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The Role of Antipsychotic Medications in Metabolic Syndrome Amongst a Predisposed Population: Review of The Saudi Case

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Abstract

Kingdom of Saudi Arabia (KSA) is the largest (in terms of area) Arab state of Western Asia with population of a nearly 20 million. 22.4% of Saudi patients reporting to services for mental disorders are suffering from schizophrenia. Globally, claims have been raised over the role of atypical antipsychotics. They have been suggested to be related with noteworthy cardiometabolic risk, and with pharmacological events that may intercede that threat. Weight gain, increased risk for dyslipidemia, diabetes, obesity, accelerated cardiovascular ailment, and premature fatality have been associated to drugs in this category as well. Amisulpride, olanzapine, risperidone, clozapine, quetiapine are the most commonly used anti-schizophrenic medications in KSA with no previous studies reported to assess their unwanted side effects. Whereby, a recent study noticed that patients on antipsychotic medications in Saudi Arabia possess several risk factors. The need for detailed research on this matter is compounded by a metabolically undesirable postnatal and gestational environment, which is widespread in the KSA, adjoins to the receptiveness of the already genetically liable person to a lifetime of insulin resistance and associated morbidities. Moreover, the prevalence of conventional risk factors for diabetes mellitus type 2, such as the full metabolic syndrome (MetSy) and its individual symptoms and criteria, have been reported in adult Saudis, 37% of whom have the full MetSy. The published literature survey is suggestive of an urgent demographical analysis and epidemiological survey to ascertain number of individuals affected with schizophrenia, this will also paw the ways to formulate strategy to address various issues pertaining to structural adjustments in health care services provided to the mentally ill patients in KSA.

Keywords: Schizophrenia; Saudi Arabia; Antischizophreic medications; Metabolic syndrome incidence; Biological and clinical associates

Introduction

Schizophrenia is a mental disease that influences about 1% of global population. Schizophrenic patients have shorter life span as balanced to their healthy associates [1,2]. The most and regularly stated cause of increased death among patients with schizophrenia is cardiovascular ailments and metabolic syndrome (MetSy) [3,4]. Full MetSy and its characteristic and diagnostic criteria, are still upsetting adult Saudis, 37% of whom have the full MetSy, while prevalence of partial MetSy was also reported. Reports have shown that dyslipidemia accounted for almost 90% of the patient population with partial and full MetSy. The characteristic and diagnostic criteria of MetSy are based on the guidelines ATP III, WHO and American Association of Clinical Endocrinologists [5-7]. MetSy in the common population has certainly offered proof for the progress of race-/ethnic-specific principles [8]. Prevalence of MetSy in schizophrenic patients in dissimilar ethnic entities is required due the differences in financial status, life style and genetic factors [9-11]. At present, it has stayed indistinct to what point these diversities in the common population are due to genetic factors or cultural causes such as life style or economic burdens [12,13]. Even prior to antipsychotic became accessible in the 1950s, irregular reactions to insulin and diabetes-like glucose tolerance curves were monitored in psychiatric patients [14-16]. A previous study demonstrated weight gain already in the middle of twentieth century in patients cured with chlorpromazine [17].

Generally, antipsychotic medications induce weight gain and dysruling of further metabolic indictors prompted people with mental sickness to an augmented risk of cardiovascular morbidity and mortality. Curing with atypical antipsychotics imposes novel rules for health educationalists and practitioners in terms of risk analysis and the assortment of pharmacotherapy. Therefore, switching to different atypical antipsychotic in schizophrenic patients who tend to get more than 5% of his initial bodyweight or if dyslipidemia or blood glucose changes [18-21]. It has been reported that drug definite variations were also noticed and various lipids be predisposed to be amplified with both olanzapine and risperidone and levels of triacylglycerols augmented and the free form of fatty acids reduced with these two drugs but not with aripiprazole. Phosphatidylethanolamine (PE) concentrations that were inhibited in schizophrenic patients were lifted by all three drugs [22,23].

