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Atypical Antipsychotics and Metabolic Syndrome

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### **Abstract**

Cardiovascular disease is the leading cause of morbidity and mortality in the U.S. Metabolic syndrome with its associated comorbidities is a major contributor to cardiovascular disease. There is a significant prevalence of schizophrenia in the U.S. and a high prevalence of cardiovascular disease in this patient population. Metabolic syndrome has significant prevalence in patients with schizophrenia who take atypical antipsychotics ((Riordan *et al*, 2011). In order to further analyze the relationship between the various atypical antipsychotics and metabolic syndrome in patients with schizophrenia a literature review was conducted. This review also aimed to find literature offering treatment modalities effective against combating this problem. Cochrane, PubMed and PsycInfo were used to identify the relevant literature from the past ten years. Among the commonly used atypical antipsychotics, clozapine was found to have the most association with metabolic syndrome while ziprasidone had the least. Metformin in conjunction with lifestyle modifications was shown to be the most effective in inducing weight loss, reduce BMI and effectively treat metabolic syndrome. This literature review also highlights the important role played by APRNs and nurses in the context of the Health Promotions Model in order to integrate pre-existing medical knowledge and provide comprehensive care for this patient population.

### Atypical Antipsychotics and Metabolic Syndrome

Schizophrenia is a serious, long-term and debilitating mental health disorder that can affect any demographic group. It is characterized by impairments and deficits in cognition, sensory perception and emotion (NIH, 2016). It affects roughly 1.1% of the U.S. adult population with only 60% of the affected seeking healthcare (Regier *et al*, 1993). Worldwide, the prevalence of schizophrenia is between 0.5-1.0% with men manifesting the disease early compared to women. Suicidality is a major feature of schizophrenia with roughly one-third attempting suicide and 10% of the attempts resulting in completion. In addition, schizophrenia carries with it substantial financial costs for a nation's economy. Health care costs and costs associated with loss of productivity added up to approximately \$6.85 billion in 2004 (CDC, 2013).

The mainstay of medical treatment for schizophrenia is the use of typical and atypical antipsychotics directed at the neurotransmitter dopamine. The goal of treatment is to control symptoms and patients are treated for the rest of their lives even during symptom free periods. Due to the higher risk of side effects such as movement disorders (ex. Tardive dyskinesia) with the first generation (typical) antipsychotics, second generation antipsychotics – also called atypicals – are preferred (Mayo, 2016). In an effort to avoid the side effects of typical antipsychotics, atypical antipsychotics have increasingly been used. However, a major unintended side effect of the atypical antipsychotics has been the increased incidence of cardiovascular disease which is the leading cause of mortality in patients with schizophrenia.

Studies have already established a significant relationship between atypical antipsychotics and metabolic syndrome possibly leading to cardiovascular morbidity and mortality (Riordan *et al*, 2011). Metabolic syndrome is characterized by high fasting

hyperglycemia, hypertension, central obesity, and dyslipidemia. It is anticipated to become the number one risk factor for ischemic heart disease independent of a schizophrenia diagnosis (NIH, 2016). With ischemic heart disease as a leading cause of death in the U.S (1 in 4 deaths) (CDC, 2015) and contributed to by metabolic syndrome, this serves as an opportunity to further analyze the side effect profiles of the various atypical antipsychotics available on the market. This literature review aims to inform our choice of atypical antipsychotics and provide guidelines for monitoring the various aspects of metabolic syndrome in this particular demographic.

### **Purpose**

Given the above-mentioned scope of problem with usage of atypical antipsychotics and their association with metabolic syndrome and its outcome, the usage of these medications needs to be further characterized. This project will focus on examining the various atypical antipsychotics used in the care of patients with schizophrenia. It will also attempt to stratify each commonly used medication – as the literature review allows – based on their side-effect profile relating to metabolic syndrome. This will examine any potential or documented cause-effect relationships between atypical antipsychotics and the various components of the metabolic syndrome.

The first step in the review process will be to identify atypical antipsychotics commonly used in treatment. This will be implemented by reviewing the latest guidelines from major reputable sources in the treatment of schizophrenia. This search will further identify the types of atypical antipsychotics that are used in the treatment of this disease. Next, the nature of metabolic syndrome with its extent of disease burden, morbidity and mortality will be detailed to set the stage for the analysis of the medications and their degree of involvement with metabolic

syndrome. The main aim of this literature review is to inform the psychiatric mental health practitioner of the varying degrees of association between certain atypicals with metabolic syndrome in order to shape his/her choices when treating patients with schizophrenia with the ultimate benefit of preventing morbidity and mortality in this patient group.

