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# Dyslipidemia and Mental Illness

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## 1. Introduction

Almost most mental illness, such as schizophrenia, bipolar disorder, and depression are associated with undue medical morbidity and mortality. It represents a major health problem, with 20 to 30 years shorter lifetime mortality are primarily due to premature cardiovascular disease (myocardial infarction, stroke...). The cardiovascular events are strongly linked to non modifiable risk factors such as age, gender, personal and/or family history, but also to crucial modifiable risk factors, such as overweight and obesity, dyslipidemia, diabetes, hypertension and smoking.

Although these classical risk factors exist in the general population epidemiological studies suggest that patients with severe mental illness have an increased prevalence of these risk factors.

Another point is the causes of increased metabolic and cardiovascular risk in this population are related to poverty, poor diet, sedentary and compared to the general population. The increased morbidity and mortality limited behaviour access to medical care, but also to the use of psychotropic medication. Over recent years it has become apparent that antipsychotic drugs can have a negative impact on some of the modifiable risk factors.

## 2. Epidemiological studies

Results of most research on the physical health of people with mental health illness suggest the morbidity and the mortality from certain physical disease is high in these populations. Patients with schizophrenia are a medically vulnerable population due to underdiagnosed medical problems, and minimal or not utilization of primary care services. Not only there is increased medical morbidity among these patients, there is also increased mortality.

Medical comorbidity in patients with bipolar disorder, is associated with an intensification of bipolar depressive symptoms and other indices of bipolar severity, as well as premature mortality. Somatic health issues remain underrecognized and suboptimally treated.

### 2.1 Mortality

An increasing number of studies have found higher rates of mortality in schizophrenia patients due to natural causes (Mortensen & Juel, 1993; Ruschena et al, 1998). Such increased rates of mortality due to natural causes highlight the failure to detect and manage physical health conditions in this group. In meta-analysis deaths due to natural causes accounted for

59% of the excess mortality in schizophrenia (Brown, 1997). Respiratory and cardiovascular diseases are the most common causes of natural death. The standard mortality ratio (SMR) for respiratory disease was 226 (95%CI, 209-244) and for cardiovascular disease 110 (95%CI, 105-115) (Brown, 1997). However, another study found an SMR of 1.78 for men and 0.86 for women with schizophrenia for ischemic heart disease (Lawrence et al, 2003). Analysis of standardized mortality ratios for deaths from natural causes showed an increased risk of death in patients with a wide range of psychiatric conditions, including substance misuse, schizophrenia, bipolar disorder and unipolar depression. The Standardized mortality ratios (SMR) showed that in schizophrenia it is 1.57 for all cause mortality, and cardiovascular and cancer deaths accounted for the largest number of deaths with SMRs of 1.04 and 1.00 respectively (Harris & Barraclough, 1998). Depression confers a 24% increased risk of dying within the next 6 years (Wulsin, 2000). A study published through the Centers for Disease Control and Prevention (CDC) compared the mortality of public mental health patients in 8 states with the mortality of the states' general population, for 1997 through 2000. In all the study states, mental health had a higher risk of death than the general population and died at much younger ages compared with their cohorts. In all states studied, cardiac disease was found to be the leading cause of death in mentally ill patients. And this population had lost decades of potential years of life, with average exceeding 25 years (Colton & Manderscheid, 2006).

Another indicator of the medical care is avoidable mortality. These indicators are calculated by selecting the number of avoidable causes of death considered amenable to health care (Rustein et al, 1976). A follow-up study of 30045 psychiatric in-patients born between 1912-1970 was conducted to specifically address avoidable mortality. The standardized rate ratios (SRR) for male patients with schizophrenia are 3.74 (95%CI, 2.38-5.89) and 3.99 (95%CI, 2.47-6.44) for females (Ringback Weitoft et al, 1998).

## 2.2 Morbidity

A study list some of the common physical conditions found in people with psychosis. These include diabetes, hyperlipidemia, cardiovascular disease, obesity, malignant neoplasms, HIV/AIDS, hepatitis, osteoporosis, hyperprolactinemia, irritable bowel syndrome and helicobacter pylori infection (Lambert et al, 2003). The prevalence of physical illness in medically screened chronic psychiatric samples has been variously reported to be 12-53% (Lyketsos et al, 2002). Another study estimate that 35% of psychiatric patients have undiagnosed physical disorder (Felker et al, 1996). Some studies have attempted to establish whether medical comorbidity exacerbates patient' psychiatric condition (Bartsch et al, 1998).

