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METABOLIC ISSUES IN PSYCHOTIC DISORDERS WITH THE FOCUS ON FIRST-EPISODE PATIENTS: A REVIEW

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SUMMARY

Before the onset of the illness, future schizophrenia patients do not weigh more comparing to their peers. However, during the later course of the illness, obesity is twice as prevalent as in general public, afflicting the half of schizophrenia patient population. There is a list of potential factors that contribute to this, including lifestyle, dietary habits, unsatisfactory monitoring of physical health etc, but nowadays side effects of antipsychotic medication become the most prominent concern when weight gain and metabolic issues in psychosis are addressed.

The fact is that second generation antipsychotics (SGA) are associated with weight gain and metabolic syndrome, but that might be the case with the first generation antipsychotics (FGA) too. Besides, obesity might be evident in patients before any exposure to medications, and all that bring lot of dilemmas into the field. This paper critically reviews available data on metabolic problems in patients with psychotic disorders, raging from genetic to molecular and environmental factors, and highlights the necessity of screening for the early signs of metabolic disturbances, as well as of multidisciplinary assessment of psychiatric and medical conditions from the first psychotic episode.

Key words: *antipsychotic agents - first episode – metabolism – obesity – schizophrenia - weight gain*

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Introduction

Schizophrenia, a core disease of the psychotic spectrum, is a devastating mental illness and signify-cant contributor to the global burden of disease. In spite of the previous estimation that the disease has a lifetime prevalence of 1% worldwide, John McGrath's data (McGrath 2006) show that there are seven to eight affected individuals per 1,000, that the disease is more common in developed than in poorer countries, and more common in immigrants than in native-born individuals. Although schizophrenia is not very frequent disease, it is among the most burdensome and costly illnesses worldwide. It usually starts in young adulthood and is characterized by a prodromal phase (Fusar-Poli et al. 2012a, Fusar-Poli et al. 2012b, Fusar-Poli et al. 2013), which is associated with subtle psychotic symptoms, cognitive deficits (Fusar-Poli et al. 2012c), and structural (Fusar-Poli et al. 2011a, Fusar-Poli et al. 2012d), functional (Fusar-Poli et al. 2010), and neurochemical (Fusar-Poli et al. 2011b, Fusar-Poli & Meyer-Lindenberg 2013) brain alterations.

Due to the fact that about 60% of patients receive disability benefits within the first year after the onset of the illness (Ho et al. 1997), preventive interventions are being developed.

It has long been known that schizophrenia is associated with morbidity and mortality rates that far exceed those of the general population (Brown et al. 2000). Patients with schizophrenia have approximately 15 years shorter life, particularly because they tend to commit suicide (Tsuang 1978). The rate of completed suicide, most often seen in the early years of the illness, is 10%. Moreover, an overall mortality rate is about as twice as that of the general population, mostly due to cardiovascular (Brown et al. 2000, Boke et al. 2008), but also gastrointestinal, endocrine, nervous, and respiratory systems diseases. Of further concern is that persons receiving antipsychotic medications are only about 25% likely to receive lipid lowering treatments compared to the general population (Redelmeier et al. 1998). Recent data from Hayes et al. (Hayes et al. 2012), who evaluated association between symptoms and all-cause mortality in patients with serious mental illnesses within the psychotic spectrum, such as schizophrenia, schizoaffective disorder and bipolar disorder, yielded that mortality was not significantly associated with hallucinations and delusions or overactive-aggressive behavior, but with physical illness/disability.

Before the onset of the illness, at the age of 16-17, future schizophrenia patients do not weigh more if compared with their peers; they actually weigh significantly less (BMI and weight are 21.2 kg/m2 and 64.2 kg in comparison to 21.8 kg/m2 and 66.3 kg, p=0.03 and 0.01, respectively) (Weiser et al. 2004). However, during the later course of the illness, obesity is twice as prevalent as in general population, afflicting half of the schizophrenia patients (Allison et al. 1999). There is a list of potential factors that contribute to this, including lifestyle, dietary habits, unsatisfactory

monitoring of physical health etc, but nowadays the side effects of antipsychotic medication become the most prominent concern when weight gain in psychosis is addressed.