### **Significance**

Schizophrenia exists in 1.1% of the US population with more than half of these patients seeking healthcare (Regier *et al*, 1993). Since the use of atypical antipsychotics is very prevalent in this demographic, this implies that a large number of people are at risk or are already affected by metabolic syndrome and its consequences such as ischemic heart disease. With 1 in 4 deaths in the US attributed to ischemic heart disease (CDC, 2015), it is safe to imply that atypical antipsychotics ultimately contribute to this statistic through their relationship with metabolic syndrome.

This relationship between atypical antipsychotic use and mortality from ischemic heart disease has multiple points of intervention which mainly revolve around understanding and choosing the right antipsychotic medications, individualizing therapy based on patients' unique co-morbidities, and implementing appropriate follow-up plans to monitor patients for metabolic syndrome. These areas of intervention can be capitalized on by health care practitioners including psychiatric mental health nurse practitioners to minimize this very undesirable side effect of pharmacotherapy in schizophrenic patients.

Potential areas of intervention include but are not limited to developing health screening methods to stratify each patient based on risk factors for metabolic syndrome; developing a work flow for electronic medical records to identify patients with the risk factors, abnormal vital signs and lab results (ex. high BMI, High blood pressure, Low HDL, high triglyceride, high fasting

blood sugar (NIH, 2016)); providing point of care resources that inform and remind staff of the different efficacies and side-effect profiles of atypical antipsychotics; reserving a special list for a panel of patients on atypical antipsychotics and designating a clinic staff (ex. RN) to follow up and recall patients on atypical antipsychotics for follow up labs; and holding information sessions at local healthcare centers, providing lectures, and presenting at major conferences to promote awareness and provide recommendations. This study seeks to integrate the findings from pre-existing literature regarding the association between atypical antipsychotics and metabolic syndrome and provide recommendations to minimize or prevent this association and ultimately avoid morbidity and mortality in our schizophrenia patient population.

### **Theoretical Framework**

A major social theory that will provide the appropriate conceptual basis of this study is the Health Promotions Model (HPM) by Nola Pender developed in 1982 and later refined. It integrated the expectancy-value theory and social cognitive theory which formed the basis of HPM from a nursing perspective. This model approached health promotion from the perspective that, behaviors that lead to increased health result from certain biopsychosocial factors that influence individuals' motives. The major components of the HPM are behavior-specific cognitions/affect, personal characteristics/experiences, and behavioral outcomes. Psychosocial factors and behaviors form a major barrier to the care of patients with schizophrenia. The theoretical framework suggested by the HPM takes this into account by focusing on these barriers and shifting the focus to the health promotion of populations through understanding our patients, their circumstances and implementing change (McEwen *et al*, 2011). Therefore, in addition to medication adjustments in schizophrenic patients with metabolic syndrome who take

atypical antipsychotics, biopsychosocial processes that play a major role in the patients' care can also be explored and changed to promote a more favorable outcome for this patient population.

This theoretical framework is therefore very useful in identifying areas of intervention in the prevention, screening, treatment and regular follow up of patients with schizophrenia who are at risk of developing or who have developed metabolic syndrome. As it will be explored in the literature review, a major threat to the validity of these studies is anticipated to arise from the loss to follow-up of patients with schizophrenia. The diagnosis of schizophrenia independently affects lifestyle choices leading to metabolic syndrome as well as interfere with the regular screening schedules for and the treatment of metabolic syndrome in schizophrenic patients being treated with atypical antipsychotics.

### **Definitions**

The patient population in the literature review is any patient with the diagnosis of schizophrenia who is currently receiving treatment with atypical antipsychotics. Atypical antipsychotics are any of the second generation antipsychotics that are currently widely used to treat schizophrenia in all age groups. Metabolic syndrome constitutes a group of endocrine and metabolism derangements contributing to cardiovascular mortality. Hypertriglyceridemia is elevation of triglycerides in the blood. Hyperglycemia is elevation of glucose in the blood and is the hallmark of diabetes mellitus.

### **Literature Review**

#### Overview

This literature review aims to present publications pertaining to metabolic syndrome and its associated symptoms in schizophrenic patients treated with atypical antipsychotic medications. Literature describing the nature of metabolic syndrome in the setting of atypical



antipsychotic use, its presentation, its risk factors (genetic and environmental), associated comorbid conditions and overall implications will be discussed. The bulk of this review section will also be dedicated to presenting the various atypical antipsychotics in use and compare their side-effect profile as it pertains to metabolic syndrome. Comparative efficacy of these medications will also be discussed where appropriate. A portion of this review section will also address the efficacy of certain modalities used in treatment and monitoring of metabolic syndrome in patients with schizophrenia who take atypical antipsychotics.

