

## Metabolic Challenges in Schizophrenia

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### Abstract

Schizophrenia is a psychiatric disorder requiring constant vigilance and lifelong intervention with psychotherapeutic counseling and administration of Antipsychotic drugs. Metabolic aberrations are documented to occur more frequently in subjects with Schizophrenia (SCH) prior to treatment and the prevalence of these metabolic alterations is significantly raised following administration of Antipsychotic drugs especially the newer ones. Adiposity in SCH prior to drug therapy is significantly increased in comparison to age matched healthy subjects (N) as documented by several indices. Body Mass Index, kg/m<sup>2</sup> (26.7 for SCH vs. 22.8 for N, p<0.003); Waist/Hip Ratio (0.99 for SCH vs. 0.86 for N, p<0.005); Total Body Fat, mm<sup>2</sup> (34681 in SCH vs. 27692 in N, p<0.01) and Intra-abdominal fat, mm<sup>2</sup> (13232 in SCH vs. 3880 in N, p<0.005). Squealed of obesity involve almost every organ and system in the body and contribute to increase both morbidity and mortality in SCH. Thus, the prevalence of other disorders constituting metabolic syndrome e.g. Hypertension, Pre Diabetes or Type 2 Diabetes and Dyslipidemia rise markedly and presence of these disorders more than double the relative risks of mortality in SCH in comparison to general population. The mortality risk is likely to be increased further with recent documentation of rising prevalence of cancer amongst subjects with obesity and diabetes. In several subjects with SCH, the initial manifestation of Diabetes is Diabetic Ketoacidosis or Hyperglycemic Hyperosmolar State resulting in hospitalization with obtundation and coma. Moreover, the severity of these metabolic changes is more pronounced at diagnosis in subjects with SCH as compared to non SCH subjects due to lack of recognition of symptoms and/or neglect on part of the subjects with SCH, leading to a far greater mortality. Moreover, increased frequency of smoking in subjects with SCH induces even greater risks of morbidity and mortality via rise in infectious and respiratory disorders. Finally, some of the newer antipsychotic drugs especially Olanzapine and Quetiapine are well documented to cause a rise in prevalence of all disorders constituting Metabolic Syndrome. Therefore, we concur with the recommendations for management of subjects with Schizophrenia formulated by the consensus development conference conducted by several organizations They include Metabolic risk considerations prior to and at initiation of atypical antipsychotics: 1) Patient, family, and caregiver education, 2) Baseline screening, 3) Regular frequent monitoring at 3-6 months' interval and 4) Referral to specialized services, when appropriate.

**Keywords:** Schizophrenia; Metabolic aberrations; Metabolic syndrome; Psychiatric disorder

### Introduction

Schizophrenia (Sch) is a psychiatric illness characterized by disordered thought process and abnormal emotional responsiveness. Common presentations of Sch include hallucinations, delusions, and disorganized thought and speech. The disease can cause significant impairment in social and occupational functioning requiring lifelong intervention with antipsychotic medications as a cornerstone of therapy. Although antipsychotic medications are essential in helping to control the symptoms of Sch and in improving the overall functioning of those afflicted, it is well known that they are associated with obesity and a range of metabolic aberrations [1-22]. In fact, metabolic aberrations are documented to occur more frequently in subjects with Sch prior to treatment, and the prevalence of these is significantly raised upon treatment with antipsychotic medications, especially the second generation antipsychotics [2,3,15,17]. These metabolic derangements are components of the metabolic syndrome and hence portend a greater risk for cardiovascular and all cause morbidities and mortality [23-30]. Therefore then, subjects with Sch are distinctly at greater risk for cardiovascular disorders (CVD) and their consequences. In actuality, CVD mortality was more than twice as prevalent among subjects with Sch as in the general population [31].

Individuals with Sch have a greater mortality than those in the general population [32-49]. The excess mortality seen in Sch is multifactorial (Table 1). Causes include lifestyle factors, such as a greater incidence of substance abuse, smoking, poor nutrition, and inactivity;

coexisting illnesses, such as HIV and hepatitis C as well as medication effects, such as obesity, hyperglycemia or diabetes, and dyslipidemia.

Cause of Death	Mortality Ratio in Men	Mortality Ratio in Women
Infectious disease	3.4	1.9
Respiratory disease	3.2	2.7
Endocrine disease	2.7	2.0
Gastrointestinal disease	2.5	2.1
Cardiovascular disease (CVD)	2.3	2.1
Urogenital disease	2.3	2.3

Because CVD is the most common cause of death in the general population, and is more than twice as common in patients with schizophrenia, it accounts for most of the excess mortality in schizophrenia [31].