Not only do patients with mental illness die of natural causes at high rate, when medical conditions occur, these patients are much more likely to underdiagnosed and undertreated. Several studies have shown that the detection rate of physical illness among patient with mental illness is very poor. A study estimated that 45% of patients in California's public mental-health system had physical disease and, of these, 47% were undetected by the treating physician (Koran, 1989). Another study of psychiatric clinic patients revealed remarkably similar findings: 43% of patients had physical illnesses and, of these, 48% had not been diagnosed by the referring doctor, non-psychiatrist physicians had missed 33% and psychiatrists had missed 50% (Koranyi, 1979). Hall et al found that 46% of patients admitted to a research ward had an unrecognized physical illness that either caused or exacerbated

their psychiatric illness; 80% had physical illnesses requiring treatment, and 4% had precancerous conditions or illnesses (Hall et al, 1981).

Research indicates that 25% to 80% of patients with schizophrenia and other mental illness have a serious medical comorbidity, yet less than half of these medical conditions are diagnosed (Cradock-O'Leary et al, 2002).

### 3. Causes of poor physical health in mental illness

A number of reasons exist to explain the poor detection of physical health problems in patient with mental illness. Some patients are unaware of any physical health problems, usually a consequence of cognitive deficits associated with their mental illness (Goldman, 1999). Often there is a reluctance to seek medical help and when it sought patient with mental health find it difficult to describe their problems to a medical practitioner, or present with atypical medical symptoms. Patient with schizophrenia have been shown to have a high tolerance for pain and subsequently are less likely to report this symptom (Dworkin, 1994). Another complexity concerns the effects of psychiatric illness on perceived physical health. For example, depression can lead to an increase in perceived physical symptoms and worsening of subjective health outcomes.

The management of medical conditions is a complex and problematic issue, arising largely because of the separation of medical and psychiatric health care services. The stigma of mental illness is one obvious barrier preventing psychiatric patients from receiving adequate physical health care, as some physicians may be uncomfortable in working with this patient. Another concern is managing physical conditions where patients that have an increased prevalence with psychiatric illness and where there is a general lack of treatment compliance. The challenging task of managing physical illness with this patient requires skill, patience and experience as patients often present late with complications. (Table 1)

System-Related Barriers
Lack of insurance coverage
Lack of access to health care
Stigmatization by health care providers
Lack of understanding of benefits of preventive services by health care workers
Lack of integration of medical and mental health systems
Patients-Barriers
Poverty
Non compliance
Poor communication skills
Denials of illness Related

Table 1. Barriers to health care for patients with mental illness. Adapted from Goldman.

#### 3.1 Lifestyle risk factors

In recent years, there is a growing concern about physical illness in patients with mental illnesses, specifically the risk of cardiovascular disease. Those patients are more likely to be overweight, to smoke, to have hypertension, hyperglycemia or diabetes, and dyslipidemia (Table 2).

Modifiable risk factors	Estimated prevalence, % (RR)	
	Schizophrenia	Bipolar disorder
Overweight	45-55% (1,5-2)	21-49% (1-2)
Smoking	50-80% (2-3)	54-68% (2-3)
Diabetes	10-15% (2)	8-17% (1,5-2)
Hypertension	19-58% (2-3)	35-61% (2-3)
Dyslipidemia	25-69% ( $\leq 5$ )	25-38% ( $\leq 3$ )
Metabolic syndrome	37-63% (2-3)	30-49% (1,5-2)

Table 2. Estimation prevalence and relative risk 5 (RR) of modifiable cardiovascular disease risk factors in schizophrenia and bipolar disorder compared to the general population. Adapted from Correll, 2007

### 3.1.1 Obesity

Excessive body weight increases the risk of morbidity from number conditions, including hypertension, dyslipidemia, type II diabetes, coronary heart disease. Excess abdominal fat is associated with dyslipidemia, hypertension and glucose intolerance. Risk of comorbid diseases has been shown to rise as BMI increases above 25 kg/m<sup>2</sup>. In psychiatric practice, weight gain is a long recognized and commonly encountered problem. A study of patients with schizophrenia reported 51% of males and 59% of females to be clinically obese, compared with 33% of people with other psychiatric disorders. This study provided an estimate of mean weight gain in patients who received standard doses of antipsychotics over 10-week period. The mean increases were 4.45 kg with clozapine, 4.15 with olanzapine, 2.92 kg with sertindole, 2.10 kg with risperidone, and 0.04 kg with ziprasidone (Allison & Casey, 2001). It is important to note that substantial weight gain is associated with both atypical (eg, clozapine, olanzapine) and conventional (eg, thioridazine, chlorpromazine) antipsychotics.

