

DSH PSYCHOTROPIC MEDICATION

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APPENDIX -- METABOLIC SYNDROME

NOTE: Directive statements and procedures described in this chapter are informational and advisory in nature.

The guidelines and monitoring recommendations reflected below are derived from general national guidelines. For drugs with specific monitoring requirements outlined in the DSH Psychotropic Medication Policy, the more specific baseline and monitoring requirements indicated in medication protocols should be followed.

I. Background:

- A. Obesity is a significant national health concern and has close associations with type 2 diabetes, dyslipidemia, and cardiovascular disease (CVD).
- B. The metabolic syndrome, as defined by the National Cholesterol Education Program (Table1), is now considered a major cardiovascular risk factor.
- C. Individuals with schizophrenia are more likely to be overweight or obese than the general population.
 - 1. Data from most studies suggest that the prevalence of obesity, glucose intolerance, and diabetes among individuals with schizophrenia and affective disorders is 1.5 – 2 times higher than the general population.
 - 2. This is partly due to the lifestyle of people with serious mental illnesses, often associated with poor dietary habits and sedentary behavior and possibly related to an increased tendency for central adiposity and insulin resistance associated with schizophrenia.
- D. Several reports have raised concerns that the prescription of second generation antipsychotic drugs further increases the risk of developing weight gain, insulin resistance, diabetes, dyslipidemia, and metabolic syndrome. (See Table 2.)
- E. Combined with an increased prevalence of smoking in schizophrenic patients, the metabolic syndrome plays an important role in the higher vulnerability of this population for cardiovascular morbidity and mortality.
- F. The American Psychiatric Association, the American Diabetes Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity convened a consensus conference in November 2003.

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1. The emphasis has been on the need to detect the metabolic syndrome early on among the mentally ill patients (with and without SGA treatment) and guidelines were developed offering recommendations for the baseline assessment and monitoring of those patients.

II. Purpose:

- A. To increase awareness of the metabolic side effects associated with the prescription of second generation antipsychotic medications among medical providers.
- B. To help detect metabolic disturbances such as metabolic syndrome, insulin resistance, dyslipidemia as early as possible among mentally ill patients treated with second generation antipsychotic medications.
- C. To ensure compliance with the consensus guidelines jointly developed by the American Psychiatric Association, the American Diabetes Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity.

III. Guidelines Summary:

A. Baseline screening

1. Assessment: Measures should be obtained before, or as soon as clinically feasible after, the initiation of any antipsychotic medication.

These include:

- Personal and family history of obesity, diabetes, dyslipidemia, hypertension, cardiovascular disease.
- Weight and height; so that BMI can be calculated (see calculation in Table 3).
- Waist circumference (at the level of the umbilicus).
- Blood pressure.
- Fasting blood sugar (FBS).
- Fasting lipid profile.

B. Conditions that need to be identified:

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1. Overweight (BMI 25 to 29.9) and obesity (BMI ≥ 30).
2. Abdominal obesity: waist circumference for men ≥ 40 inches (102 cm) and women ≥ 35 inches (88 cm).
3. Pre-diabetes (FBS 100 mg/dL to 125 mg/dL) or diabetes (FBS ≥ 126 mg/dL).
4. HTN (Blood pressure $>140/90$ mmHg).
5. Dyslipidemia (increased TC >200 mg/dL
 - LDL >130 mg/dL
 - TG >150 mg/dL
 - HDL <40 mg/dL for men and <50 mg/dL for women) or both.

C. Recommendations

1. General Management:
 - a. Clinicians should sensitize individuals, family members and caregivers to the health risks associated with excess weight and emphasize the risks of developing diabetes and dyslipidemia when SGA therapy is initiated.
 - b. Individuals should be encouraged to monitor and chart their weight. Benefits of modest weight loss are presented in Table 4.
 - c. Nutrition and physical activity counseling should be provided for all individuals who are overweight or obese (BMI >25) or who present with waist circumference >35 " for a woman and >40 " for a man.
 - d. Referral to a healthcare professional or program with expertise in weight management may also be appropriate.
 - e. Health care professionals, served individuals, family members and caregivers should be aware of the signs and symptoms of diabetes, especially those with acute decompensation of diabetes such as diabetic keto-acidosis (DKA).
 - f. Mental health providers should ensure that patients with diagnosis of diabetes (FBS >126 mg/dL) are followed by a health care professional who is knowledgeable about diabetes.