The current review paper discusses a new area in Saudi mental health research. Previous and few studies were only emphasized on the incidence of mental illnesses without effort to study the national characteristics of schizophrenia. However, a few studies have shown that amongst all the psychotropic medications, antipsychotics were profoundly consumed and the regularity was observed to be considerably elevated in the case of inpatients compared with out-patients [24, 25]. Such a way could cause several unwanted side-effects amongst the Saudi patients in the concept of applied research. Side effects of antipsychotic medications in Saudi Arabia have reported and

also were associated with numerous risk factors, such as overweight, dyslipidemia, obesity and smoking [26]. However, no specific research was conducted on the prevalence of MetSy on schizophrenic patients undergoing antipsychotic medications.

Arabs in the Middle East have shown considerable prevalence of the MetSy in the general population [5] but not the schizophrenic population. To further enhance the literature of the studies regarding MetSy among Arab schizophrenic patients, this review was done. It summarizes the research studies carried out in Saudi Arabia retrieved from PubMed and some local and international journals on MetSy, schizophrenia, predisposing factors, anti-psychotic drugs and biological associates of MetSy and SCZ.

Schizophrenia

Schizophrenia is a chronic and severe mental illness that influences how a person thinks, feels, and behaves [27]. Schizophrenia is classified as a primary psychotic disorder [28,29]. Clinical signs of schizophrenia frequently begin between the ages of 16 and 30. In unusual conditions, children have schizophrenia as well [30,31]. The clinical signs of schizophrenia fall into three groups: cognitive, negative and positive [32]. Positive signs of schizophrenia are psychotic behaviors which are not usually seen in healthy people ("lose touch" with some characteristic of realism). Positive symptoms include thought disorders, hallucinations, movement disorders and delusions. The negative symptoms are linked with interferences with ordinary sensations and behaviors and involve reduced affect display, anhedonia, difficulty beginning and sustaining activities, and glossophobia. Schizophrenia is diagnosed based on criteria in either the American Psychiatric Association's fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), or the WHO's International Statistical Classification of Diseases and Related Health Problems (ICD-10). These standards utilize the self-reported practices of the patients and reported defects in behavior, followed by a clinical evaluation by a psychiatrist [33,34]. Numerous aspects are associated with the risk of getting schizophrenia such as environmental, genetic substance abuse and developmental factors. The interactions between genetic and environmental factors contribute over 80% of the accountability for schizophrenia. Genetic studies have shown that some chromosomal regions and identified genes have been "associated" to the hazard for developing schizophrenia [35-40]. Regardless of serious investigations and magnificent progress in molecular biology, however, no particular gene discrepancy has been constantly linked with a superior probability of developing the sickness and the exact nature of the genetic involvement is still ambiguous up to date [40]. Environmental aspects associated to an elevated probability of getting schizophrenia include cannabis abuse, gestational infection or malnutrition and prenatal complications. The etiological relevance of these factors remains unclear. On the hand, the interaction of genetic and environmental factors interact to cause schizophrenia needs further neurobiological mechanistic studies to explain the etio-pathogenesis of schizophrenia. Heterogeneous etiologies, multifaceted pattern of genetic aspects and gene-environment interaction, and insufficiently clarified schizophrenia pathogenesis are amongst the clarifications raised to clarify our insufficient understanding of the etio-pathogenesis of this ailment [41-43].

This ailment has an international prevalence around 0.3-0.7% in 2011. Females has are less susceptible to schizophrenia compared to males with and characteristically materializes earlier in men at age of 25 years while in female at age of 27 years. Schizophrenia in childhood is greatly scarce, as is commencement in middle or old age. The World Health Organization recently reported that the percentage of people influenced and the number of new cases that appear each year is approximately comparable around the world, with age-standardized incidence per 100,000 ranging from 343 in Africa to 544 in Japan and Oceania for men, and from 378 in Africa to 527 in Southeastern Europe for women. About 1.1% of adults have schizophrenia in the United States [44-46].