### 3.1.2 Smoking

The prevalence of smoking greatly exceeds that in the general population (Table 1) Heavy cigarette smoking is intimately associated with schizophrenia and it may have implications for the underlying neurobiology of the disease. Smoking is a good example of how behavior and treatment interact to increase morbidity at a number of levels. It is a risk factor for respiratory and ischemic heart disease and stroke. Cigarette smoking induces hepatic microsomal enzymes, which increase the metabolism of psychotropic medication, reducing plasma levels of antipsychotics notably olanzapine and clozapine. It may influence the patient's behavior and the treatment outcome. Therefore smokers usually require greater levels of antipsychotic medication than non-smokers to achieve similar blood levels.

### 3.1.3 Diabetes

It is another risk factor for coronary atherosclerosis that is associated with metabolic abnormalities that result in changes in the transport, composition and metabolism of lipoproteins.

### 3.1.4 Hypertension

Is a cardiovascular risk factor as it produces structural changes within the arteries. The sequel of hypertension are greatly affected by comorbidities such as dyslipidemia, smoking, diabetes, lack of physical activity, sodium intake, and stress.

Other risk factors are attributable to unhealthy lifestyle, including social scale such as unemployment, poorer financial standing, poor diet and sedentary behaviour.

Concerning diet, a study (Mc Creadle, 2003) examined in detail the dietary intake of 102 people with schizophrenia in Scotland. Their fruit and vegetable consumption averaged 16 portions per week, less than half the recommended intake.

Brown et al, 1999 and Mc Creadle, 2003 found that patients with schizophrenia tended to take only small amounts of exercise. Factors such as features of the illness, sedative medication and lack of opportunity and general motivation may be relevant.

### 3.2 Medication

Psychotropic medication is associated with a host of physical complications and side effects. Old antipsychotic medication was associated with neurologic side effects, including involuntary movement disorders, such as akathisia, parkinsonism, tardive dyskinesia. New antipsychotics are more commonly used. Despite the low propensity of new antipsychotics towards extra pyramidal side effects other adverse effects associated with them include excessive weight gain, metabolic disturbances. Medical conditions attributed to the use of typical and atypical antipsychotic medication include diabetes, hyperlipidemia, and cardiovascular disease: specifically hypertension and cardiac arrhythmias, obesity (Meyer, 2002; Davidson, 2002).

## 4. The metabolic syndrome

Much attention has been focused on the metabolic syndrome which brings together a series of abnormal clinical and metabolic findings which are predictive of cardiovascular risk. The most commonly used definition for the metabolic syndrome are the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), (Jama, 2001) and the adapted ATP-III-A proposed by the American Heart Association following the American Diabetes Association lowering of the threshold for impaired fasting glucose 100mg/dl. (Quindy et al, 2005 ; Alberti et al, 2006).

Another recent definition, by the International Diabetes Federation (Alberti et al, 2006; Sarafidis & Nilsson, 2006) stressed the importance of waist circumference, using ethnic/race specific criteria (Table 3).

	ATP III 3 out of 5 criteria required	ATP III A 3 out of 5 criteria required	IDF waist + 2 criteria required
Waist (cm)	M>102, F>88	M>102, F>88	M≥94, F≥80
Blood pressure	≥130/85*	≥130/85*	≥130/85*
HDL cholesterol (mg/dl)	M<40, F<50	M<40, F<50	M<40, F<50
Triglycerides (mg/dl)	≥150	≥150	≥150
Fasting glucose (mg/dl)	≥110**	≥100**	≥100**

\*or treated with antihypertensive medication

\*\*or treated with insulin or hypoglycemic medication

Table 3. Definitions of metabolic syndrome: The metabolic syndrome has been shown to be an important risk factor for the development of both type 2 diabetes and cardiovascular disease.

In the study, the clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), one third of patients met the NCEP criteria for metabolic syndrome at baseline (Mc Eoy et al, 2005 ; Meyer et al, 2005).

And from this study, 88% of patients with dyslipidemia were not receiving treatment, as were 62% of the hypertensive patients and 38% those with diabetes (Nasrallah et al, 2006). The presence of the metabolic syndrome increases the risk for the distribution of fat within the body is a key factor. Abdominal fat distribution, particularly visceral adiposity, increases the risk of dyslipidemia, glucose intolerance, and cardiovascular disease. Multiple organ systems are affected, including adipose, muscle, hepatic, nervous, and adrenal tissues, and the most important site of impact is the vasculature. The concept of insulin resistance is central to the metabolic syndrome. Insulin resistance is a major contributor to glucose intolerance, and the lipoprotein abnormalities seen in the metabolic syndrome are also predictable, at least in part, from the known effects of insulin to inhibit lipolysis in adipocytes. With resistance to insulin, unchecked lipolysis leads to increased delivery of free fatty acids to the liver for triglyceride synthesis and packaging into very low-density lipoprotein (VLDL) particles. Higher VLDL levels contribute to lower HDL levels because of the reciprocal exchanges between these lipoproteins mediated by cholesterol ester transfer protein. It has been shown that blood pressure is related to insulin resistance independent of differences in age, gender, and degree of obesity (Zavaroni et al, 1992). Visceral obesity is the primary determinant of insulin resistance and, as such, represents the fundamental pathophysiologic change leading to the metabolic syndrome. The risk of insulin resistance increases with adiposity, particularly the amount of visceral adiposity. Insulin resistance is associated with impaired glucose control, increase plasma triglycerides, reduced high-density lipoprotein (HDL) cholesterol, increased blood pressure, increased risk of blood clotting, and increases in markers of inflammation, all which are associated with an increase risk for cardiovascular disease. Thus, markers of insulin resistance, such as elevated fasting plasma Triglycerides, can be a key point for monitoring and evaluating a patient's risk.