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- i. Close communication is necessary between primary care and mental health care providers especially when changes in medication may affect glucose control.
- ii. These individuals should carry diabetes identification.
- g. Mental health providers should be aware of the National Cholesterol Education Panel/ Adult Treatment Panel III guidelines-NCEP/ATP III report (Table 5) for screening and treatment of dyslipidemia and refer their patients to a primary care provider or an internist for follow-up.

ATP III recommends a 2-step approach to cholesterol management:

- Priority goes to attaining the goal for LDL-cholesterol
- Thereafter emphasis shifts to management of the metabolic syndrome and other lipid risk factors.
- h. Mental health providers should identify individuals who fulfill the criteria for the metabolic syndrome and should ensure that a primary care provider closely monitors them.

2. Initiation of treatment:

- a. Potential for weight gain and increase CHD risk factors should be considered in the choice of any antipsychotic medication.
- b. For persons at higher risk for diabetes, dyslipidemia and metabolic syndrome, and in those treated with medications that may increase these risks (e.g., valproic acid, lithium, Depo-Provera), it may be preferable to initiate treatment with an SGA that appears to have lower propensity for weight gain, glucose intolerance and lipid disturbances.

IV. Follow-up of Individual after initiation of second generation antipsychotic therapy:

A. Monitoring

- 1. Personal and family history should be reassessed annually.
- 2. Mental health providers should monitor weight and chart BMI for every patient at 4, 8 and 12 weeks after initiating SGA therapy.

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- a. Once the weight stabilizes, quarterly thereafter at the time of routine visit
 - b. More often if the patient is overweight
 3. Waist measurements should be taken annually.
 4. Fasting glucose should be followed at 12 weeks and annually or more frequently for those who have a higher baseline risk for diabetes.
 - a. During each visit, a schizophrenia patient should be asked about polydipsia and polyuria.
 - b. Hemoglobin A1c should be considered for those with unstable FBS findings.
 5. Blood pressure should be measured at 12 weeks and annually or more frequently for those who have a higher risk for hypertension.
 6. Fasting lipids testing should be performed at 12 weeks and at 5-year intervals or more frequently if clinically indicated.
 - a. As a group, individuals with schizophrenia should be considered at high risk for CHD
 - b. In these patients, lipids screening should be carried out at least once every year when LDL level is normal
 - c. Or once every 6 months when LDL level is >130 mg/dL.
- B. Recommendations for intervention:
1. A gain of one BMI unit in a normal-weight or overweight patient should lead to an intervention.
 - a. Interventions may include extensive nutritional counseling, initiation of a personal exercise program, use of an adjunctive treatment to reduce weight (including Sibutramine or Orlistat).
 - b. Some authors also have reported Topiramate and metformin as effective in reducing weight.

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2. Referral to a healthcare professional or program with expertise in weight management may also be appropriate.
 3. Mental health care givers should also initiate an intervention if the individual's waist circumference is >35" for a woman and >40" for a man.
 4. All individuals who develop diabetes (FBS >126mg/dL) when on SGA medication should be referred to an ADA-recognized diabetes self-management education program if available.
 - a. Referral to a clinician with experience in diabetes treatment is recommended.
 - b. These patients should carry diabetes identification.
 5. Consultation with an internist or other primary care physician is required for patients presenting with:
 - a. Symptomatic or severe hyperglycemia (random glucose values > 300mg/dL.
 - b. Symptomatic hypoglycemia.
 - c. The presence of DKA symptoms requires immediate evaluation and treatment.
 6. Mental health providers should ensure that NCEP III guidelines are followed for all individuals who develop dyslipidemia while on antipsychotic medication.
 - a. A referral to a primary care physician is recommended.
 - b. If SGA treatment is continued, then treatment with statin and/or fibrinate medication should be considered.
- C. Change of SGA:
1. If an individual gains >5% of his/her initial weight at any time during therapy, one should consider switching the SGA.
 - a. In such situation the panel recommends cross-titration to be the safest approach.