Schizophrenia in Saudi Arabia

Saudi Arabia is the biggest (in terms of area) Arabic country in west Asia with population of an approximately twenty million [47]. Saudi Arabia follows a governmentally controlled multi-levels health system with a network of more than 2000 primary healthcare center spread across the country [48-50]. Psychiatric health services are provided in different major regions of KSA in specialized firms called "Alamal" hospitals. Statistical reporting and demographic information technology-based infrastructure are highly required to determine number of individual affected with mental ailments. Research on schizophrenia will be facilitated with such enhancement and more insights will be withdrawn from such data pools and decision makers will be able to formulate their policies and procedures. The highest rate of hospital entrance was due to drugs (83.5%), followed by schizophrenia (6.9%) and bipolar affective disorders (4.8%) [51]. It is important to note that information SCZ in Saudi Arabia is unpredictably limited, with few published papers concerning schizophrenia–related characteristics. Interestingly no epidemiological data is available for the prevalence of schizophrenia in Saudi Arabia the Saudi ministry of health reported that 22.4% patients reporting to outpatient services for mental disorders are suffering from schizophrenia related disorders (it does not specify schizophrenia) ministry of health 2008. However WHO in 2004 has estimates of Disability-adjusted life year (DALY) rate, due to schizophrenia, in KSA is 270 which are quite high [52].

Research on Schizophrenia is considered low, but there is only one study was carried out in 2015 [51] which was only for schizophrenia but was all psychological ailments. Authors depicted the statistical pattern of schizophrenia. Their results showed that schizophrenia was more widespread within young adults (21-40 years) (74.7%) and male population (76.6%). Schizophrenia was rare in childhood and late elderly. Majority of the patients are from the Saudi capital (Riyadh), jobless, single and primary level of education [51].

Metabolic Syndrome (MetSy)

Three definitions of MetSy have been recognized. Despite the standard measures of MetSy, four major factors are involved lipid profile (elevated triglycerides (TG), low high-density lipoprotein and cholesterol (HDL-C) concentration), central obesity (waist circumference), blood pressure and plasma glucose as shown in (Figures 1 and 2). The diagnosis of MetSy in clinical settings does not only depend on the existence abdominal obesity. But it must showed three of the five criteria previously mentioned [53-55]. At least 3 organizations (ATP III, WHO and American Association of Clinical Endocrinologists) have suggested clinical standards for the diagnosis of MetSy. The criteria used are similar in many respects, but there are considerable distinctions. Despite of the diagnostic standards utilized, there was conformity that weight decrease and increased exercise are the lead therapy for MetSy. MetSy has numerous causing factors that operate jointly and these include overweight, obesity, an inactive

lifestyle, age, and insulin resistance. In this review we are trying to explain the role of antischizophreic medications on MetSy [56,57].

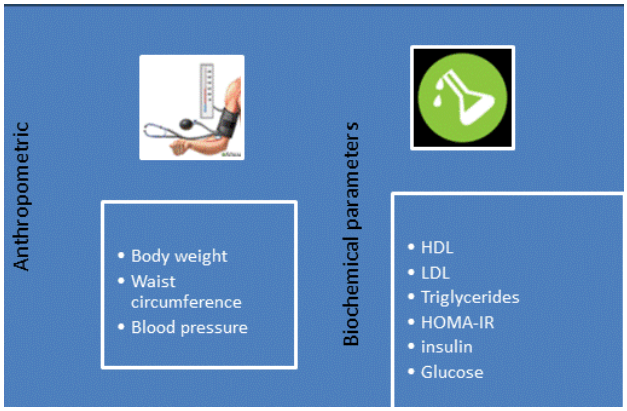

Figure 1: ATP-III (Adult Treatment Panel) defined criteria for MetSy. HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.

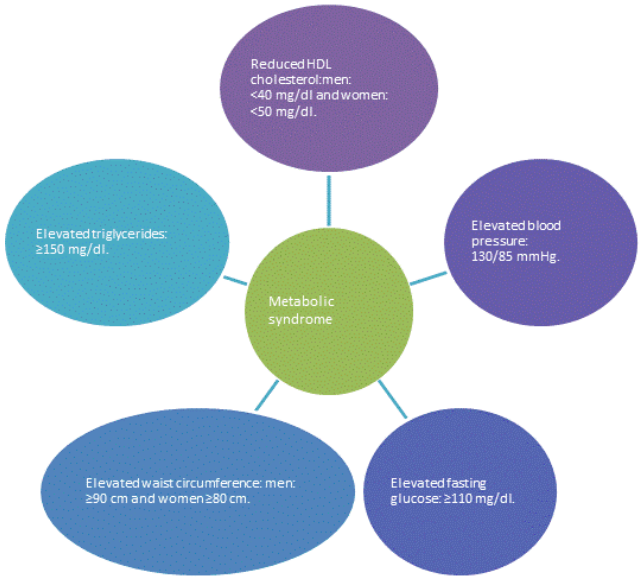

Figure 2: ATP-III defined criteria for MetSy, according to which MetSy sufferers were recognized by, as having three or more of the above.

