

Schizophrenia, antipsychotics and metabolic changes

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Antipsychotics, schizophrenia and glucose metabolism

Although the effect of neuroleptics (first-generation antipsychotics, AP1G) on glucose metabolism was only exceptionally a matter of research interest and its practical impact has been generally considered negligible (even The Fourth Generation of Progress in Psychopharmacology does not mention changes of glucose metabolism among their significant side-effects^[1]), since the very beginning of era of psychopharmacology there were known reports of changed glucose tolerance in schizophrenia^[2,3,4]. After phenothiazines were introduced in psychiatry, sporadic reports of their effect on blood sugar levels were published^[5]. This situation persisted until nineties of the last century, when a new generation of antipsychotics entered the marketplace. This group of compounds, originally called “novel” or “atypical” antipsychotics, is now labeled “Antipsychotics of the second generation”, AP2G.

There are only few common features of AP2G, distinguishing them from classical neuroleptics: In the therapeutic dose, AP2G elicit less extrapyramidal symptoms, less tardive dyskinesias, and less cataleptic effects. On the other hand, they are supposed be effective also in negative and affective symptoms of schizophrenia. It may be a result of a different profile of their receptor affinity in comparison to classical neuroleptics: Occupancy of dopamine receptors (D₂) is lower (about 40-70%); target structures are different (affinity of AP2G is higher to mesocortical and mesolimbic rather than to nigrostriatal dopaminergic pathways); dissociation from D receptors is higher; there is also higher affinity to other types of D receptors than D₂ (D₁ etc.); there is relatively high affinity to serotonin 5-HT receptors (e.g., antagonism on 5HT_{2A,C} and agonism on 5HT_{1A}). In general, AP2G are better tolerated than classical antipsychotics, with consequent higher compliance and better quality of life of the patients. Meta-analysis of clinical trials indicates at least equal or even higher antipsychotic efficacy of AP2G in comparison to classical Antipsychotics^[6]. Lesser pronouncement of extrapyramidal symptoms in AP2G opened the space for paying attention to other undesirable side-effects, which were hitherto either rare or under recognized, e.g., weight gain. In a comprehensive meta-analysis of weight change after 10 weeks of treatment at a standard dose, main increases were as follows: clozapine, 4.45kg; olanzapine, 4.15kg; risperidone, 2.10kg; and ziprasidone, 0.04kg^[7]. Data for quetiapine were insufficient, but some studies indicate it's high propensity for gain. Aripiprazole, the newest AP2G (some authors classify it as AP3G because of its dual effect), is considered to be weight neutral. Since the weight gain belongs to the major risk factors for development of diabetes mellitus II type (table 1), epidemiology of metabolic disorders in schizophrenia has been recently paid the attention.

It has been repeatedly shown that schizophrenia is associated with 1.5-2.6 times higher average mortality. Average life-span in schizophrenic patients is about 20% shorter^[12,13]. The main causes include suicides and accidents. About 60%, however, can be explained by other factors such as cardiovascular and metabolic disorders, poor nutrition etc. The possible relationship between schizophrenia and

diabetes came into serious consideration after epidemiological study showing 15.8% prevalence of diabetes among schizophrenic patients compared to 3.5% in general population^[14]. Although later studies found lower rates, the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is approx. 1.5-2.0 times higher than in the general population. Canadian Diabetes Association, for example, recently added schizophrenia to the list of risk factors of type II diabetes mellitus^[15]. Nevertheless, as the important benchmarks of metabolic disorders (BMI and family history) were not separately followed for the treatment modalities and other conditions, it is still unclear what is the proportion in which psychiatric conditions *per se*, their treatments or other risk factors (like more sedentary behaviour) account for the increased prevalence.