### Metabolic Syndrome and Cardiovascular Mortality

In line with the statistics of the general population without the diagnosis of schizophrenia, cardiovascular disease is also the number one cause of mortality in patients with schizophrenia. 30% of all deaths in the US are attributed to a cardiovascular cause. It has been established that metabolic syndrome as a side-effect of atypical antipsychotic use largely contributes to the cardiovascular mortality of patients with schizophrenia with roughly 1/3<sup>rd</sup> of deaths attributed to a cardiovascular cause. With 2.2 million American adults affected by schizophrenia and with the ubiquitous use of atypical antipsychotics potentially contributing to 20-60% prevalence of metabolic syndrome in these patients, the disease and financial burden on our patients and the healthcare system is significant (Riordan *et al*, 2011). This patient demographic has also been noted to have a 1.5 to 2 times more likelihood of developing obesity, hypertension, hyperlipidemia, and type 2 diabetes mellitus, diseases that constitute metabolic syndrome. This risk is in addition to their risk of developing this syndrome independent of atypical antipsychotic use. Metabolic syndrome is defined by five parameters which include large waist circumference (35 inches or above for women; 40 inches or above for men); high triglyceride level (150 mg/dL

or above); low HDL (less than 40 mg/dL in men and 50 mg/dL in women; blood pressures 130/85 or higher; and high fasting glucose (100 mg/dL or higher) (Mayo, 2016). Per the International Diabetes Federation, patients with central obesity and two of the other factors meet the criteria for metabolic syndrome (Riordan *et al*, 2011). The components of the syndrome are otherwise commonly diagnosed in the general population raising the likelihood of a shared metabolic/endocrine pathway that underlies these disease processes and is affected by atypical antipsychotics. Various mechanisms have been proposed that link these medications to metabolic syndrome including regulation of gene expression, dopamine, histamine, anabolic neuropeptides, neuronal receptors, and failure of glucose regulation (Coccarello *et al*, 2010, Mulder *et al*, 2007, Liou *et al*, 2013). Poor life-style choices such as physical inactivity, smoking, and poor diet associated with the diagnosis of schizophrenia are also major contributors to the development this syndrome (Riordan *et al*, 2011).

#### Genetic Predisposition to Metabolic Syndrome in Atypical Antipsychotic Use

Certain genetic variants have also been identified that may play a role in the pathway that links atypical antipsychotic treatment and metabolic syndrome. Certain variations or polymorphisms in the serotonin receptor gene identified as 5-hydroxytryptamine receptor 2C (HTR2C) were previously implicated in diabetes and obesity in the general population. This was a cross-sectional study drawing 112 patients from a pool of 200,000 patients with schizophrenia/schizoaffective disorders. The study patients were treated with clozapine, olanzapine and risperidone and were followed using strict parameters (blood pressure, triglycerides, HDL, and waist circumference) with the primary endpoint being metabolic syndrome. One variation of this gene termed HTR2C rs3813929 was linked to atypical

antipsychotic use and metabolic syndrome (Mulder *et al*, 2007). Another study added that another HTR2C polymorphism typed rs 1414334 was strongly associated with clozapine and risperidone use leading to metabolic syndrome. Furthermore, a polymorphism in the MTTP gene typed MTTP rs 1800591 conferred increased risk of metabolic syndrome. This was a gene involved in triglyceride metabolism (Liou *et al*, 2013). This was also a cross-sectional study but with a larger sample size (n=456) and with a more stringent inclusion and exclusion criteria. It used the same 3-month follow-up time after initiation of the same antipsychotics (clozapine, olanzapine, risperidone) as the previous study but defined metabolic syndrome in terms of the International Diabetes Federation criteria as described earlier by Mayo Clinic. These studies both used accepted criteria to define metabolic syndrome and raised congruent points that highlight the contribution genetic variations can make in predisposing schizophrenic patients with atypical antipsychotics to metabolic syndrome.

#### Cost of Care

With regards to the total cost of care for patients with schizophrenia on atypical antipsychotics, there was no short-term difference in cost. Despite the higher risk of diabetes and weight gain with olanzapine compared with risperidone, a head-to-head comparison of the total monthly cost of care did not reveal a significant difference (Riordan *et al*, 2011). Whether there is a long-term difference in healthcare cost between the other atypical antipsychotics is unclear given that the consequences of metabolic syndrome manifest after longer duration of medical therapy.