**Table 1:** Main Causes of Mortality in Patients with Schizophrenia. Ratio of Observed Deaths in Patients with Schizophrenia to Expected Deaths in General Population.

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In a recent study, fifteen subjects with Sch without a current treatment with drugs were compared with 15 age-matched healthy volunteers. Seven subjects with Sch were drug-naïve, and the remaining 8 had without oral drug therapy for at least 6 weeks and intramuscular administration of any drugs for at least 6 months. The study documented presence of generalized obesity as expressed by body mass index and total body fat determination as well as visceral obesity as defined by waist-to-hip ratio and greater intra-abdominal fat in patients with Sch during the drug free period (Table 2) when compared with age matched healthy controls [3]. Ryan et al. [8] demonstrated similar findings with respect to glucose intolerance in drug-naïve patients with Sch (Table 3). In this study, subjects with Sch manifested a greater mean fasting plasma glucose and insulin concentrations as well as a decreased insulin sensitivity, as measured by a homeostasis model assessment [8]. Moreover, the prevalence of the state of impaired fasting glucose or pre-diabetes was significantly higher in subjects with Sch in comparison to normal subjects [8]. Finally, the occurrence of these metabolic abnormalities appears to rise on initiation of antipsychotic therapy (Figure 1).

A meta-analysis examined more than 80 studies involved with assessment of body weight after 10 weeks of antipsychotic therapy. The studies were divided into 2 groups (Table 5): 1) typical 1<sup>st</sup> generation antipsychotics (molindone, fluphenazine, haloperidol, chlorpromazine, and thioridazine/mesoridazine), 2) 2<sup>nd</sup> generation atypical antipsychotics (ziprasidone, risperidone, olanzapine, and clozapine). Both groups of studies were placebo controlled. In this meta-analysis, use of all drugs were associated with some degree of weight gain, only exceptions being molindone in the group of 1<sup>st</sup> generation and ziprasidone in the newer atypical agents, both seem to be weight-neutral. On the opposite end of the spectrum, olanzapine and clozapine were associated with the maximum weight gain (4.0-4.5 kg) over the course of the study (Figure 2). Thus, with a relatively marked weight gain in a short period of 10 weeks, the potential distinctly exists for even a higher weight gain with the continued use of these medications for months and years required

Measure	Schizophrenia* Patients With (n=15)	Controls Healthy (n=15)	p Value
Mean age (years)	33.7	30.1	NS
BMI (kg/m <sup>2</sup> )	26.7	22.8	<0.003
Waist-to-hip ratio	0.99	0.86	<0.005
Total body fat (mm <sup>2</sup> )	34,680.9	27,692.5	NS
Intra-abdominal fat (mm <sup>2</sup> )	13,232.0	3879.9	<0.005

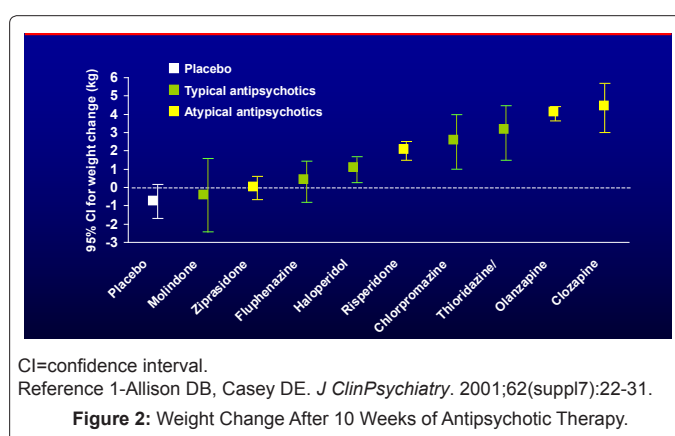
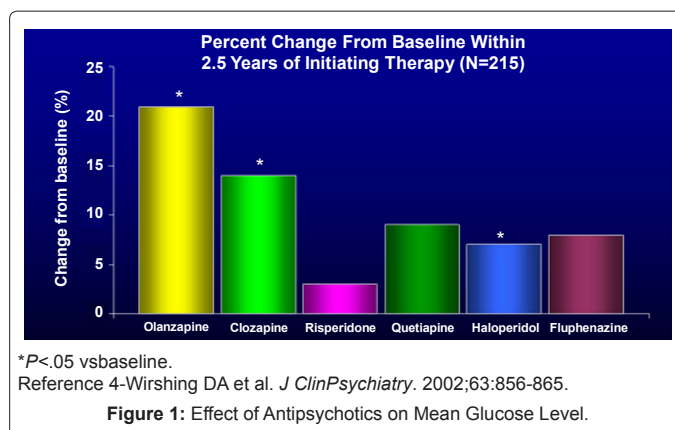
\*Patients were either drug-naïve (n=7) or had been free of oral neuroleptics for ≥ 6 weeks and IM neuroleptics for ≥ 6 months (n=8). NS=not significant [3].