Not more than one half of patients treated with SGA are adherent to their medications (Staring et al. 2010). Although many reasons might be listed for such low level of adherence, Pogge et al. (2005), who evaluated rates and predictors of adherence to atypical antipsychotic medication in new patients, yielded that the only side effect that predicts nonadherence was rapid weight gain during the hospitalization. Weight gain as a consequence of antipsychotic use has increasingly been recognized as a serious clinical issue (Maric et al. 2007, Doknic et al. 2011). Here, we will critically review the available evidence indicating metabolic problems in patients with psychotic disorders.

Weight gain (WG), metabolic syndrome and second-generation antipsychotic drugs

The reported prevalence of overweight and obesity in patients with psychotic spectrum disorders has been found to range from 40% to 62% (Green et al. 2000, Carpiniello et al. 2011). Weight gain occurs shortly after the treatment starts, and it is linked to decreased energy expenditure, increased caloric intake, and decreased physical activity (Baptista et al. 2004), although it is not yet known how it is induced by antipsychotics.

According to METEOR study (Falissard et al. 2011), in 2,270 adults with schizophrenia, the prevalence of glycemic disorders was 31.1% (FGA) and 27.6% (SGA). No difference in prevalence was observed for disorders of glucose homeostasis, dyslipidemia or metabolic syndrome, while the hypertension was more prevalent in FGA group. The proportion of women (but not men) who were overweight or obese was higher in the SGA group. Additionally, patients treated with SGA had significantly higher frequencies of impaired fasting glycaemia, low HDL cholesterol and metabolic syndrome (36.7% vs. 30.7%).

The facts that SGA are associated with weight gain and metabolic syndrome (increased waist circumference combined with hypertension/raised fasting glucose/ raised triglycerides/low HDL), that FGA might be associated too, as well as that obesity might be evident in patients before any exposure to medications bring lot of dilemmas into the field. Namely, metabolic disturbances, impaired glucose tolerance and insulin resistance, accompanied with weight gain, were documented in pre-neuroleptic era. Considering epidemiological data from the mental health supplement of the 1989 National Health Interview Survey (NHIS), body mass index (BMI) of individuals with schizophrenia was generally similar to or higher than in general population and, thus, a substantial proportion were obese even before the widespread use of novel antipsychotic drugs (Allison et al. 1999) (for a detailed review of metabolic syndrome in persons with schizophrenia, see De Hert et al. 2009).

Focus on first-episode patients

Weight gain, metabolic abnormalities, even changes in peak bone mass (Maric et al. 2005) might also complicate the course of the first psychotic episode. Recent survey by Curtis et al. (2011) on 85 patients of 16-27 years of age showed that over one third of them treated for the first episode psychosis (FEP) had metabolic syndrome, or showed metabolic abnormalities. Additionally, 42% of females from this Australian sample were overweight or obese at median treatment duration of 8 months. In the earlier study, De Hert and colleagues (De Hert et al. 2007) included larger sample of 230 drug naive FEP patients, of 22 years of age in average, who were followed 3 years after initiation of SGA therapy. Incidence of metabolic syndrome in this sample was 30 percent, i.e. 2.5 times more than in the patients treated with FGA (13% had metabolic syndrome on the basis of historical comparison). SGA associated weight gain in antipsychotic naive adult patients occurs rapidly, within the first few weeks, and continues during the following months, as it was shown by meta-analysis of Tarricone et al. (2010). The most alarming recent data on metabolic issues and SGA came from child and adolescence cohort examined by Correll et al. (2009). In the sample of drug-naive young patients treated by SGA, significant weight gain (4-9 kg) and metabolic abnormalities were registered within first 12 weeks of the treatment. Since SGA are commonly and increasingly prescribed (Maric et al. 2011) to children and adolescents as a first-line treatment for psychotic and non-psychotic mental disorders, the recommendation is to consider lower-risk alternatives before prescribing atypical antipsychotic medications in youth.