## 5. Effects of antipsychotics treatment

Antipsychotic treatment is associated with metabolic side effects that include various degrees of weight gain, dyslipidemia and susceptibility to type 2 diabetes (Newcomer, 2005).

Elevated blood lipids, particularly triglycerides, are associated with some typical antipsychotic agents. Shortly after their introduction, phenothiazines were found to elevate serum triglyceride and total cholesterol levels. Then much was written on the effects of specific atypical drugs on lipid profiles. Both clozapine and olanzapine have been shown to cause significant hypertriglyceridemia compared with typicals. Studies have also reported a significant association between weight gain and triglyceride change for patients under atypical antipsychotic therapy (Meyer, 2001).

The atypical antipsychotics vary in their propensity to induce weight gain (Table 4): clozapine and olanzapine produce the most weight gain, quetiapine and risperidone produce intermediate weight gain, and ziprasidone and aripiprazole produce the least weight gain (Allison et al, 1999; American Diabetes Association [ADA], 2004). The differences in weight gain associated with these agents reflect their order of risk for insulin resistance, gluoregulatory dysfunction, and dyslipidemia (Haupt & Newcomer 2002; ADA, 2004).

Antipsychotic	Weight	Risk for diabetes	Worsening lipid proli B
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Ziprasidone	+/-	-	-
Aripiprazole	+/-	-	-

<sup>a</sup>Adapted with the permission from the American Diabetes Association Abbreviation:

D = discrepant results

Symbols: + = increased effect, - = no effect

Table 4. Atypical antipsychotic drugs and metabolic disturbances<sup>a</sup>

Metabolic disturbances related to atypical antipsychotics may result from a direct alteration of insulin sensitivity and/or insulin secretion. Antipsychotic affinity at both histamine and muscarinic acetylcholine receptors correlates with weight gain and metabolic liability (Matsui-Sakata, 2005) and impaired parasympathic regulation of  $\beta$  all activity may contribute to metabolic risk (Silvestre & Prous, 2005). Certain antipsychotic agents may directly impair glucose transporter function. Direct attenuation of glucose transporter function by antipsychotic agents would result in elevations in circulating glucose and a compensatory hypersecretion of insulin, which overtime may further reduce insulin sensitivity, triggering the cascade of events leading to metabolic syndrome and type 2 diabetes (Dwyer & Donohoe, 2003).

Some antipsychotic drugs increase appetite and this leads to adiposity. Affinity of the antipsychotic drugs for histamine-1 (H1) receptors closely correlates with weight-gaining potential and appears to involve H1 receptor-linked activation of hypothalamic AMP-kinase. Also, 5-HT<sub>2C</sub> receptor antagonism may contribute to weight gain. The H1 and 5HT<sub>2C</sub> blocking effects of antipsychotic medications may interfere with leptin-mediated appetite suppression (Reynolds, 2006; Matsui-Sakata et al, 2005).

Adiposity alone does not explain the potential side effects of atypical antipsychotic medications. Animal and human studies describe the adverse effect of clozapine and olanzapine on insulin and glucose metabolism (Hasnain & Vieweg, 2008). Significant insulin resistance has also been documented in non-obese patients receiving clozapine or olanzapine versus those receiving risperidone (Henderson et al, 2006). Diminished or inefficient insulin release from pancreatic beta cells as well peripheral insulin resistance may underlie the diabetogenic effect of some antipsychotic medications. Blocking muscarinic type 3 and 5-HT<sub>1A</sub> receptors may be a factor to diminished pancreatic beta-cells responsiveness and blocking 5HT<sub>2A</sub> receptor may suppress glucose uptake in muscle (Nasrallah, 2008). Some antipsychotic medications may impair and/or alter the action of insulin on adipocytes leading to progressive lipid accumulation (Vestri et al, 2007). The impaired effect of insulin on adipocytes may explain weight gain independent dyslipidemia (De leon et al, 2007, Birkenaes et al, 2008).