Table 2: Adiposity in Patients with Untreated Schizophrenia.

Variable	Patients with Schizophrenia (n=26)	Healthy Controls (n=26)	p Value
Frequency of IFG (%)	15.4	0	<0.02
Mean FPG level (mg/dL)	95.8	88.2	<0.03
Mean fasting insulin level (µU/mL)	9.8	7.7	<0.05
Degree of insulin resistance (measured by homeostasis model assessment)	2.3	1.7	<0.01

IFG=impaired fasting glucose [8]

Table 3: Glucose Intolerance in Drug-Naïve Patients with Schizophrenia.



to sustain remission of symptoms of this disorder. Long-term studies confirm the lack of weight gain with ziprasidone whereas the weight gain with quetiapine and risperidone reaches a plateau at approximately 2.0-5.6 kg (4 lb-12 lb) and the weight gain with olanzapine is apparently maximum reaching peak and stabilizing at approximately 12 kg (26 lb); an increase well documented to induce significant aberrations in carbohydrate and lipid metabolism leading to adverse cardiovascular outcomes [50].

In a long term study of 1 year, weight changes between treatments with risperidone and olanzapine therapy were examined. The study included in 94 adult inpatients during the first year of therapy with risperidone or olanzapine. In the total cohort, mean weight gain was 10.7 lb and 17.5 lb for patients receiving risperidone and olanzapine respectively with both changes being statistically significant compared to baseline body weights prior to initiation of either therapy [6]. Finally, it is apparent that weight gain associated with antipsychotics may ensue soon after treatment initiation. In a clinical trial, the subjects randomized to receive olanzapine gained an average of 8 lb within 6 weeks. In contrast, subjects assigned to ziprasidone gained weight an average of 2 lb, a significantly less (p<0.001) than in the other group [11]. However, fortunately, weight gain with administration of some antipsychotics, e.g. risperidone and olanzapine may be halted or even reversed within a short period of 6 weeks on discontinuation of these drugs and initiating therapy with ziprasidone, a desirable alternative in this regard [7].

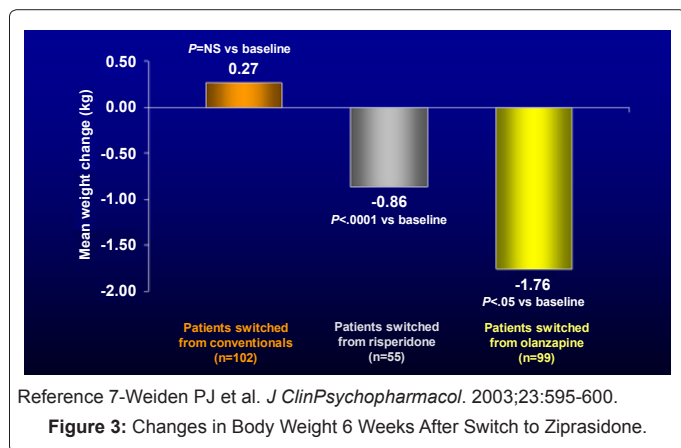
This study involved subjects in whom therapy with either 1<sup>st</sup> generation conventional antipsychotics e.g. haloperidol or with 2<sup>nd</sup> generation agents, risperidone and olanzapine was discontinued and

ziprasidone was initiated (Figure 3). 102 subjects with prior treatment with conventional antipsychotics experienced a no significant gain of 0.27 kg whereas subjects who were changed from risperidone experienced a weight loss of 0.86 kg ( $p < 0.0001$  vs. baseline). Moreover, subjects with prior therapy with olanzapine showed a greater weight loss: 1.76 kg ( $p < 0.05$  vs. baseline). However, it is also clinically important to note that the weight loss was related to the actual body weight prior to initiation of treatment with ziprasidone, e.g. higher the initial body weight, the greater was the weight loss.