Neurobiology of weight gain in schizophrenia

Sparse literature from the previous century noted association of “increased sugar and schizophrenia” (for a review, see Kohen 2004) with a substantial methodological simplifications. Molecular genetics data nowadays provide evidence that genes that regulate glucose metabolism may also influence susceptibility to schizophrenia. The data from European-US sample (that evaluated genes on several chromosomes PFKFB2 (1q32.2), hexokinase 3 (HK3; 5q35.3), and pyruvate kinase 3 (PK3) chromosome 15q23 (Stone et al. 2004)) and from three independent case-control samples of Scandinavian origin (several gene variants in the glycolysis associated with risk of schizophrenia: mitogen-activated protein kinase 14 gene (MAPK14), phosphoenolpyruvate carboxykinase 1 (PCK1), fructose-1,6-biphosphatase (FBP1) and several haplotypes within enolase 2 gene (ENO2) (Olsen et al. 2008)), support the view that relationship between glucose dysregulation and schizophrenia might be inherent to the disorder, not merely epiphenomena related to medication or other treatment factors.

Finally, several post-mortem studies have identified down-regulation of numerous genes involved in energy metabolism in schizophrenia (Altar et al. 2005, Middleton et al. 2002).

Beside genetic factors, environmental factors play an important role. Accumulating evidence supports the model that peripheral metabolic hormones (leptin from the adipose tissue, pancreatic insulin, gut ghrelin) and central signals (serotonin, histamine) converge in the hypothalamus and profoundly modulate activity of the orexigenic and anorexigenic neurons in the hypothalamic arcuate nucleus.

Attempts to link sites regulating body weight homeostasis and those involved in psychiatric disorders promote a new line of psychiatric research.

The hypothalamus plays an essential role in coordinating neuroendocrine, autonomic and behavioral responses necessary for survival of the individual and of the species. An enormous progress has been made in understanding the role of hypothalamus in the control of energy homeostasis and particularly the link between feeding and emotion. Two peripherally produced hormones, ghrelin - a peripheral orexigen and leptin - a peripheral anorexigen, which exert opposite effects on specific hypothalamic neuronal populations, play key role in regulating energy intake and output. Ghrelin, a hormone secreted by stomach (Kojima et al. 1999) activates neuropeptide Y neurons in the hypothalamus and increases appetite in rodents and humans following its administration (Wren et al. 2001, Cowley 2003). Leptin, the anorexigenic signal from the adipocytes, acts through its receptors by activating hypothalamic melanocortin neurons which generate the anorexigenic hormone alpha-melanocyte-stimulating hormone (Cowley 2003, Coll et al. 2005). Accumulating evidence supports the model that stimulation of leptin- and ghrelin-responsive hypothalamic neuronal pathways, including the central melanocortin system, contributes to the maintenance of energy balance and body weight. Melanocortin neurons integrate signals of energy state and have critical role in the control of eating behavior and fat mass (Cowley 2003, Coll et al. 2005). Monoamines are of particular interest in energy homeostasis because it has been shown they interact with melanocortin system, another hunger/satiety regulatory systems in the hypothalamus and other parts of the CNS. For example, 5-HT-driven disregulation of melanocortin system appears to be significantly involved in SGA induced obesity and diabetes. In hypothalamus, there is an overlap between leptin and serotonergic signaling pathway (Nonogaki et al. 1998), but also an association between leptin and melanocortin signaling (Kishi & Elmquist 2005), resulting in altered energy intake and expenditure. Downstream variants of the melanocortin-4 receptor (MC4R) gene have been associated with obesity in various populations (Chowdhury et al. 2013).