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- b. The profile of the subsequent drug will determine the initial dose and escalating strategy.
 - c. Particular consideration should be given before discontinuing Clozapine because of the potential for serious psychiatric sequelae.
- 2. In case of worsening glycemia while on antipsychotic medication, experts recommend considering switching to a SGA that has not been associated with significant weight gain or diabetes.
- 3. In case a patient develops hyperlipidemia (LDL > 130 mg/dL) or dyslipidemia of the metabolic syndrome while on antipsychotic medication, experts recommend considering switching to SGA that has not been associated with significant dyslipidemia.

V. Additional information: The emerging CHD risk factors

During the recent consensus conference cited above, no recommendation has been made regarding new testing that could help in the stratification of individuals at risk for cardiovascular disease among those already presenting with metabolic disturbances.

Several studies, however, advocate the benefit of adding other tests, in order to improve the prognostic value of the evaluation.

These tests are described below and can represent future optional choices for individual assessment and follow-up.

A. High-sensitivity C-reactive protein (Hs-CRP):

- 1. Hs-CRP is a marker of inflammation that predicts incident myocardial infarction, stroke, peripheral vascular disease, and sudden cardiac death among healthy individuals with no history of cardiovascular disease, and recurrent events and death in patients with acute or chronic coronary syndromes.
- 2. To date, more than 20 prospective epidemiological studies have demonstrated that hs-CRP independently predicts cardiovascular risk.
- 3. Hs-CRP confers additional prognostic value at all levels of cholesterol, Framingham coronary risk score, severity of metabolic syndrome, and blood pressure.
 - i. 8 cohort studies have demonstrated additive prognostic value to the Framingham Risk Score at all levels of metabolic

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syndrome or in cardiovascular risk prediction associated with type 2 diabetes.

- ii. Hs-CRP values of less than 1, 1 to 3, and greater than 3 mg/l are associated with lower, moderate and higher cardiovascular risks, respectively.
4. In contrast to several other biomarkers that also reflect biological aspects of inflammation, hypofibrinolysis, and insulin resistance, hs-CRP measurement is inexpensive, standardized and widely available.
5. Given the consistency of prognostic data for hs-CRP and the practicality of its use several authors believe that it should be added as a clinical criterion for the metabolic syndrome and for patients presenting with insulin resistance.

B. Intima media thickness (IMT) measurements:

1. The measurement of intima-media thickness (IMT) of large superficial arteries, especially the internal carotid artery, using high-resolution B-mode ultrasonography has emerged as one of the methods of choice for determining the anatomic extent of atherosclerosis and for assessing cardiovascular risk.
 - a. IMT measurement obtained by ultrasonography correlates very well with pathohistologic measurements and the reproducibility of this technique is excellent.
 - b. Population studies have shown a strong correlation between carotid IMT and several cardiovascular risk factors, and it has also been found to be associated with the extent of atherosclerosis and end-organ damage of high-risk persons.
 - c. Therefore, increased carotid IMT is recognized as a surrogate marker of subclinical (asymptomatic) cardiovascular disease, and a predictor of subsequent vascular events.
 - d. Because of its quantitative value, carotid IMT measurement is more and more frequently used in clinical trials to test the effects of different preventive measures, including drugs.
2. More recently, there has been interest in the use of this technique for detecting preclinical atherosclerosis and for identifying subjects at high risk.

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- a. When used in large numbers of patients with diabetes, prediabetes, and the metabolic syndrome, these imaging tools may also be useful in developing and validating thresholds for the use of lipid-lowering therapy as well as clear therapeutic goals for this population.
 3. Measurement of carotid IMT could influence a clinician to intervene with medication and to use more aggressive treatment of risk factors in primary prevention, and in individuals with atherosclerotic disease in whom there is evidence of progression and extension of atherosclerotic disease.
 - a. For more extensive use of this method in clinical practice a consensus concerning the standardization of methods of measurement and precise definition of threshold between normal and pathologic IMT value is needed.
 - b. The attribution of a specific ICD code for its use in current practice remains an important issue.
 - C. Brachial artery flow-mediated dilation:
- Brachial artery flow-mediated dilation is a measure of nitric oxide release from the forearm arterial endothelium.
1. It has also been recognized as a surrogate marker of subclinical cardiovascular disease.
 2. In patients with healthy endothelium, forearm ischemia induces greater nitric oxide release and therefore greater brachial artery dilation.
 3. Endothelial dysfunction is one of the first abnormalities found in atherosclerosis, dyslipidemia and type2 diabetes.
 4. Although no clear recommendation exists in the literature, this second surrogate marker might be used to diagnose early manifestation of cardiovascular disease among individuals at risk.
- D. Electron beam computerized tomography:

As the availability of electron-beam CT increases, it is appropriate to question the balance of its use among medical science, individual care, and profits.