Serious clinical sequelae of weight gain and obesity such as hypertension, type 2 diabetes, and osteoarthritis, and sleep apnea, cardiovascular disorders including coronary heart disease and stroke as well as cancers involving several organs are well documented [26]. Subjects with Sch are prone to be overweight and obese because of lack of adequate physical activity further exacerbated by therapy with some antipsychotic drugs. Furthermore, the stigmatization, social rejection, and loss of self-esteem that accompany obesity are particularly heavy burdens for patients with Sch because they often lack the interpersonal and cognitive skills to cope with them. Weight gain tends to perpetuate social withdrawal and further impairs quality of life, rendering these subjects an additional risk for treatment discontinuation and disease relapse [26].

The Framingham data estimated the number of excess deaths associated with weight gain similar to that produced by antipsychotics. In patients with initial BMI between 23 kg/m<sup>2</sup> and 27 kg/m<sup>2</sup>, weight gains of this magnitude is expected to cause a relatively small change in the number of excess deaths, ranging from a decrease of 32 deaths per 100,000 among those gaining 2.5 kg to an increase of 287 deaths in those gaining 12.5 kg. However, among overweight or obese schizophrenic subjects (BMI > 27 kg/m<sup>2</sup>), 257 to more than 2000 excess fatalities per 100,000 individuals over the same interval are anticipated following the same weight gains respectively (Figure 4). The investigators estimated that the lives saved due to prevented suicides might be almost totally offset by the deaths due to weight gain in subjects administered drugs inducing a significant weight gain such as clozapine [28].

The same study assessed the clinical impact of antipsychotic induced weight gain on hypertension in subjects with BMI between 23 kg/m<sup>2</sup> and 27 kg/m<sup>2</sup> over a 10-year period [28]. The data suggest that the number of cases of hypertension may rise by 1971 per 100,000 individuals with a weight gain of 2.5 kg whereas a gain of 12.5 kg would increase the incidence to nearly 10,000 per 100,000 individuals. The authors also indicate that the incidence of hypertension may be exaggerated in overweight or obese (BMI > 27 kg/m<sup>2</sup>) schizophrenic



Agents	Adjusted Odds Ratio	p Value
No antipsychotics	Reference	
Conventional antipsychotics	1.4	0.004
Olanzapine	5.8	0.001
Risperidone	2.2	0.079

Odds of Developing Diabetes with Atypical vs. Conventional Antipsychotics.

Agents	Adjusted Odds Ratio	p Value
Conventional antipsychotics	Reference	
Olanzapine	4.2	0.008
Risperidone	1.6	0.290

Cases: n=451 Controls: n=2696 [5]

**Table 4:** Diabetes Associated With Typical and Atypical Antipsychotics. Odds of Developing Diabetes in Antipsychotic Users vs. Nonusers.

Agents	Adjusted Odds Ratio	p Value
No antipsychotics	Reference	
Conventional antipsychotics	1.38	<0.001
Olanzapine	4.65	<0.001
Risperidone	1.12	0.720

Odds of Developing Hyperlipidemia with Atypical vs. Conventional Antipsychotics.

Agents	Adjusted Odds Ratio	p Value
Conventional antipsychotics	Reference	
Olanzapine	3.36	<0.001
Risperidone	0.81	0.520

Cases: n=1268, Controls: n=7598 [5].

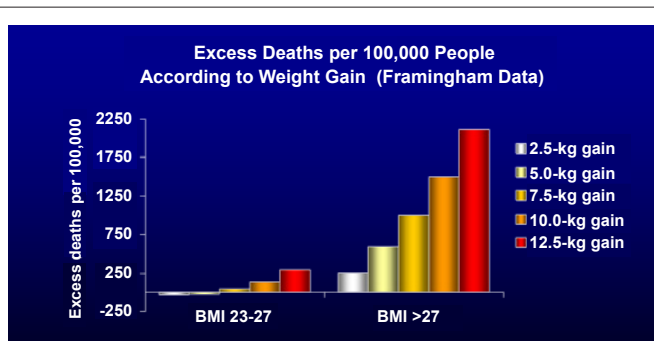
**Table 5:** Hyperlipidemia with Typical and Atypical Antipsychotics. Odds of Developing Hyperlipidemia in Antipsychotic Users vs. Nonusers.

patients over the course of 10 years with anticipated number of 1,823-8,320 excess cases of hypertension per 100,000 subjects (Figure 5).