Diabetes mellitus type II and second generation antipsychotics

Coincidence of epidemiological data on metabolic disorders in schizophrenia and the onset of AP2G brought series of case-reports describing newly diagnosed diabetes in patients treated with these drugs (for review see Cohen, 2004^[16] and Libiger, 2005^[17]; [table 2](#)). The more potent antipsychotic (clozapine, olanzapine) the higher prevalence of obesity and/or diabetes ([table 1](#)). Nevertheless, the number of reported cases reflects not only diabetogenic potential of the respective antipsychotic, but also the length of the time during which the drug is on the market. So the absolute numbers listed in [tab. 2](#) are difficult to interpret. More conclusive might be parameters of binary statistics from comparative studies (OR and CI in [table 2](#)). They clearly show that in spite of presence of diabetogenic risk factors in schizophrenia as such, AP2G are to some extent associated with an increase in weight and the risk of diabetes, but this varies from agent to agent (and from patient to patient). For this reason, the FDA has notified the manufacturers of the AP2G that product labeling for these drugs will require a warning about hyperglycaemia and diabetes^[19]. A recent consensus development conference conducted by the ADA, the American Association of Clinical Endocrinologists, the American Psychiatric Association, and the North American Association for the Study of Obesity^[11] concluded that the data regarding risk of association with diabetes are more consistent for clozapine or olanzapine versus risperidone or quetiapine, where some studies showed an increased risk for diabetes whereas others did not. The panel also concluded that although the two most recently approved second-generation antipsychotic medications, aripiprazole and ziprasidone, have relatively limited epidemiologic data, available clinical trial experience with these drugs has not shown an increased risk for diabetes. Citrome and Volavka^[20], however, argue that the risk attributable to antipsychotics appears small compared with established risk factors such as family history and advancing age. Watching TV, for example, increases the risk of diabetes in women by 14%^[21]. On the other hand, weight gain after olanzapine does not seem to be dose dependent^[22]. So from the evidence, choosing a second-generation antipsychotic medication does not, in and of itself, have significant predictive value for treatment-emergent diabetes. Moreover, the report^[11] did not adequately address the complex issues regarding antipsychotic efficacy.

To assess properly above mentioned associations one should carefully distinguish variables feeding the increased risk of diabetes. For example, OR for weight gain is 2.36, being male 1.27, concurrent medication with valproate 1.97, and with SSRI 1.63^[23]. These factors are not dependent each other. Obesity, particularly abdominal obesity is a part of metabolic syndrome^[24] and its increment enhances the

risk of diabetes. Weight gain is associated not only with use of AP2G (table 1), but to some extent also with AP1G thioridazine, chlorpromazine, haloperidol and drug combinations^[7]. Both antipsychotic treatment and the disease are associated with impaired life-style, changes in nutritional habits and even social downfall. All of this can hypothetically represent a connection between the treatment and the risk of diabetes. Nevertheless, why do we suppose that antipsychotics as such add some odds to the risk?

First, in many cases diabetes regresses after the withdrawal of antipsychotics a vice versa^[16]. After the cessation of clozapine and olanzapine the results of glucose tolerance test improve in 78% of patients^[25]. In the association with a treatment, 60% of newly developed diabetes occurs in 1-12 weeks after onset of antipsychotics^[26]. Moreover, in many patients treated with antipsychotics, diabetes occurs even without any weight gain.

Pathogenesis of AP2G induced diabetes

What the mechanism of diabetogenic effect of antipsychotics could be? If the weight gain were at least partly the mediator, then the association between antipsychotics and diabetes could be explained by antagonism on D₂ (movements attenuation and decrease of motivation), histaminergic H₁ (sedation and weight gain), and serotonergic 5-HT_{2C} (weight gain, particularly in association with polymorphism SNP 795C/T of HT_{2C} gene) receptors. In addition, serotonin turnover in the brain is negatively correlated with the peripheral insulin sensitivity^[27] and serotonin antagonism leads to the elevation of glycaemia^[28].

Other explanation includes also leptin, levels of which positively correlate with the resistance to insulin. After clozapine, plasma levels of leptin elevate regardless body weight^[29]. Another important target structure is glucose transporter (GLUT), a protein, which shifts from cytoplasm to the membrane after the activation of insulin receptor, and so enables the transport of glucose into the cell. The rate of *in vitro* inhibition of GLUT after antipsychotics risperidone, clozapine, and its analogues correlates with their respective induction of hyperglycemia *in vivo*^[30]. It suggests that the drugs may block glucose accumulation directly at the level of the glucose transporter (GLUT).

Higher than expected prevalence of ketoacidosis (table 2) after antipsychotics in diabetes mellitus type II indicates the possible direct toxic effect of these drugs on pancreatic beta-cells. However, using the hyperglycemic clamp before and after the treatment with olanzapine, clozapine and placebo, Sowel et al. did not find pharmacologically impaired beta-cells secretion in healthy volunteers, when the impact of weight change was accounted for by multivariate regression analyses^[31]. The impaired pancreatic insulin secretion can be also a result of previous insensitivity to insulin, which evolves as a consequence of down-regulation of insulin receptors due to high insulin levels, which are increased in obesity. Insulin resistance leads to hyperglycemia and triglycerides elevation in plasma. This way the magic circle of insulin resistance and hyperglycemia is closed in diabetes mellitus type II.