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1. Well-designed clinical trials are still required to define fully the appropriate indications for and limitations of electron-beam CT.
2. Such trials will eventually clarify the medical applications of the technique and determine its suitability as a screening procedure for cardiovascular disease.
3. Until then, the use of electron-beam CT, like that of all tests in medicine, should be based on a clearly defined rationale and should be coupled with a comprehensive medical evaluation by a physician.
4. No recommendation exists in the literature for its use as a screening tool in persons presenting with metabolic disturbances.

Table 1: Diagnosis of Metabolic Syndrome

National Cholesterol Education Program

Risk Factor	Defining Measures
Abdominal obesity • men • women	Waist circumference at umbilicus: • >40 inches (>102 cm) • >35 inches (>88 cm)
Blood pressure	≥130/≥85mmHg
Fasting glucose	≥110mg/dL
Triglycerides	≥150 mg/dL
HDL-C • men • women	• <40mg/dL • <50mg/dL
≥ 3 risk factors comprise the metabolic syndrome (ICD –9 Code 277.7)	

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Table 2: Second Generation Antipsychotics and Metabolic Abnormalities

DRUG	WEIGHT GAIN	RISK FOR DIABETES	WORSENING LIPID PROFILE
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	different results	different results
Quetiapine	++	different results	different results
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

*newer drugs with limited long-term data

Table 3: Calculation of BMI:

BMI= Weight (kg)/body surface (m ²)

Table 4: Benefits of modest weight loss

- Increased life expectancy
 - 2.2-lbs. weight loss increased survival by 3 to 4 months
 - 2.2-lbs. weight loss could restore 35% of reduction in life expectancy
- Loss of 15 – 30-lbs. (10%) in obese subjects reduced glucose by 29 g/dL and HbA1c by 1.1%
- Loss of 10-lbs. (5%) reduced diastolic blood pressure by 5 %
- Loss of 6 lb (3%) in obese men decreased:
 - Total cholesterol by 17%
 - LDL-C by 9%
 - Triglycerides by 35%

Wing RR et al. Arch Intern. Med. 1987; Lean MEJ et al. Diabetes Med. 1990; Halle M et al. Metabolism 1999.

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Table 5: NCEP / ATP III Guidelines

CATEGORY	LDL-C GOAL	INITIATE TLC	CONSIDER DRUG THERAPY
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100mg/dL (optional <70 mg/dL)	≥100 mg/dL	≥100mg/dL (<100mg/dL, consider drug option)
Moderate/high risk: 2+ risk factors (10-year risk 10-20%)	<130mg/dL	≥130 mg/dL	≥130 mg/dL (100 – 29 mg/dL, consider drug option*)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130mg /dl	≥130 mg/dL	≥160 mg/dL
Lower risk: 0-1 risk factor	<160 mg /dl	≥160 mg/dL	≥190 mg/dL (160 – 189 mg/dL, consider drug option)

- CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease), diabetes and 2+ risk factors with 10-year risk of CHD > 20%.
- Any person at high risk or moderate/high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglycerides, low HDL-cholesterol, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify risk factors *regardless* of LDL.
- When LDL-lowering drug therapy is employed in high-risk or moderate/high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least 30% to 40% reduction of LDL-c levels.

*Factors that might favor use of LDL-lowering drug in moderate/high risk category with LDL < 130mg/dL include advancing age, more than 2 *severe* risk factors (e.g., continued cigarette smoking, a strongly positive family history of premature atherosclerosis, high triglycerides (>200mg/dL), low HDL-cholesterol (<40 mg/dL), the metabolic syndrome, and/or the presence of emerging risk factors (e.g., serum high sensitivity C-reactive protein > 3 mg/dL or coronary calcium > 75 percentile for a person's age and sex).

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