

The metabolic syndrome and schizophrenia: A comorbidity or an association?

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Individuals with schizophrenia have 2-3 times higher rates of mortality than the general population. Causes of excessive mortality are increased suicide rates and mortality of natural causes such as cardiovascular events.^[1] During the last two decades, there has been an increase in the schizophrenia literature discussing the high prevalence of type II diabetes mellitus and pre-diabetic states such as the metabolic syndrome with a consistent pattern of increased metabolic syndrome prevalence in patients suffering from chronic schizophrenia.^[2] Patients suffering from schizophrenia seem to be more prone to have an abdominal obesity, an excess of circulating cortisol as a consequence of their central obesity, and an increased risk of developing insulin resistance. In addition, their reaction to continuous stress hyper-activates their hypothalamo-pituitary-adrenal axis. Moreover, some genetic features might be commonly shared by both schizophrenia and metabolic syndrome. Nevertheless, the lifestyle of patients with schizophrenia is accompanied with risk factors that may increase the risk of development of a metabolic syndrome or aggravate its evolution. Those lifestyle components are excessive sedentarism, excessive smoking, low socio-economic status, low adherence to medical care, etc.^[3]

According to a large number of studies, patients suffering from schizophrenia for which they receive antipsychotic drugs are at an increased risk of developing a metabolic syndrome

than the general population as well as than other drug-naïve schizophrenia patients. The overall prevalence of metabolic syndrome in those patients is 32.5%.^[4] The exact mechanism of metabolic syndrome's risk augmentation, because of antipsychotic drugs intake, is still not well elucidated despite some hypotheses regarding their central and peripheral antagonism of some receptors such as the histaminergic, serotonergic, and muscarinic ones.^[5] The risk of metabolic syndrome induction in patients with schizophrenia seems to be increased by every class of antipsychotic drugs administered, with atypical drugs being more risky than typical antipsychotic drugs. Among atypical antipsychotic drugs, clozapine and olanzapine seem to impose the highest risk of metabolic syndrome induction. The combination of several antipsychotic drugs or any other form of psychopharmacologic drugs combination seems to impose a higher risk as well. Despite expected controversies, some patient-related risk factors for the development of metabolic syndrome in patients with schizophrenia receiving atypical antipsychotic drugs are found in the literature. These, non-exhaustively, include: Age (whether higher or lower), body mass index, family history of obesity, cannabis abuse, gender (whether male or female), ethnicity and socio-cultural lifestyle aspects, etc.^[6,7]

The severity of schizophrenia symptoms especially when it concerns negative and cognitive symptoms might hypothetically be related to an increase in metabolic syndrome's risk under antipsychotic drugs, since the persistence of these symptoms alters patients' adherence to any medical recommendations while also aggravating the patient's metabolic syndrome-predisposing lifestyle. The clinical severity of schizophrenia as a risk factor of metabolic syndrome in patients receiving antipsychotic drugs has not been sufficiently investigated in the medical literature. In this regard, the benefit residing behind the administration of any

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type of antipsychotic drugs seems to remain superior to the cardio-metabolic risk imposed by these drugs not only because of the risk reduction of other schizophrenia-related causes of mortality such as completed suicide, but also, speculatively because of improvement in the clinical severity of the mental disorder.^[8]

To date, the nature of the relationship between schizophrenia and the metabolic syndrome consists of an association between both diseases although many arguments are in favor of comorbidity. In order to clearly determine whether the metabolic syndrome is a comorbidity of schizophrenia, in other words, whether patients with schizophrenia are predisposed after years of development of their mental disorder (since theoretically schizophrenia has the lower age of onset) to develop a metabolic syndrome despite being treated or not with antipsychotic drugs, prospective studies considering patients with schizophrenia not treated with any antipsychotic drug, need to be designed. Intuitively, this kind of study design is challenged by some serious ethical considerations.

In this issue of the “Journal of Pharmacology and Pharmacotherapeutics”, Chadda *et al.*^[9] present a comprehensive review of the literature concerning studies related to the domain of metabolic syndrome or any of its components, in drug-naïve and antipsychotic drug-treated patients suffering from schizophrenia. The most important finding of this review resides in the fact that it clearly demonstrates how the metabolic syndrome prevalence increases between drug-naïve patients and antipsychotic treated patients [see metabolic syndrome prevalence in Table 1 in the review of Chadda *et al.* and compare it with post-treatment prevalence available in the same table and in Table 2 of the same review]. This finding

highlights the fact that any patient suffering from schizophrenia and receiving an antipsychotic drug should be considered as a patient who is at risk for the development of a cardiovascular disease or a type II diabetes mellitus unless proven otherwise, that is, until his metabolic profile has been determined and found to be reassuring.

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