Fontaine et al also examined data from more than 5,000 participants in the Framingham Heart Study to estimate the clinical impact of antipsychotic-induced weight gain on glucose tolerance over a 10-year period [28]. The data revealed that a gain of 2.5 kg in subjects with initial BMI between 23 kg/m<sup>2</sup> and 27 kg/m<sup>2</sup> may increase the number of cases of IGT or diabetes by 274 per 100,000, whereas a gain of 12.5 kg would raise the number of cases to 1915 per 100,000 thus suggesting a progressive rise in incidence of pre-diabetes and diabetes with a greater weight gain. These authors hypothesized that among overweight or obese patients with Sch (BMI > 27 kg/m<sup>2</sup>), similar weight gains may cause 637 to 4,152 excess cases of IGT or diabetes per 100,000 individuals respectively, a distinctly dire consequence (Figure 6).

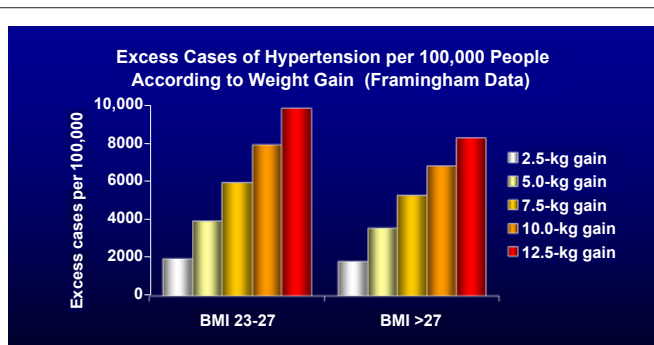
In another retrospective analysis discussed earlier, changes in fasting glucose level were compared in patients who had been using either risperidone or olanzapine for 1 year [6]. Risperidone did not produce any significant change from baseline, but use of olanzapine was associated with an increase of 7.26 mg/dl ( $p \leq 0.05$  vs. baseline). Moreover, among the subset of younger subjects < 60 years old, the increase in fasting glucose level with olanzapine was even greater (10.8 mg/dl) and the difference between these 2 age groups was statistically significant ( $p=0.03$ ) indicating that younger subjects may more susceptible to pre-diabetes and diabetes following administration of olanzapine [6].

A further examination of glucose regulation was conducted with determination of fasting plasma insulin and glucose levels in subjects with Sch or another schizoaffective disorder [19]. Participants were



Reference 28-Fontaine KR et al. *Psychiatry Res.* 2001;101:277-288.

Figure 4: Antipsychotic-Induced Weight Gain: Estimated Impact on Fatalities.



Reference 28-Fontaine KR et al. *Psychiatry Res.* 2001;101:277-288.

Figure 5: Antipsychotic-Induced Weight Gain: Estimated Impact on Hypertension.

randomized to 6 weeks of therapy with ziprasidone or olanzapine. Median fasting plasma insulin increased by 3.3 μU/mL in olanzapine-treated subjects ( $p < 0.0001$  vs. baseline) and by 0.25 μU/mL (a no significant change from baseline) in patients receiving ziprasidone. However the difference between 2 drugs at the end of observation period was significant ( $p = 0.05$ ). No significant change in fasting glucose was observed in either olanzapine or ziprasidone treated subjects [19]. Therefore, it is apparent that insulin sensitivity as determined by insulin × glucose product, a reliable index of insulin sensitivity [51] declined following therapy with olanzapine but not with ziprasidone.

In another extensive though retrospective study, a long term use of antipsychotic drugs on mean glucose level was assessed. Wirshing et al. reviewed the charts of 215 patients [4]. Glucose levels prior to initiation of treatment and again around 2½ years after initiation of olanzapine, clozapine, risperidone, quetiapine, haloperidol, or fluphenazine were documented (figure 1). This multivariate analysis examined the influence of other variable factors e.g. patient age, duration of antipsychotic treatment, other medications that may affect glucose level, and initial laboratory values and still concluded that olanzapine, clozapine, and haloperidol were associated with statistically significant glucose elevations compared with baseline. Moreover, the clinical significance of the change in plasma glucose concentration is underscored by the fact that 13% of the patients treated with clozapine required a glucose-lowering agent after starting the antipsychotic, and 6% of the olanzapine group required a dose increase in their glycemic therapy. In contrast, none of the subjects in the risperidone, quetiapine, haloperidol, or fluphenazine groups required glucose-lowering intervention [1].