### Direct Comparison Between the Atypicals

Seven systematic reviews of randomized controlled trials performed a head-to-head comparison of the efficacy and side effect profiles of the various atypical antipsychotics on the market including clozapine, olanzapine, aripiprazole, amisulpride, risperidone, ziprasidone, quetiapine, sertindole, and zotepine. Among the side effects compared were risk of metabolic syndrome and its constituents, weight gain and diabetes. The purpose of these systematic reviews was to select one atypical antipsychotic and compare its efficacy and side effect profile with the rest of the medications in its class. Regardless of the increased efficacy, clozapine was associated with the highest risk of inducing metabolic syndrome, with olanzapine as the second highest cause. Both medications also carried the most risk of inducing type II diabetes mellitus compared to the others in their class (Komossa *et al*, 2010). On further exploration, the seven systematic reviews had various points of agreement as well as discrepancy when stratifying the metabolic risk profile for each atypical antipsychotic. After first taking into account the systematic reviews' common findings regarding the risk of developing metabolic syndrome, the atypical antipsychotics can be stratified as such based on their metabolic risk profile from the highest to the lowest: clozapine > olanzapine > quetiapine/sertindole > risperidone > amisulpride/aripiprazole > ziprasidone. Medications grouped together and not stratified further within the spectrum indicates lack of adequate comparative data to draw firm conclusions. Along the same line, direct comparisons of quetiapine with amisulpride, sertindole and zotepine were not performed (Asmal *et al*, 2013). In addition, amisulpride was only compared head-to-head with olanzapine and risperidone in which it showed less risk of weight gain. But, comparison with ziprasidone was inconclusive (Komossa *et al*, 2010). However, in a direct comparison Ziprasidone had a lower metabolic risk profile compared to amisulpiride, olanzapine and

risperidone (Komossa *et al*, 2009). With regards to comparison of risperidone's metabolic risk profile with the other medications on the spectrum, definitive conclusions could not be drawn but worse metabolic risk profile was suggested when compared with amisulpride, aripiprazole and ziprasidone (Komossa *et al*, 2011). In a similar fashion, sertindole was only compared with risperidone and it showed increased metabolic risk profile (Komossa *et al*, 2009). Clozapine also showed more risk of weight gain compared to risperidone (Asenjo *et al*, 2010).

The discrepancies between some of the systematic reviews with regards to risk of metabolic syndrome and associated conditions mainly occurred in the study that compared quetiapine with the other medications. Due to discontinuation of therapy by a significant number of patients (60%) within a few weeks, this systematic review could not establish a meaningful comparison of quetiapine with risperidone, clozapine and aripiprazole with which it was purported to have similar metabolic risk profile (Asmal *et al*, 2013). However insignificant, quetiapine's standing in comparison to the other medications on the metabolic risk spectrum happens to be supported by the other studies. Despite the systematic reviews analyzing as many as 50 randomized-controlled trials in the olanzapine study (Komossa *et al*, 2010), and 45 randomized-controlled trials in the risperidone study (Komossa *et al*, 2011), no firm conclusions could be drawn from them due to the overall high attrition rate in these studies approaching 60% which threatens their internal validity. In addition, the review that analyzed Sertindole only included 2 studies (Komossa *et al*, 2009) and the review that looked at Amisulpride was only a short to medium term study (Komossa *et al*, 2010). Despite the above-mentioned obstacles to drawing solid conclusions, some suggestions can be made – as laid out in the metabolic risk profile spectrum in the previous paragraph – with regards to the various atypical antipsychotics and their associated risk of metabolic syndrome. Another study was conducted that also

highlighted the increased risk of metabolic side effects with four atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone). This was a randomized study with a design that consisted of complete randomization and clinician's choice methods where 1 or 2 medications can be excluded per psychiatrist or patient wishes. Despite the high therapy discontinuation rate and shorter duration of treatment (median 26 weeks), a high cumulative incidence of metabolic syndrome was still noted (36.5% in 1 year) for all of the atypical antipsychotics in the study. The randomization method in this study appears suitable for this patient population since it accounts for the "real world" adjustments that take place in response to the medications' side effects. If the study was done with true double-blinded fashion, significantly less number of patients would stay within the group since they most likely would not tolerate the side-effect. This study's design gave patients the option to leave out 1-2 of the medications and stay longer within the study. The high attrition rate, shorter duration of treatment, prior exposure to atypical antipsychotics, inclusion of various psychiatric diagnoses and age group of subjects > 40 years all negatively affect the internal and external validity of the study. Despite the limitations, these four commonly used atypical antipsychotics were associated with higher incidence of metabolic syndrome (Jin *et al*, 2013).