Anti-Schizophrenic Medication

Managing SCZ regularly concerned numerous techniques including psychological, pharmacological, social, educational, and employment-related interventions heading for treatment. Even though hospitalization is frequently favored in many foremost psychiatric ailments, such as schizophrenia, curing outpatients is also used to preserve social integrity and a patient's independence, thus ensuing in satisfactory medical results while still decreasing overall expenses. Curing schizophrenia altered noticeably in the mid of twentieth century with the growth and introduction of the first antipsychotic chlorpromazine [58,59]. Others such as haloperidol and trifluoperazine quickly go behind [60]. Atypical antipsychotics are linked with important cardiometabolic risk, and with pharmacological effects that may moderate that hazard. Weight gain, increased risk for dyslipidemia, obesity, diabetes mellitus, accelerated cardiovascular illness, and premature fatality have been associated to drugs in this category as well (Table 1) [61-63].

Role of Anti-schizophrenic on Metabolism

The mechanism underlying augmented occurrence of MetSy amongst patients with schizophrenia is not sound explored. A numeral of enlightenments such as standard of living and nutritional behaviors that ease the increase of obesity amongst schizophrenic patients, direct antipsychotic drug role on carbohydrate and lipid metabolic pathway [64-66]. The tendency to accumulate intra-abdominal adiposity and fat, definite changes of the hypothalamic pituitary-adrenal axis (HPA) produce hypercortisolemia, uncontrollable blood glucose, and its genotypic expression in the form of truncal obesity, and probable linked changes in hippocampal volume have been suggested [67-70]. However, the main explanation for the occurrence of MetSy is the connection between various anti-psychotic drugs utilized in the cure of schizophrenia [71]. Many studies investigated the metabolic possessions of atypical and typical antipsychotics in drug naive individuals with schizophrenia that were not under any considerable sickness before the initiation of the medication. The results of these studies proved the antipsychotic efficiency of these medicines with notable side effects such as weight gain and pathological alterations of glucose metabolism that may cause diabetes [70,72].

It was claimed that schizophrenia itself is connected with changes in neurotransmitter systems and alterations in neuronal membrane phospholipids. But this claim was not exposed to a full assessment and mapping of universal lipid transformations in schizophrenia alone, and upon the use with antipsychotics [22,73]. This kind of mapping could offer new discoveries about disease pathogenesis and metabolic negative effects of medications utilized for its cure. Kaddurah-Daouk has reported that nearly fifty lipids have the tendency to be elevated with both olanzapine and risperidone and levels of triacylglycerols augmented and free fatty acids reduced with both drugs but not with aripiprazole [22].

It has been observed that food-craving enhancing properties, hereditary aspects, inactive daily life and metabolic deregulation are the main factors in initiating weight gain after antipsychotic use. The pathogenesis of weight gain is interceded by cholinergic, monoaminergic and histaminergic neurotransmission [74]. Accordingly superior weight gain noticed in regards to clozapine and olanzapine is explained by changeable affinity for H1 and serotonin 5-HT2C receptors. It has been observed that the metabolic alterations linked with the utilization of atypical antipsychotics are a direct result of change of insulin sensitivity [75]. Altered parasympathetic system of B-cell activity moderated by blockade of histaminergic and muscarinic system may cause an increased metabolic risk. Development of type 2 diabetes mellitus is a direct result of the antipsychotic mediated malfunction of glucose transporter function via changes in the insulin signaling pathway resulting in augmented circulating glucose levels, reduced insulin sensitivity, and compensatory insulin hyper secretion [76,77].