Another literature review of onset of diabetes mellitus after initiating atypical antipsychotic therapy with various agents reported 52 cases with use of olanzapine, 30 with clozapine, 4 with quetiapine, 2 with risperidone, 1 with ziprasidone, and none with aripiprazole [10]. The difference may be partly attributed to the fact that olanzapine and clozapine have been on the market for a longer time than newer agents such as ziprasidone and aripiprazole. However, the single case reported with ziprasidone presented in this literature review as diabetes mellitus, was in fact transient hyperglycemia. Moreover, fatalities due to diabetic states are reported in three subjects treated with olanzapine, and 1 with clozapine, underscoring the serious nature of these adverse outcomes. Finally, this study also documented a greater adverse impact on glycemic control with use of olanzapine and clozapine when compared with other agents [10].

Melkersson and Dahl [10] also reported that the difference between antipsychotics in diabetic risk level is supported by a comparison of cases reported via the US FDA Med Watch surveillance system plus published cases [10]. New-onset diabetes was reported in 242 patients taking clozapine, 225 taking olanzapine, 78 taking risperidone, and 10 taking haloperidol. The number of cases of metabolic acidosis or ketosis and the number of fatal hyperglycemic episodes were also far greater with clozapine and olanzapine than with the other antipsychotics in this analysis.

In a population-based, nested, case-control study [5], 451 patients with Sch with diabetes were compared with 2696 patients with Sch without diabetes (Table 4). When compared with the patients who did not use antipsychotics, those taking 1<sup>st</sup> generation antipsychotic agents had a small but significant increase in the odds of having diabetes. In subjects using risperidone, the risk of onset of diabetes more than doubled when compared with antipsychotic nonusers, whereas olanzapine users showed almost a 6-fold increase in the risk of developing diabetes. In comparison between users of atypical 2<sup>nd</sup> generation agents and the users of conventional 1<sup>st</sup> generation agents,

Drug	Weight Gain	Risk of Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

+ = increase; - = no effect; D = discrepant results.

\*Newer drugs with limited long-term data [51].

Table 6: Metabolic Abnormalities with Atypical Antipsychotics.

Measurement	Baseline	4	8	12	Every	Every	Every
		Weeks	Weeks	Weeks	Quarter	Year	5 Years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
BP	X			X		X	
FPG	X			X		X	
Fasting lipid profile	X			X			X

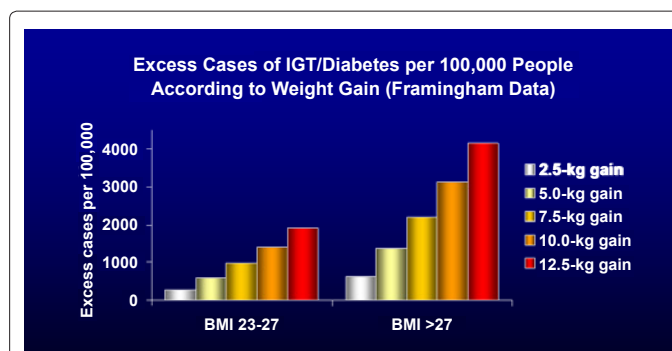
Consider switching to a different atypical antipsychotic if patient gains ≥ 5% of initial body weight or develops worsening glycemia or dyslipidemia.

Table 7: Recommended frequency of follow-up monitoring.

risperidone was associated with a no significant increase in risk, whereas olanzapine more than quadrupled the risk of occurrence of diabetes. Moreover, the risk persisted after elimination of other risk factors including concomitant use of other drugs implicated in onset of diabetes.