#### Periodic Monitoring of Metabolic Syndrome in Atypical Antipsychotic Use

Patients who are on atypical antipsychotics require frequent monitoring for and potential treatment of metabolic syndrome and the different derangements/diagnoses it carries (i.e. hypertension, obesity, hyperlipidemia, impaired fasting glucose). Risk factor modification is the focus of managing metabolic syndrome in an effort to prevent cardiovascular mortality and includes adjusting diet, exercising, achieving adequate blood pressure control, and treating

hyperlipidemia/hyperglycemia (Riordan *et al*, 2011). Furthermore, multiple atypical antipsychotic use was not associated with increased risk of metabolic syndrome compared with single medication use. Nonetheless, initiation of periodic monitoring of blood pressure, fasting lipid panel and glucose is recommended in patients who start taking atypical antipsychotics. Riordan *et al* point out that only a minority of the patients do actually get monitored for these parameters of the metabolic syndrome. The proposed recommendations for monitoring include measurements at baseline, at 4 weeks, at 8 weeks, at 12 weeks, every 3 months, every year and every 5 years. Periodic metabolic monitoring in these patients is essential given their vulnerability (Riordan *et al*, 2011).

#### Treatment of Metabolic Syndrome in Schizophrenic Patients on Atypical Antipsychotics

Treatment of metabolic syndrome in these patients includes risk factor modification through lifestyle changes and pharmacotherapy. Lifestyle modifications include behavioral therapy, dietary guidance and enrollment in an exercise program (Wu *et al*, 2008). Pharmacotherapy includes off-label use of metformin for better glycemic control (Wu *et al*, 2008, Jesus *et al*, 2015). The study that examined the role of lifestyle modifications and metformin use was a randomized controlled trial that assigned 128 patients with schizophrenia to 4 groups: placebo, lifestyle modification only, metformin only, and lifestyle modification with metformin. The patient population was selected carefully and the subjects were 18-45 years with their first psychotic episode of schizophrenia diagnosed using the DSM-IV. Weight gain of more than 10% of their weight prior to initiating the atypical antipsychotics (clozapine, olanzapine, risperidone, and sulpiride) was used as inclusion criteria. Strict monitoring of the patients' lifestyle, including diet intake was instituted. Lifestyle modification plus metformin use at 750

mg per day showed the most effect on weight loss, decrease in BMI, and reduction in waist circumference. This group had a mean BMI decrease of 1.8, insulin resistance index decrease of 3.6 and decrease in waist circumference of 2.0. Metformin alone was also found to be better than lifestyle modification alone (Wu *et al*, 2008). This was a very well designed and very well implemented study with stringent inclusion and exclusion criteria as well as close follow up. It has very good internal validity but can only be generalized to the age group between 18-45 years. The benefit of metformin in atypical antipsychotic-induced metabolic syndrome was supported by a review article which showed that metformin use in this patient population resulted in better glycemic control, improved weight loss and these effects were evident in patients with and without diabetes. In contrast to the trial by Wu *et al*, metformin in this review of 12 articles was especially beneficial when started in young adults who are initiated on these medications (Jesus *et al*, 2015). Additionally, a meta-analysis of four randomized trials and 105 patients concluded that metformin use resulted in approximately 5% weight reduction in patients on olanzapine who had developed metabolic syndrome. This weight reduction was more than the weight loss achieved by other approved medications such as orlistat and sibutramine. Furthermore, the adverse effects of metformin were similar to placebo (Praharaj *et al*, 2010). This meta-analysis had no significant heterogeneity but only consisted of 4 randomized trials with a small pooled sample size.

This extensive Literature review shows that atypical antipsychotics are associated with a greater risk of developing metabolic syndrome especially in patients with schizophrenia. Furthermore, despite the lack of strong conclusions from the reviewed studies, there exists a spectrum of metabolic risk profile for these medications with each atypical antipsychotic falling somewhere on the spectrum from highest to the lowest risk. Among the medications reviewed,



the consensus is that clozapine is deemed to have the highest risk while ziprasidone has the lowest risk of leading to metabolic syndrome. However, the high attrition rate in most of the systematic reviews comparing the medications has resulted in the lack of a strong comparison between the different medications in this class. There is strong evidence that Metformin in conjunction with a healthy diet and exercise has shown the maximum benefit in reducing weight, BMI, and waist circumference in patients with atypical antipsychotic-induced weight gain even when compared to standard weight-reduction pharmacotherapy.