Side effects of antipsychotics on inducing MetSy differ based on the drug class. Patients on typical antipsychotics are liable to have a

superior incidence of extrapyramidal side-effects while some atypicals are linked with substantial weight gain, diabetes and risk of MetSy; this is most obvious with olanzapine, whereas risperidone and quetiapine are also connected with weight gain. Risperidone has a comparable rate of extrapyramidal symptoms to haloperidol [18,78-80].

Glucuronidation and phase I oxidation are the main metabolic pathways for olanzapine. Experimental research showed that cytochromes (CYPs 1A2 and 2D6) and the flavin-containing monooxygenase system are responsible for the oxidation of olanzapine. Research has mentioned that olanzapine holds a superior threat of causing and aggravate diabetes than another frequently used atypical antipsychotic, Risperidone of all the atypical antipsychotics, olanzapine is one of the mainly probable to persuade weight gain based on different measures. Dose dependent metabolic side effects of olanzapine have been proved in experimental and clinical research. This atypical antipsychotic may reduce insulin sensitivity and increase triglyceride levels [78,81,82].

Antipsychotics	Class	Mode of action	Used for
Amisulpride	Atypical antipsychotic	Combination of D2 and D3 dopamine receptor antagonism. Amisulpride displays low affinity for serotonergic, α-adrenergic, histaminergic receptor subtypes, and muscarinic receptors and sigma sites. Amisulpride is also an antagonist at 5HT7 receptors.	schizophrenia with: – positive and negative symptoms
clozapine	Atypical antipsychotic	Combination of 5HT1, 5HT2, 5HT3, 5HT6, 5HT7 serotonin, D4 dopamine, M1 muscarinic, H1 histamine, and α1-adrenergic receptor antagonism. It also has weak D2 blocking properties. Treatment-resistant" or "Refractory" schizophrenia	The treatment of schizophrenia in Patients who have severe, untreatable, neurological adverse reactions to other antipsychotic agents
olanzapine	Atypical antipsychotic	Combination of 5HT2A, 5HT2C, 5HT6 serotonin, H1, H2 histamine, D1, D2, D3, D4, D5 dopamine, M5 muscarinic, α1, and α2-adrenergic receptor antagonism. It also has moderate M1, M2, and M3 blocking properties	Schizophrenia in adults
Paliperidone	Atypical antipsychotic	Combination of serotonin 5HT2A, 5HT7, dopamine D2, and α1-adrenergic receptor antagonism. IT also blocks, to a lesser extent, histamine H1 and α2- adrenergic receptors.	- Schizophrenia in adults. - Psychotic or manic symptoms of schizoaffective disorder in adults
Quetiapine	Atypical antipsychotic	The therapeutic activity of quetiapine is mediated through a combination of 5HT1A and 5HT2 serotonin, H1 histamine, D1 and D2 dopamine, α1 and α2-adrenergic receptor antagonism. Norquetiapine also has high affinity for the NET, norepinephrine transporter, and M1 muscarinic receptors.	The treatment of schizophrenia in adults, including preventing relapse in stable schizophrenic patients who have been maintained on quetiapine.
Risperidone	Atypical antipsychotic	The therapeutic activity of risperidone is mediated through a combination of 5HT2, 5HT1C, 5HT1D, and 5HT1A serotonin, D2 dopamine, and α1-adrenergic receptor antagonism. Risperidone also blocks, to a lesser extent, histamine H1 and α2-adrenergic receptors.	The treatment of schizophrenia in adults.
Haloperidol	Atypical antipsychotic	Binds preferentially to D2 and α1 receptors at low dose and 5-HT2 receptors at a higher dose.	treating schizophrenia, acute psychosis, and for tics and vocal utterances of Tourette's syndrome
Ziprasidone	Atypical antipsychotic	The therapeutic activity of ziprasidone is mediated through a combination of 5HT2A, 5HT2C, 5HT7, and 5HT1D, serotonin, H1 histamine, D2 and D3 dopamine, α1 and α2-adrenergic receptor antagonism. Ziprasidone acts as an agonist at the 5HT1A receptor, and is a moderate NE, norepinehphrine and serotonin reuptake inhibitor.	The treatment of schizophrenia and agitation associated with schizophrenia in adults.
Aripiprazole	Atypical antipsychotic	The therapeutic activity of aripiprazole is mediated through a combination of 5HT2A, 5HT2C, and 5HT7 serotonin, D3 and D4 dopamine, H1 histamine, and α1-adrenergic receptor antagonism. Aripiprazole also acts as a partial agonist for D2 dopamine, and 5HT1A serotonin receptor.	schizophrenia in adults and adolescents above 15 years of age

Table 1: Classification, mode action, uses of antischizophrenic medications.