Another study examine whether patients taking selective serotonin reuptake inhibitors (SSRIs) are more likely to have elements of the metabolic syndrome compared with those



taking no psychotropic drugs. Patients taking SSRIs had a significantly increased prevalence of obesity, abdominal fat, and hypercholesterolemia. The associations with these factors were significant after adjustment for age, gender, and several covariates. The individual SSRIs might display differences in their side effect profile, the study performed analysis of the various SSRIs. Paroxetine was strongly associated with general and abdominal obesity but not with hypercholesterolemia, whereas citalopram was associated with neither obesity nor dyslipidemia. Patients taking sertraline, fluoxetine, or fluvoxamine, SSRI treatment was significantly associated with abdominal obesity and with hypercholesterolemia. SSRIs induce transcriptional activation of cholesterol and fatty acid biosynthesis. The lipogenic effect could represent a common mechanism for explaining in part the lipid disturbances (Reader et al, 2006).

Weight gain is a major side effect of the main mood stabilizers. Chronic treatment with lithium is associated with increased weight, reaching more than 10kg in 20% of patients (Garland et al, 1998). Valproic acid leads to unequivocal weight gain. Lamotrigine, another anticonvulsant that acts as a mood stabilizer, is not associated with significant weight gain (Zimmermann et al, 2003).

With regard to mood stabilizers, additional factors could be involved. An insulin-like action caused by lithium at the treatment stage could increase fat deposition. In addition, edema secondary to sodium retention and subclinical hypothyroidism also contribute to weight gain (Garland et al, 1998). The mechanism by which the valproic acid causes weight gain is still little explored; an action in the sense of inhibiting oxidation of fatty acids might be involved (Isojärvi et al, 1998).

Studies are not in accordance. A controlled study, with children undergoing anticonvulsant treatment, did not find significant changes in HDL and triglycerides levels associated with use of carbamazepine or valproic acid. But, in the group taking carbamazepine, there was a significant increase in total cholesterol levels (Fanzoni et al, 1992).

Another study assessed 101 patients undergoing anticonvulsant therapy for at least 3 months. Compared with controls paired for gender and age, patients taking valproic acid presented significantly lower total cholesterol and LDL levels; patients taking carbamazepine presented significantly increased HDL and apolipoprotein A levels (Calandre et al, 1991).

## 6. Screening and monitoring

Identification of treatable pathology in a high-risk population, that is, screening for diabetes, dyslipidemia, hypertension is important and facilitates preventive strategies and early diagnosis. Another goal is to track metabolic disturbance in relation to antipsychotic treatment. Dyslipidemia is a general term that defines an increase in the serum concentration of various lipoproteins. Lipoproteins are usually classified into three major categories:

- Low-density lipoproteins (LDLs) are cholesterol-rich particles whose concentration is directly correlated with the risk of myocardial infarction and death.
- Very-low-density lipoproteins (VLDLs) are triglyceride-rich particles whose concentration is strongly correlated with the level of insulin resistance and inversely proportional to the serum concentration of high-density lipoproteins (HDLs).
- HDL particles are antiatherogenic lipid particles, and high serum levels of HDL are protective against coronary artery disease.

### 6.1 Screening

In the general population, lipid screening with a fasting lipid profile (total chol, LDL, HDL and triglyceride) is recommended for all adults aged 20 years and older, repeated every 5 years in asymptomatic individuals (Expert Panel on Detection, Evaluation and Treatment, of High Blood Cholesterol in Adults, 2001). Adequate fasting, about 10 to 12 hours is necessary to obtain valid LDL and triglyceride levels-Target LDL levels are determined by a Framingham assessment based on age, sex, chol, HDL, systolic blood pressure, and smoking status (Wilson et al, 1998). Patients on antipsychotic treatment frequently have a metabolic dyslipidemia with elevations of triglyceride and reduced HDL (Cohn et al, 2004), along with associated features of the metabolic syndrome. Some SSRIs induced metabolic disturbance particularly hypercholesterolemia.

Treatment of metabolic dyslipidemia is a secondary goal for intervention following achievement of LDL targets. Clinical trials show that LDL-lowering therapy reduces risk for coronary heart disease (CHD). For these reasons, ATP III continues to identify elevated LDL cholesterol as the primary goal of cholesterol-lowering therapy. Those with diabetes or established cardiovascular disease are considered high risk and are treated to the most stringent LDL targets. Risk determinants in addition to LDL cholesterol include the presence or absence of CHD, other clinical forms of atherosclerotic disease, and the major risk factors other than LDL. Other major risk factors are cigarette smoking, hypertension, low HDL cholesterol, family history of premature CHD, diabetes and age. These major risks are commonly observed in patients with mental illness.