### **Methods**

An online search was conducted through the Harley E. French Biomedical Library at the University of North Dakota. In an effort to identify the highest level of evidence the literature search was initiated with the Cochrane database of systematic reviews. The search terms “atypical”, “antipsychotics”, “metabolic” were used yielding 604 results. A filter was applied to identify those grouped under mental health which narrowed the results to 179. The subgroup filter was applied isolating those dealing with Schizophrenia and Psychosis which narrowed the results to 142. The list was further narrowed to 43 by further specifying atypical antipsychotics. Seven systematic reviews comparing the various atypical antipsychotics including their risk profile for developing metabolic syndrome were included for the literature review. PubMed was subsequently searched using the terms “atypical”, “antipsychotics”, “metabolic”, “syndrome”, “comparison”. This yielded 20 results. Only one randomized trial was picked comparing 4 atypical antipsychotics. Two other studies fit the criteria but only compared two atypicals which were already compared in the previous study. PsycInfo was also searched using the terms “atypical”, “antipsychotics”, “metabolic”, “syndrome”, and “genes”. 14 results were available. 2 were selected to highlight the genetic context of developing metabolic syndrome in

schizophrenic patients and one more study was picked due to its review of two atypical antipsychotics' association with diabetes. PubMed was revisited to find studies that dealt with treatment. The search terms used were “metabolic”, “syndrome”, “treatment”, “atypical”, “antipsychotics”. One review of 12 studies and another systematic review with a meta-analysis were chosen for the literature review. The remaining results from the 3 databases were not included due to the low quality nature of the studies or because of topics covered that were not relevant to this literature review.

Given the widespread use of atypical antipsychotics in the treatment of schizophrenia, this literature review will explore the varying degrees of association between the atypical antipsychotics used and the development of metabolic syndrome. Furthermore, therapeutic options will be explored and recommendations synthesized from the available literature. The highlights of this review will be presented via a power point format (See Appendix) to fellow graduate students of the Psychiatric and Mental Health Nurse Practitioners program as well as the instructors at the University of North Dakota. This literature review as well as the presentation will also be shared with colleagues.

### **Results**

The project set out to identify available literature on the topic. The 3-database search yielded literature including 7 systematic reviews, 1 systematic reviews with meta-analysis, 1 randomized-controlled trial, 1 equipoise-stratified randomized trial, 2 cross-sectional studies and 3 qualitative reviews. The literature picked specifically dealt with metabolic syndrome in the setting of atypical antipsychotic use in schizophrenic patients. No guidelines were identified for monitoring of metabolic syndrome in this patient population. These patients were more or less treated with the guidelines developed for the general population at risk for metabolic syndrome

(ex. Lipid and glucose monitoring). In addition, there were no specific guidelines regarding treatment of metabolic syndrome in schizophrenics who use atypical antipsychotics. As noted in this literature review, this unique patient population requires additional care in monitoring as well as treatment in addition to the standard of care afforded to the general population with metabolic syndrome.

### **Discussion**

This project was successful in identifying the pertinent available literature on the topic of metabolic syndrome in patients with schizophrenia who are on atypical antipsychotics. As alluded to in the beginning, metabolic syndrome is a major contributor of cardiovascular morbidity and mortality in this patient group as well as in the general population. As such, a multifaceted approach is necessary to address the problem and reduce the disease burden in this very vulnerable patient population. The APRN should integrate the Health Promotions Model into caring for these patients by taking into account the various biopsychosocial factors that influence the patients' motives. Adequate symptom control in Schizophrenia empowers patients and provides them with the mental stability they need to actively participate in their own care. This leads to a better health outcome. The APRN's provision of care includes prevention, screening, timely diagnosis/treatment of metabolic syndrome, making medication adjustments, providing counseling and ensuring appropriate close follow-up. Patients with schizophrenia on atypical antipsychotics also require every guideline-based disease management offered to the general population in order to prevent metabolic syndrome and its dreaded complications. In addition, they also require a highly individualized comprehensive care plan that takes into account their mental health burden. In addition to implementing the Health Promotions Model, the APRN should be knowledgeable about the commonly available atypical antipsychotics along