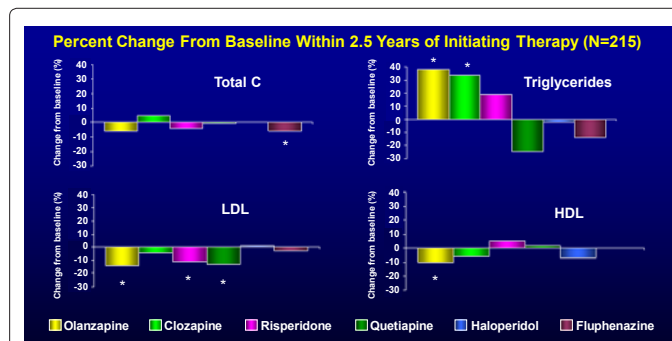
The importance of early diagnosis and aggressive treatment to achieve prompt desirable glycemic control in delaying or preventing micro vascular complications is never over-emphasized. Moreover, diabetes is deemed 'cardiovascular risk equivalent' because of the extensive documentation in several studies that the presence of type 2 diabetes sharply increases the likelihood of developing macro vascular disease by 2 to 4 fold in comparison to age matched subjects without diabetes and the occurrence of initial myocardial infarction in subjects with diabetes is almost identical to recurrence of myocardial infarction in subjects without diabetes [24,27,29,30]. Moreover, the mortality risk during initial MI in subjects manifesting diabetes is not significantly different from the subjects without diabetes with a prior MI [24]. A similar pattern has also been observed regarding the incidence of stroke; patients with diabetes without a prior MI manifest approximately the same risk as those without diabetes but with a prior MI (10.3% vs. 7.2%).

In addition to providing data regarding changes in glucose levels prior to and following antipsychotic therapy for 2½ years, Wishing et al. also reported lipid levels from the same study [4]. The changes in total cholesterol levels were relatively small with fluphenazine alone inducing a significant decrease of 6% from the baseline concentration. However, the alterations in triglyceride levels were more pronounced. Both olanzapine and clozapine produced significant increases from baseline (38% and 34%, respectively) and these changes were significantly greater than those associated with haloperidol and fluphenazine. In fact, more than half of the patients receiving clozapine experienced clinically significant triglyceride elevations (defined as ≥ 200 mg/dl). Fortunately none of the antipsychotics significantly raised low-density lipoprotein (LDL) levels. Indeed, the patients taking olanzapine, risperidone, and quetiapine actually had significant decreases, all of similar magnitude. Most of the drugs induced a modest though no significant decline in HDL, with the exception of olanzapine, which induced a significant decrease of 10%. This undesirable effect of olanzapine on HDL level may neutralize its apparent benefit regarding LDL level (Figure 7). In another study [6], 2 drugs, risperidone and olanzapine differed markedly in their effects on lipid levels, in which metabolic outcomes were compared in 94 adult inpatients during the first year of therapy. Olanzapine increased fasting cholesterol by 23.6 mg/dl, a significantly greater risk than that induced by risperidone (7.2 mg/dl,  $p=0.029$ ). Olanzapine was also associated with an increase of 88.2 mg/dl in fasting triglycerides, significantly greater than 29.7 mg/dl rise noted with risperidone ( $p=0.042$ ). Olanzapine had an even more striking effect in the subset of patients <60 years old, whereas risperidone had approximately the same impact on the subset as the total cohort [2]. Similar to antipsychotic-induced weight gain, antipsychotic-induced dyslipidemia may be at least partially reversed by switching to a metabolically neutral antipsychotic agent. In 3 studies, outpatients with Sch, the current conventional antipsychotic agent or risperidone was discontinued because of lack of adequate response or onset of adverse side effects and ziprasidone was initiated. Only after 6 weeks, no significant declines in triglycerides and total cholesterol ensued in subjects with prior therapy with conventional agents. In contrast, subjects receiving risperidone previously showed a significant lowering of both serum triglycerides (29 mg/dl,  $p<0.01$ ) and total cholesterol (12 mg/dl,  $p<0.005$ ). Finally, the benefits of switching



IGT=impaired glucose tolerance. Reference 28-Fontaine KR et al. *Psychiatry Res.* 2001;101:277-288.

Figure 6: Antipsychotic-Induced Weight Gain: Estimated Impact on IGT/Diabetes.



LDL=low-density lipoprotein.\* $P<.05$  vs. baseline. Reference 4-Wirshing DA et al. *J Clin Psychiatry.* 2002;63:856-865.

Figure 7: Effect of Antipsychotics on Mean Lipid Levels.

from olanzapine were even more prominent with the reductions of 50 mg/dl in triglycerides and 17 mg/dl in total cholesterol respectively ( $p<0.0001$  for both). A similar nested, case-control study, the association between antipsychotic drug use and presence of hyperlipidemia defined by either the documentation of elevated serum cholesterol and/or triglycerides, or by a history of use of a prescription for lipid-lowering drugs was examined [5]. A comparison was conducted between population of 1268 subjects with hyperlipidemia and 7598 patients without hyperlipidemia. The data revealed essentially a similar pattern as described in the diabetes analysis. Compared with nonuse of antipsychotics, the use of conventional agents was accompanied by a small but a significant increase in the risk of developing hyperlipidemia whereas Olanzapine more than quadrupled the risk with risperidone showing no aberrant effect. Therefore, the authors concluded that the potential cardiovascular consequences of olanzapine therapy, and its association with the metabolic syndrome, warrant serious consideration of its risk/benefit ratio by treating physicians. Another recently approved antipsychotic agent Asenapine also presents the same dilemma regarding adverse influence on body weight, cardiovascular and metabolic outcomes including glycemia and serum lipid concentrations especially because of lack of availability of the data over the long term use [16].