Silvestre and Prous^[32] recently aimed to identify those receptors that most likely mediate antipsychotics-induced diabetes. Two independent measures taken from literature to indicate the risk of type 2 diabetes associated with 25 typical and atypical antipsychotic drugs were considered, along with their binding affinities to 21 specific receptors. Binding affinities (pKi) to human neurotransmitter receptors and

monoaminergic transporters were used as independent variables. Measures to determine the risk to induce new-onset type 2 diabetes were used as the dependent variables. Parallel analyses were also conducted for other measures (average therapeutic dose, weight gain, extrapyramidal side effects, hyperprolactinemia, anticholinergic signs, hypotension, and sedation) associated with antipsychotics. As a result, affinity for the cholinergic muscarinic M3 receptor subtype was found as the best predictor for the propensity of antipsychotics to induce type 2 diabetes. This study provides the evidence to indicate that antipsychotic agents with high binding affinity to the muscarinic M3 receptor are associated with an elevated risk for type 2 diabetes. M3 receptor is involved in glucose-dependent parasympathetic acetylcholine regulation of insulin secretion by pancreatic beta-cells.

In any case, however, the absolute risk directly attributable to individual antipsychotic medications in an individual patient is difficult to determine from available data. As mentioned, schizophrenia itself is a risk factor. Other risk factors may also be present, such as higher age or a family history of diabetes mellitus. It appears that choice of an antipsychotic may not necessarily predict the development of type 2 diabetes mellitus, although this association requires increased attention in clinical practice.

Practical implications

Consensus of experts^[11] recommend monitoring protocol for patients on AP2G as listed in [table 3](#). If any of these assessments indicates a risk of diabetes, appropriate treatment should be initiated. Psychiatrist should not hesitate to refer the patient to the specialist knowledgeable in treating metabolic disorders.

Practical recommendations in patients treated with AP2G involve:

- a) monitoring protocol ([table 3](#));
- b) structured questions on diabetic symptoms such as increased thirst, polyuria, changed appetite, weight gain, and related symptoms like irregular pulse, impaired vision or sexual dysfunctions;
- c) in case of any risk employ preventive measures such as low fat, low caloric diet, physical exercise, nutritional recommendations (vegetable, fish), smoking cessation, alcohol abstinence;
- d) in case of occurrence of metabolic syndrome consider the change of antipsychotic in relation to risk/benefit ratio of the treatment; consult a specialist; antipsychotic should be anyway changed if the weight rapidly gained more than 2.3 kg in four weeks^[17].
- e) in case of diabetes mellitus of type II introduce a proper treatment and refer a patient to a specialist.

All patients treated with second generation antipsychotics should be adequately educated and well informed about the risk of a treatment.

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TABLES:

Drug	Weight gain	Risk for diabetes	Worse lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

Table 1. AP2G and risk for diabetes. According to Diabetes Care 2004^[11]. **D**=discrepant results; * newer drugs with limited long-term data

Drug	Cases of Diabetes mellitus reported	No of Ketoacidoses reported	No of deaths related to diabetes	OR	CI
Clozapine	384	80	25	1.2-7.4	1,2-34,7
Olanzapine	237	80	15	1.2-3.5	1,0-1,43
Risperidone	131	26	4	1.5	1,12-2,04
Quetiapine	46	21	11	1.3-1.7	1,1-2,4
AP1G	NCD	NCD	NCD	1.31-1.34	1.1-1.6

Table 2. New onset of DM during the treatment with second generation antipsychotics (AP2G). **AP1G**= classical neuroleptics; **NCD**= no comparable data; **OR**= odds ratio to AP1G or placebo (in AP1G); **CI**= confidence interval. Merged literary data and data from FDA monitoring. According to Libiger 2004^[17] and Citrome and Jaffe^[18].

Item	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
BMI	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X
Glycosylated hemoglobin	X			(X)		X	

Table 3. Monitoring protocol for patients on AP2G. More frequent assessments may be warranted based on clinical status. Risk factors of diabetes: **Diabetes** of type II in the history; **BMI**>25 (overweight) or >30 (obese); **Waist circumference** >102cm (M) >88cm (F); **BP** >13/85; Fasting **plasma glucose** >6 mmol/l; **Triglycerides** >1.7 mmol/l. Three or more factors define Metabolic syndrome. Glycosylated hemoglobin **HbgA_{1c}** >8% shows insufficient compensation of diabetes. Modified according to^[11,17].