with their level of efficacy, side-effect profile including metabolic syndrome, and management of their complications. Long-term periodic monitoring of metabolic syndrome parameters (glucose, lipid panel, and BMI) is highly recommended. This type of monitoring should also be done in schizophrenic patients in general due to biopsychosocial factors that may lead to metabolic syndrome independent of treatment with atypical antipsychotics. It is also very important to ensure timely follow up for continuity of care. Based on the literature review, the spectrum of risk of developing metabolic syndrome with the various atypical antipsychotics is as follows from high risk to low risk. clozapine > olanzapine > quetiapine/sertindole > risperidone > amisulpride/aripiprazole > ziprasidone. Assessing comparative efficacy between the different medications was beyond the scope of this project. The APRN can use this spectrum of risk profile to inform point-of-care medical decision-making while treating a schizophrenic patient who needs to be on long-term atypical antipsychotic. High side-effect profiles of these medications contribute to non-adherence, worsening of schizophrenia-related symptoms and inability to follow through with other treatment recommendations. For example, a common theme with the literature review was the high attrition rate of the study subjects in most of the randomized controlled trials which prevented firm conclusions from being drawn. However, comparisons could still be made regarding the side effect profiles of most of these medications. Independent of being on atypical antipsychotics, patients with schizophrenia are also at an increased risk of developing metabolic syndrome. This is likely due to their poor mental health interfering with their ability to make good lifestyle choices. The addition of atypical antipsychotics adds to the disease burden. Treating these patients' metabolic syndrome requires a multifaceted approach. The literature review has identified that low dose metformin at 750 mg per day combined with lifestyle modifications (ex. health diet, exercise) has shown significant

benefits through reduction of weight and treatment of hyperglycemia in metabolic syndrome. The role of metformin suggested here is primarily for weight loss where as in the general population it is used to treat pre-diabetes and diabetes, both of which are components of the metabolic syndrome.

APRNs, RNs, and LPNs are uniquely situated to improve the outcomes for this patient population. Founded on the solid knowledge of the various atypical antipsychotics with their efficacy and side-effect profiles, APRNs can better treat schizophrenia improving the quality of life and longevity of their patients. RN and LPN health coaches can then perform periodic metabolic monitoring, provide encouragement to patients as well as carry out home visits to maximize adherence to treatment regimen. Through involvement in research, APRNs can implement better research designs that minimize attrition and ensure adequate sample size in comparative trials. They can also participate in educating their multidisciplinary colleagues as well as the patients about this issue, participate in advocacy and help bring about healthcare policy reform.

### **Summary**

In conclusion, metabolic syndrome in schizophrenic patients is a common diagnosis associated with cardiovascular morbidity and mortality in line with the general populations. Treatment with atypical antipsychotics compounds this risk. Despite the level of attrition of study subjects, various randomized controlled trials have established a comparative risk of metabolic syndrome among the various atypical antipsychotics. Clozapine and olanzapine have been associated with the most risk of metabolic syndrome while ziprasidone and aripiprazole are associated with the least amount of risk. Analysis of comparative efficacy was beyond the scope of this independent project. Management of metabolic syndrome in this patient population

includes prevention, screening, neuroleptic medication adjustment, and treatment of medication complications including metabolic syndrome. These patients require a multifaceted approach to treatment including choosing the right medication, implementing lifestyle modifications and also take into account the various biopsychosocial factors that affect their motivation to work toward a better outcome. Low dose metformin in conjunction with healthy diet and exercise has shown the most benefit in reducing BMI, waist circumference and ultimately metabolic syndrome. The APRN should play a leading role in advancing research in this field, helping educate colleagues, and participation in guideline development as well as participate in advocacy to shape healthcare policy.