Melanocortin system seems to have the critical role in the control of energy balance since its activation is anorexigenic. Serotonin affects energy homeostasis by stimulating melanocortin neurons through 5-HT2C receptors (Kishi & Elmquist 2005). Antagonism at this serotonin receptor increases appetite which might explain the propensity of clozapine and olanzapine to induce weight gain. Also, food consuming is a highly rewarding and positively reinforcing process. Satiety is associated with decreased function of reward system secondary to insulin and leptin actions in the mesolimbic system. In schizophrenia, changes during reward anticipation are present from the beginning of the disease, in antipsychotic naive patients (Nielsen et al. 2012). Additionally, SGA with antidopaminergic properties may affect the reward aspects at the cost of increased appetite and insulin resistance (Filakovic et al. 2007). Second generation antipsychotics also target the deregulated hypothalamic-pituitary-adrenal (HPA) axis. The intrinsic “stress” in schizophrenia patients leads to deregulated function of the HPA axis in sense that they turn on the alarm system and overdrive HPA axis. HPA axis has a great role in allocating glucose to the brain and according to this theory less active HPA axis will inadequately supply the brain with energy sources so at the hypothalamic level compensatory increase in food intake will occur (Peters et al. 2007).

Positive changes in energy balance in healthy subjects lead to increased circulating leptin and insulin levels, while plasma ghrelin levels decrease. Leptin may be associated with some SGA-induced weight gain in patients with schizophrenia (Doknic et al. 2011, Atmaca et al. 2003).

The mechanisms of SGA induced weight gain and metabolic syndrome

There is quite lot of evidence for the association between weight gain, SGA and psychosis, yet clear mechanism of this association is still unknown.

There are some suggestions which need further investigation:

1. SGA can contribute to decreased energy expenditure and subsequent weight gain via diminished physical activity owing to their pronounced sedative effects;
2. SGA may enhance the opioidergic activity which could further deteriorate the pre-existing hedonic alterations in schizophrenia patients;
3. SGA might alter the function of lateral hypothalamic area, the critical anatomical site for weigh regulation, trough its serotonin and/or histamine-mediated actions;
4. Dopamine agonists may reduce weight gain (amantadine counteract olanzapine weight gain), while dopamine antagonists may induce it;
5. SGAs can act not only via transmitters but also they can alter glucose uptake by blocking glucose

accumulation directly at the level of the glucose transporter (GLUT) protein in cells derived from both peripheral and brain tissue: in neuronal PC-12 cells. Clozapine, quetiapine, risperidone, and their various metabolites differentially affect glucose uptake (Ardizzone et al. 2001);

6. Animal experiments showed that SGAs were able to induce insulin resistance directly (with respect to stimulation of glucose transport) and, at the same time, promote triglyceride accumulation by stimulating lipogenesis and inhibiting lipolysis (Vestri et al. 2007).

There has been some success with behavioral interventions, dietary and exercise counseling, but also with use of adjunctive medications such as: amantadine, H2-antagonists, metformin, orilistat and topiramate. However, there are no agents for management of WG approved by FDA and the widespread use of pharmacological interventions cannot be recommended.

Conclusions

Ten to fifteen years ago metabolic issues in psychotic disorders were not a part of research and clinical interest of psychiatrists. During the last decade we all became aware of the fact that patients with serious mental illness are at higher risk of developing metabolic abnormalities (e.g., weight gain, increased blood pressure, glucose or lipid levels) in comparison to general population (Coulson et al, 2012, Kozumplik et al. 2010, Jakovljevic et al. 2007), that the risk increases following initiation of SGA therapy, and that we have to assess carefully risks and benefits when choosing a particular antipsychotic drug (Protopopova et al. 2012, Jukic et al. 2003, Uzun et al. 2010). Excessive WG and metabolic syndrome has to be prevented or attenuated by proper drug selection, combining or switching antipsychotic agents, nutritional assistance and physical exercise, because psychiatrists need antipsychotics and patients benefit from them. In addition, novel strategies are needed to treat the side effects in clinical population of psychotic patients, particularly prone to poor compliance and under a high risk of additional metabolic disturbances, cardiovascular complications and unfavorable, debilitating course of the illness. Therefore, new drugs without side effects addressed in this review should be in the pipeline. Ensuring routine monitoring of weight and metabolic indices and promoting physical health in young mental health services are strongly recommended.

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