Role of Atypical Antipsychotics in Increasing the Risk Factors Associated with Metabolic Syndrome

Mechanisms of action of atypical antipsychotic medications may be associated to obstruction of dopamine, serotonin, and histamine receptors. Typical antipsychotics robustly antagonize dopamine receptors. This interaction with various biochemical pathways leads an amplified hazard of diabetes and MetSy [22,83-86]. The use of diverse antipsychotics is linked with different impacts on body weight experienced with amisulpride, ripiprazole, ziprasidone, aolanzapine and clozapine. However, it is obvious that weight increase is not an unconditional requirement for the development of insulin resistance, dyslipidemia, imbalanced glucose tolerance, or T2DM. Considerable substantiation indicates that elevations in adiposity are linked with reduction in insulin sensitivity in psychiatric and non-psychiatric patients. The role of increasing adiposity, as well as other impacts, may cause elevations in plasma lipids and glucose noticed during the cure with some antipsychotics. A strong hypothesis was assumed on the effects of the pharmacologic factors that contribute to these adverse effects in susceptible population. The adverse effects antipsychotics are probable linked to the increased rates of cardiovascular mortality and morbidity observed in schizophrenia patients [31,32,62,87].

Biological Associates of Metabolic Syndrome in Schizophrenia

Some researchers have tried to recognize biological indicators for MetSy in schizophrenia and have demonstrated that low levels of adiponectin, lower uric acid, and high white blood cell count, high alanine transferase, low levels of leptin, hyperhomocyseniemia, high C-reactive protein, and high monocytes to be associated with MetS in schizophrenia. Some papers have tried to depict the genetic root of elevated incidence of MetSy in schizophrenia. Methylenetetrahydrofolate reductase (MTHFR) gene has been the most frequently investigated and a little research has shown that MTHFR 677T allele and MTHFR 677C/T as compared to 677C/C allele is more likely to be correlated with MetS. Arg347 allele in Alpha-1A adrenergic receptor (ADRA1A) has been depicted to be correlated with a high incidence and alpha-2A adrenergic receptor (ADRA2A) 1291-G allele with lower incidence of MetSy. Likewise, COMT158Val allele was demonstrated to be linked with MetSy incidence in one of the studies.

Research on the Prevention of Metabolic Syndrome

The amplified mortality and of morbidity caused by schizophrenia are demanding factors for further research on the prevention of this ailment's consequences. Suicide and other natural causes of death are attributed to morbidity of schizophrenia. Whereby, recent research has focused on cardiovascular risk factors and weight gain. Therefore, recognition, prevention, and adjustment of the cardiovascular risk aspects should be one of the significant therapeutic goals in managing schizophrenia. This very actuality encourages regular screening of schizophrenic patients for the existence of MetSy. It is significant to recognize the high risk patients and teach them concerning the precautionary actions. Efforts should be done to alter unhealthful standard of living like inactivity; smoking, overeating, and use of suitable psycho-educational plans in this regard require to be performed. Even though, the facts with respect to relationship of MetSy and psychotropics in schizophrenia stay questionable, nevertheless, a watchful approach in prescribing psychotropics is advisable. Studies in schizophrenia patients do propose that atypical like clozapine and olanzapine pose a higher risk of metabolic abnormalities hence, due consideration should be given to their probable to cause metabolic disorders while prescribing an agent, and whenever used, the prescription should be revised regularly to uphold a balance between suitable control of symptoms and minimal metabolic abnormalities [88-90].

Conclusion

In conclusion, this review revealed the lack of follow-up epidemiologic and clinical researches in regards to schizophrenia in Saudi Arabia. This will allow concerned bodies to translate research findings to aggressive health policies at the grassroots level and authoritarian accomplishment of drug prescription. Predisposing and risk factors for MetSy of the Saudi population should also be considered in schizophrenic patients.

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