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## Appendix

<h3>Atypical Antipsychotics and Metabolic Syndrome</h3> <p>Tehut Tefera UND School of Nursing, PMHNP Graduate Program</p>	<h4>Objectives</h4> <ul style="list-style-type: none"> <li>• Understand the scope of the problem of cardiovascular disease in the setting of schizophrenia and atypical antipsychotic use</li> <li>• Understand the association between metabolic syndrome and cardiovascular morbidity and mortality</li> <li>• Identify the degree of relationship between the various atypical antipsychotics and metabolic syndrome</li> <li>• Explore treatment options for patients with schizophrenia who are at risk for or develop metabolic syndrome while on atypical antipsychotics</li> </ul>
<h4>Background</h4> <ul style="list-style-type: none"> <li>• Accounting for 30% of all deaths, cardiovascular disease is the leading cause of morbidity and mortality in the U.S.</li> <li>• Risk factors for cardiovascular disease include hypertension, obesity, type 2 diabetes, and dyslipidemia.</li> <li>• Metabolic syndrome is characterized by high BMI, high triglycerides, low HDL, high blood pressure and high fasting glucose levels.</li> <li>• Metabolic syndrome contains most of the major risk factors that lead to cardiovascular disease</li> </ul>	<h4>Background, continued</h4> <ul style="list-style-type: none"> <li>• Schizophrenia has a prevalence of 1.1% in the U.S. population</li> <li>• Metabolic syndrome has a prevalence of 20-60% in patients with schizophrenia <ul style="list-style-type: none"> <li>• Some estimates put the likelihood of metabolic syndrome 2x that of the normal population</li> </ul> </li> <li>• Metabolic syndrome is also the #1 risk factor for ischemic heart disease in patients with schizophrenia - independent of the schizophrenia diagnosis.</li> </ul>
<h4>Role of Atypical Antipsychotics</h4> <ul style="list-style-type: none"> <li>• Also called second-generation antipsychotics</li> <li>• Various drugs are available in the market with differing efficacy and side-effect profiles</li> <li>• Atypical antipsychotics are preferred over the first generation or typical antipsychotics because of their overall favorable side-effect profile (ex. tardive dyskinesia)</li> <li>• Widely used for the treatment of schizophrenia</li> </ul>	<h4>Atypical Antipsychotics and Metabolic Syndrome</h4> <ul style="list-style-type: none"> <li>• Atypical Antipsychotics significantly contribute to the development of metabolic syndrome and its cardiovascular complications</li> <li>• This relationship between the medications and the syndrome is multifaceted including genetic predisposition and the medications' mechanism of action</li> </ul>
<h4>Methods for the Literature Review</h4> <ul style="list-style-type: none"> <li>• Cochrane, PubMed and PsycInfo were used for the database search</li> <li>• The search focused on identifying systematic reviews and individual randomized controlled trials.</li> <li>• 7 systematic reviews, 1 meta-analysis, 1 randomized trials, 2 cross-sectional studies and 3 qualitative reviews were identified</li> <li>• Search terms included "metabolic", "syndrome", "atypical antipsychotics", "treatment"</li> </ul>	<h4>Findings of the Literature Review</h4> <ul style="list-style-type: none"> <li>• The 7 systematic reviews compared each atypical antipsychotic with other selected ones</li> <li>• The comparison was made in different areas including efficacy and side effects</li> <li>• Their contribution to metabolic syndrome was selected for review</li> <li>• The comparison included clozapine, olanzapine, quetiapine, sertindole, risperidone, amisulpride, aripiprazole, and ziprasidone</li> <li>• Clozapine had the highest risk of metabolic syndrome while Ziprasidone had the lowest</li> </ul>

### Findings of the Literature Review

- Synthesis of the various systematic reviews of the individual drugs revealed the following spectrum, from the highest to lowest risk of developing metabolic syndrome
- clozapine > olanzapine > quetiapine/sertindole > risperidone > amisulpride/aripiprazole > ziprasidone
- The paired medications did not differ significantly

### Study Limitations

- A significant limitation of the systematic reviews was the high drop out rate of the study population
- This limited the strength of the recommendations made by the studies
- However, some conclusion could be drawn about the relative efficacy and side effect profile of the different atypical antipsychotics

### Findings of the Literature Review

- The genetic polymorphisms (variations) in the microsomal triglyceride transfer protein (MTTP) and 5HT2C receptors were linked with a predisposition to metabolic syndrome in patients taking atypical antipsychotics

### Literature Review, Disease Management

- Metformin at a dose of 750 mg daily coupled with lifestyle modifications showed the most benefit in reducing weight, BMI and treating metabolic syndrome,
- This combination was more effective than either metformin or lifestyle modifications alone
- Lifestyle modifications included diet and exercise

### Further Recommendations

- Screening methods used for metabolic syndrome in the general population should be pursued more intensely in this psychiatric population
  - Regular weight, blood pressure and cholesterol checks
- The Health Promotions Model by Nola Pender is a useful nursing theory that can be used in delivering optimal care for this patient population.
  - This model takes into account the various biopsychosocial factors that can influence a patient's motives to pursue health promoting behavior.
- These patients should have regular close follow up with their mental health providers as well as their primary care providers.
  - RN health coaches can be indispensable in ensuring treatment adherence

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