Thus, it is apparent that subjects with schizophrenia are more prone to manifest weight gain and its consequences including metabolic derangements raising the risk of adverse cardiovascular outcomes [50]. Furthermore, the risk is exaggerated with use of various antipsychotics required for attaining and maintaining remission of

clinical manifestations and improving quality of life in these subjects (Table 6). Although the exact pathophysiologic mechanism responsible for occurrence of glycemic dysregulation with the use of these agents is uncertain, it may be attributed to weight gain and change in body composition. Limited data suggest that most of the weight gained is fat. It is also possible that the antipsychotics have a direct effect on  $\beta$ -cell function or insulin sensitivity [8].

Therefore, management strategies for prevention or delay of onset as well as treatment of these metabolic disorders deserve priority especially because of their impact on all cause mortality but specifically on cardiovascular outcomes. Several paradigms have been tested. Educational programs involving subjects with Sch and their caregivers consisting of therapeutic life style changes including nutrition and exercise apparently assist in preventing weight gain [52]. Treatment with metformin, 1000 mg daily for 12 weeks has been associated with decreases in BMI and body weight by 5-7%, as well as a decline in fasting plasma insulin resulting in improvement in insulin sensitivity [53,54]. In a meta-analysis, the same regimen showed a decrease in body weight of 5.02 Kg; decrease in BMI of 1.82 kg/m<sup>2</sup>; and decrease in waist circumference of 1.42 cm [55]. In addition, angiotensin receptor blockers (ARBs), valsartan and telmisartan daily for 12 weeks were shown to be associated with a decline in BMI, abdominal circumference, fasting insulin, and insulin resistance [56]. Therefore, the treatment for antipsychotic-induced metabolic syndrome is multifaceted, and includes therapeutic lifestyle changes, metformin, ARBs, statins, and aspirin [57].

Therefore, a Consensus Development Conference was organized by several groups consisting of psychiatrists, endocrinologists, cardiologists and experts in management of obesity [50]. The panel concluded that atypical or second-generation antipsychotics offer significant benefits to patients with a variety of psychotic disorders. However, the panel also affirmed the increased risk of weight gain, glucose dysregulation including diabetes and its complications such as DKA and dyslipidemia associated with use of these agents. The panel attributed the maximum incidence of weight gain, glucose dysregulation including diabetes and worsening lipid profile to treatment with clozapine, olanzapine and quetiapine, an intermediate risk to administration of risperidone and the lowest risk with the use of aripiprazole and ziprasidone. The panel cautioned, however, that little epidemiologic long term safety information is available with the use these two newer agents. The panel also provided guidelines for assessment and monitoring in management of subjects manifesting schizophrenia prior to and following use of these effective agents in order to prevent and/or treat ensuing consequences of short and long term use of these agents. The panel recommended an algorithm for monitoring for prevention and onset of metabolic disorders in subjects with Sch (Table 7). We concur with these recommended measures: 1) Assessment of metabolic and cardiovascular risk factors and endocrine disorders prior to initiating atypical antipsychotic agents as well as subsequent periodic monitoring for onset by encouraging patients and caregivers to keep a written record of their body weight, 2) A special attention to use of other drugs with predisposition to induce diabetes or weight gain, e.g. valproic acid, lithium, anticonvulsants, antiretroviral agents, oral contraceptives in young women etc. 3) Education of patients and their families or caregivers in understanding the possible rising risk of weight gain, diabetes, and dyslipidemia as well as the effect on their cardiovascular health. 4) Education of individuals involved in care of patients regarding recognition of signs and symptoms of diabetes, especially acute decompensations such as diabetic ketoacidosis. 5) Initiation of prompt management strategies in case of occurrence either

by providers themselves or via a referral to a specialist, a diabetes self-management program, or a weight-management program as deemed appropriate.

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