A variety of medical conditions and drugs can exacerbate hyperlipidemias. Elevations of the serum LDL cholesterol level can occur in response to hypothyroidism and nephrotic syndrome. Hypertriglyceridemia and decreased HDL levels are commonly seen with insulin resistance, diabetes, and the metabolic syndrome. This fact is usually seen in patients with mental illness. Individuals are characterized by their coronary risk profile according to the National Cholesterol Education Program Adult Treatment Panel III guidelines, as shown in Table 5.

Lipoprotein and serum concentration	Status
Low-density lipoprotein (LDL) cholesterol) (primary target of therapy) <100 mg/dl 100-129mg/dl 130-159 mg/dl ≥160 mg/dl	Optimal Near optimal Borderline high High
Total cholesterol <200 mg/dl 200-239 mg/dl ≥ 240 mg/dl	Desired Borderline high High
HDL cholesterol <40 ≥60	Low High

Table 5. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

## 6.2 Monitoring

To monitor for antipsychotic - associated metabolic disturbances, patients should be assessed before antipsychotic treatment is initiated. The results of such an assessment can also influence antipsychotic choice, particularly when patients have existing metabolic pathology or elevated risk factors. The frequency of subsequent assessments is different as it is reflected in the various antipsychotic monitoring guidelines: Mount Sinai (Chobarian et al, 2003), Australia (Lambert et al, 2004) ADA-APA(ADA,2004) Belgium (De Nayer, 2005), United Kingdom (Expert Consensus Meeting, 2004), Canada (Canadian Diabetes Association, 2005), France (Saravane et al, 2009) (Table 6). To summarize these recommendations, there are many areas of general agreement about the importance of baseline monitoring before starting treatment and that patients should be followed more closely for the first 3 to 4 months of treatment, with subsequent ongoing reevaluation. The utility of the following tests and measures was emphasized: fasting plasma glucose, fasting lipid profile, weight and height, waist circumference, and blood pressure.

A recent study characterizes associations between the combined warnings and recommendations and baseline metabolic testing and Second-Generation Antipsychotic Drugs (SGA). A total of 109451 patients receiving Medicaid who began taking SGA was compared to a control cohort of 203527 patients who began taking albuterol but did not receive antipsychotic medication. The main outcome measures were the monthly rates of baseline serum glucose and lipid testing for SGA-treated and propensity-matched albuterol-treated patients and monthly share of new prescriptions for each SGA drug. In a Medicaid-receiving patients, baseline glucose and lipid testing for SGA was infrequent and showed little change following the monitoring recommendations. Initial testing rates for SGA-treated patients were low: glucose, 27%; lipids, 10%. The warning was not associated with an increase in glucose testing among SGA-treated patients and was associated with only a marginal increase in lipid testing rates: 1.7%;  $P = .02$ . (Morrato, 2010).

The important question is given the risks in patients with mental illness, how should they be monitored and how should they be treated?

Current studies indicate that patients with mental illness do not receive adequate evaluation and effective treatment of their cardio-metabolic problems. Effective communication between the primary care physician and the psychiatrist is very important for the mentally ill because of their impaired capacity to care for themselves. Such communication will improve monitoring, help early detection of metabolic disorders, and limit duplication of clinical or laboratory workup. Monitoring for metabolic side effects is primarily the responsibility of the physician prescribing antipsychotic medication and in most cases that would be a psychiatrist.

If the primary care physician observes that the patient is being prescribed such drugs without being monitored effectively, he/she should discuss this with the psychiatrist. The psychiatrist may not have the expertise to manage any abnormalities that are detected and in such situations the primary care physician will most likely take over both monitoring and management. Liaison should extend to any healthcare professionals involved in the care of patients with mental illness.

Given the serious health risks, patients taking antipsychotic drugs should receive appropriate baseline screening and ongoing monitoring.

	Mount Sinai	Australia	ADA-APA	Belgium	UK	Canada	France
	Patients to monitor						
	Schizophrenia any antipsychotic	All patients any antipsychotic	All patients SGA	Schizophrenia SGA	Schizophrenia any antipsychotic	Schizophrenia	All patients any antipsychotic
Fasting Plasma Glucose (FPG)	x	x	x	x	x	x	x
Random glucose		x			x		
Hba1c	If FPG not feasible				x		
OGTT						Follow up	
Lipids	x	x	x	x		x	x
Weight	x	x	x	x		x	x
Height	x	x	x	x		x	x
Waist circumference	x	x	x	x		x	x
Hip		x					x
Family and medical history	x	x	x	x		x	x
Ethnicity	x	x		x			
Tobacco				x			
Diet activity		x		x		x	
Signs and symptoms of diabetes	x		x	x	x	x	x
ECG							x
Blood pressure		x	x	x		x	x

Table 6. Recommended guidelines to monitor and initial workup.

