamins  | 24,031       | \$40,005.72    |
| Loratadine   | 23,881       | \$221,410.62   |
| Clonazepam   | 20,967       | \$98,514.91    |
| Lorazepam  | 17,849       | \$96,938.92    |
| Albuterol  | 17,541       | \$541,412.53   |
| Omeprazole   | 14,389       | \$455,888.40   |
| Mutivitamins W/Minerals  | 13,345       | \$38,806.61    |
| Lisinopril   | 12,537       | \$44,608.19    |
| Risperidone  | 12,393       | \$1,589,559.46 |
| Ferrous Sulfate  | 12,172       | \$13,002.25    |
| Levothyroxine Sodium   | 12,129       | \$84,134.60    |
| Diazepam   | 10,782       | \$284,829.17   |
| Quetiapine Fumarate  | 10,411       | \$3,120,244.14 |
| Furosemide   | 9,572        | \$28,716.58    |