### 6.2.1 Baseline monitoring

The recommendations are that baseline screening measures be obtained before or as soon as clinically feasible after, the initiation of any antipsychotic medication. We have to consider ethnicity, dietary habits, physical activity, support system, smoking, and alcohol and drug

abuse. Keep in mind that psychotropic medications other than antipsychotic drugs such as some antidepressants and mood stabilizers may link to weight gain. The baseline assessments include:

- Personal and family history of obesity, diabetes, dyslipidemia, hypertension or cardiovascular disease
- Weight and height, so that BMI can be calculated
- Waist circumference at the level of the umbilicus
- Blood pressure
- Fasting plasma glucose
- Fasting lipid profile

If any abnormalities are identified, first, patients should be informed of their condition and supported in making lifestyle changes to adopt a healthier diet and increase physical activity. Psychiatrists should not hesitate to refer the patient to the appropriate health care professional or specialist knowledgeable about these disorders.

Even for patients free of metabolic disorders, monitor potential risk factors. Weight gain may not be dose-dependent and patients with low body mass index at baseline may be particularly vulnerable to weight gain. Glucose and lipid metabolism abnormalities may occur without weight gain.

### 6.2.2 Follow-up monitoring

The patient's weight should be reassessed at 4, 8, and 12 weeks after initiating or changing SGA therapy and quarterly thereafter at the time of routine visits. If a patient gains > 5% of his or her initial weight at any time during therapy, one should consider switching the medication. When switching, consideration should be given to all aspects of the individual's condition, the comparative risks and benefits of changing medications, and the individual's response to medication in managing the primary symptoms of the mental illness. In some cases, cost and availability may also be a consideration.

Fasting plasma glucose, lipid profile, and blood pressure should also be assessed 3 months after initiation of medication. Thereafter, blood pressure, plasma glucose values, lipid profile should be obtained annually or more frequently in those who have a higher baseline risk for the development of diabetes, dyslipidemia or hypertension.

## 7. Treatment

With all the risk factors and in the case of dyslipidemia and to reduce the global mortality of patients with mental illness we should consider lipid goal of therapy for these patients. The benefits and risks of different therapeutic agents used in the treatment of dyslipidemia and its comorbidities should be considered in the context of the patient's psychiatric condition and treatment.

### 7.1 Drugs

ATP III recommends a multifaceted lifestyle approach to reduce risk for coronary heart disease (CHD). This approach is designated therapeutic lifestyle changes (TLC). Some patients whose short-term or long-term risk for CHD is high will require LDL-lowering drugs in addition to TLC. When drugs are prescribed, attention to TLC should always be maintained and reinforced. Available drugs are:

- HMG-CoA reductase inhibitors: statins, their side effects are myopathy and increased liver enzymes
- Bile acid sequestrants, their side effects including gastrointestinal distress, constipation and decreased absorption of some drugs
- Nicotinic acid side effects are essentially flushing, hyperglycemia, hyperuricemia (gout), upper gastrointestinal distress and hepatotoxicity
- Fibric acids, with their side effects including dyspepsia, gallstones, myopathy, unexplained non-CHD deaths in WHO study

All these drugs reduced major coronary events, CHD deaths but we have to be careful with their side effects and contraindications when prescribing these drugs.

Beyond the underlying risk factor, therapies directed against the lipid and nonlipid risk factors of the metabolic syndrome will reduce CHD risk.

The management of dyslipidemia in mental health is defined, as recommended by the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes by: The lifestyle interventions with diet, increased physical activity and smoking cessation. They are the first-line treatments to decrease the risk for cardiovascular disease in patient with metabolic syndrome.

## 7.2 Diet

Interventions that address nutrition and weight management should become a routine part of psychiatric care. Patients with mental illness did not know the components of a healthy diet. The healthy eating behavior includes:

- Cutting down fast food
- Increased healthy food items like fruits, vegetables, fish and decreased high glycemic index food items and monounsaturated fats
- Decreased processed fat free food
- Consume 4-6, but small meals
- Minimizing intake of soft drinks with sugar and with artificial sweetener

The lifestyle changes should be gradual and adapted individually for each patient. There are various educational and psychosocial programs that address the issues of health and wellness exist, like 'The Healthy Living' program (Vreeland, 2007; Hoffmann et al, 2006).

## 7.3 Physical activity

Patients who developed psychosis are more likely to be physically inactive (OR=3.3, 95% CI 1.4-7.9) and to have poor cardio respiratory fitness (OR=2.2, 95% CI 0.6-7.8) compared with those who did not develop psychosis (Koivukangas et al, 2010). Modern guidelines on managing the physical health risks associated with schizophrenia include a recommendation about the importance of physical activity levels and fitness. This recommendation includes:

- To advise patients to engage at least 30 minutes of moderately vigorous activity on most days of the week
- Reduce sedentary behaviors such as TV watching, video/computer games
- Treating/reducing sedation and extra pyramidal effects of medications

Some studies showed that physical activity, with and without diet, resulted in modest weight loss, reduction of blood pressure and decreases in fasting plasma concentrations of glucose and insulin (Vancampfort et al, 2009).

#### 7.4 Medication

In the general population there are many studies evaluating the impact of lipid lowering in primary and secondary prevention of coronary heart disease and stroke, but there are some concerns about its value in primary prevention, especially in vulnerable population (Vreecer et al, 2003).

Whether a low or lowered serum cholesterol level is associated with harm has been the subject of debate for a long time; ever since the unexpected finding of an increased risk of noncardiovascular mortality in early trials of lipid-lowering therapy. Subsequent research has generated conflicting evidence regarding the relation between cholesterol and violent behavior, mental illness, with positive studies imputing alterations in central serotonergic activity as a potential underlying mechanism. A case-control study studied a cohort of 94441 individuals, 458 had newly diagnosed depression and 105 had a recorded diagnosis of suicide risk. Compared with matched control subjects, and even after adjustment for potential confounders, neither dyslipidemia nor its treatment was associated with an increase risk of depression. Similarly, no association was found between treatment and suicide risk. (Yang, 2003).

A 3-month study demonstrated that statins prescribed to patients with schizophrenia and severe dyslipidemia whilst taking antipsychotic medication led to a significant improvement in lipid profiles (Hanssens et, 2007). An earlier study with rosuvastatin proved effective in managing dyslipidemia in schizophrenic patients on antipsychotics. This study showed improvement in lipid profiles but not benefits in terms of high-density lipoprotein, waist measurement, BMI or glucose homeostasis (De Hert et al, 2006).

This last study supports the view that statins can be safely used in the short term to control abnormal lipids levels. However, there are no long-term data on its impact on either relapse or all-cause mortality, and again this is a priority for research.

The presence of metabolic syndrome is an indication for more aggressive lipid-lowering measures. Medications that raise HDL, nicotinic acid or fibrates, may be particularly beneficial in patients with metabolic syndrome, but they have not been as widely studied as medications that lower LDL-cholesterol in patients with mental illness.

The preferred initial management is still very much a lifestyle modification approach including exercise and diet.

#### 8. Conclusion

Despite the availability of published clinical guidelines, patients with mental illness receiving medications remain vulnerable to the cardio-metabolic complications of these drugs. Implementation of a coordinated metabolic monitoring and management program for patient with mental illness will require a review of current practice and the introduction of new procedures, both of which will require time and effort on the part of the health care community.

Involvement of patient with mental illness in their treatment program will require the provision of information about their condition and medication and the development of approaches that empower, encourage, and support patients in their decisions on treatment and well-being.

The evaluation of new therapies should include detailed assessments of physical health and future risk estimates in addition to standard psychiatric outcomes. Psychiatrists have to arrange the appropriate examination and investigation of patients at risk of developing

significant physical morbidity, working very closely with general practitioners and with other specialists when appropriate. We have to weight up the risk of metabolic disturbance and its potential impact on future cardiovascular risk when selecting an antipsychotic drug. We have to take a careful medical history and be prepared to monitor weight and other metabolic risk, such as glucose and lipid profile. The lipid area is significantly understudied in patients taking antipsychotic medications. Lipids may be more important than diabetes because dyslipidemia appears to occur at a higher prevalence in this patient population. Lipid levels are a significant problem because physicians are seeing hypertriglyceridemia. Knowing what we know about what causes and contributes to cardiovascular disease, we are obliged to play detective and figure out why psychiatric patients are dying sooner and more often of cardiovascular disease than the general population. The big challenge for all is to ensure that the physical health of patients with mental illness is given the priority it deserves, helping them to face their future with the lowest possible morbidity and mortality odds stacked against them.

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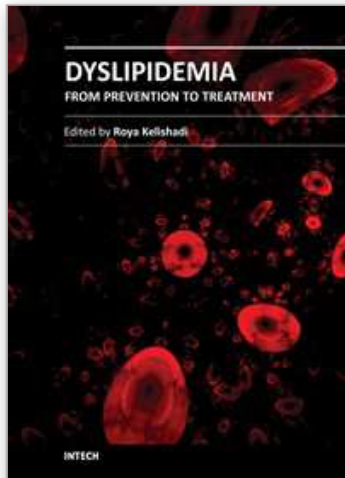
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## **Dyslipidemia - From Prevention to Treatment**

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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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