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Detection of the Metabolic Syndrome in Schizophrenia and Implications for Antipsychotic Therapy: Is There a Role for Folate?

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Abstract

In general, presence of the metabolic syndrome is associated with significant cardiovascular mortality and represents a growing public health concern in the United States. Patients with a schizophrenia have a three times greater risk of death compared to the general population, with cardiovascular disease being the most common cause of this mortality. Use of the atypical antipsychotics (AAPs) to treat schizophrenia contributes significantly to this cardiovascular disease risk. While currently several different clinical guidelines exist to monitor for the metabolic consequences of AAP use, implementation is lacking. Due to the under monitoring of side effects and the lack of alternative treatment choices in schizophrenia, research has focused on the identification of various biomarkers and pharmacogenomic targets to focus on those at greatest risk for metabolic syndrome, thus aiming to increase the efficacy and minimize the side effects of the AAPs. This has led to several different lines of research. This manuscript focuses on summarizing the differing metabolic syndrome criteria, monitoring guidelines for AAPs and the role of folic acid as it relates to metabolic syndrome within the schizophrenia population. It will concentrate not only on the pharmacogenomics of folic acid metabolism, but also its epigenetic interaction with the environment. From this work, genetic variation within both the methylenetetrahydrofolate reductase (*MTHFR)* and catechol-o-methyl transferase (*COMT*) genes has been associated with increased metabolic syndrome risk in schizophrenia patients treated with AAPs. Furthermore, the combination of folate pharmacogenetics and epigenetics has uncovered relationships between methylation, schizophrenia disease, treatment type and metabolic syndrome. Despite the several areas of biomarker research for schizophrenia related metabolic syndrome, translation to the clinical setting is still lacking and further studies are needed to bridge this gap. Future folate supplementation research may prove to be an easy and effective clinical tool for the prevention and/or treatment of metabolic syndrome associated with AAP treatment, but clearly more work needs to be done in this area.

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1. Introduction

In the general population, the presence of the metabolic syndrome is associated with significant cardiovascular mortality and represents a growing public health concern in the United States (1,2). While the term, metabolic syndrome, has been coined within the past 20 years (previously called Syndrome X), the constellation of symptoms that make up metabolic syndrome (such as central adiposity and elevations in cholesterol, blood glucose, and blood pressure) have historically been recognized as risk factors for cardiovascular disease (3–5). Metabolic syndrome is seen in about 25% of men and women (6). For those meeting metabolic syndrome criteria, the population-attributable risk estimates for cardiovascular disease, coronary heart disease, and diabetes mellitus are 34%, 29%, and 62% for men and 16%, 8% and 47% for women (7). Thus, presence of the metabolic syndrome criteria is associated with increased risk for significant cardiovascular morbidity and mortality and has undoubtedly become a national health crisis as the rates of this illness continue to rise. Unfortunately the risks for metabolic syndrome in those with a serious mental illness such as schizophrenia or bipolar disorders are more than double that seen in the general population which has also resulted in a significant proportion of the morbidity and mortality seen within these populations (8–10). Although the exact cause for this increased risk for the metabolic syndrome in serious mental illness is unknown, the high prevalence of atypical antipsychotic use has been suggested as being a major contributor (8,11). Much work has been done examining the pharmacogenomics of atypical antipsychotic metabolic consequences; however consensus regarding these risks currently does not remain. One promising line of work has focused on folic acid and its pharmacogenetically regulated metabolism through the methylenetetrahydrofolate reductase (MTHFR) enzyme. Thus the purpose of this review is to focus on the increased risk for metabolic syndrome within the schizophrenia population. It will give a brief background examining the different criteria used for a diagnosis of metabolic syndrome followed by a summary regarding monitoring for metabolic syndrome within the schizophrenia population. Lastly the role of biomarkers for the detection of metabolic syndrome within schizophrenia will be touched on with a summarization of the available literature regarding folate pharmacogenomics and epigenomics in antipsychotic-associated metabolic syndrome within this population.

2. Criteria for Diagnosis of Metabolic Syndrome

Before discussing the increased incidence of the metabolic syndrome within the schizophrenia population, a thorough understanding of the different criteria currently available is necessary. Although there is significant overlap between these differing criteria, there is no one set of criteria that are consistency used by all, and as such this lack of consistency makes comparing the rates of metabolic syndrome across populations difficult. Additionally differing patient populations (i.e. treatment naïve and non-treatment naïve) are often included when examining the true incidence of metabolic syndrome due to atypical

antipsychotic use. Thus, current estimates range from 13.4%, as seen within the Comparison of Atypicals for First Episode (CAFE) trial (12) which included younger drug naive subjects, to 40%–52% as reported in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, as well as other recent larger database studies which did not include treatment naïve subjects (9,11,13).

In looking at the different criteria available for the diagnosis of metabolic syndrome, those defined by the National Cholesterol Education Program (NCEP) in 2001, and the International Diabetes Federation (IDF) in 2006 (14,15) appear to be the most commonly cited and referenced when examining the overall risk in schizophrenia. In examining the NCEP criteria it can be seen that a diagnosis of metabolic syndrome can be given when patients meet at least 3 of the following criteria: abdominal obesity (waist circumference ≥ 40 inches in males or 35 inches in females), elevated triglycerides (≥ 150 mg/dL), low HDL (< 40 mg/dL in men or < 50 mg/dL in women), elevated blood pressure (≥ 130 / 85 or on antihypertensive medication), or elevated fasting glucose (≥ 100 mg/dL or on medication for diabetes) (16). This popular NCEP definition, which was subsequently updated with a lower impaired fasting glucose threshold by the American Heart Association in 2005, was published in the third Adult Treatment Protocol (ATP III-A). Since 2001, various definitions have typically been updates to the original ATP III definition (17) and so these competing definitions have significant overlap with key components such as glucose dysregulation, and central adiposity. It is only the NCEP ATP III-A guideline that do not require any core elements be present for a diagnosis of metabolic syndrome. In contrast to this, both the International Diabetes Foundation and the European Group for the Study of Insulin Resistance require either a BMI >30 kg/m^2 or elevated insulin levels, respectively as part of their core definition. Thus for all of these guidelines, at the heart each are the same core risk factors, it is just how they are used in defining a diagnosis of metabolic syndrome that potentially allows for some of the variation seen in the incidence of metabolic syndrome within the seriously mentally ill populations. To overcome this, some groups have worked together to create a more symbiotic approach to developing metabolic syndrome criteria (with added ethic and race specificity) such as the consensus definition suggested by Alberti and colleagues (18). Thus while it is easy to understand that presence of the metabolic syndrome confers with it an increased risk for cardiovascular disease, understanding the specific criteria that need to be met in order to obtain this diagnosis is often not so simple which may contribute to the confusion often associated with metabolic syndrome and its diagnosis (19). The anticipated release of the ATP-IV guidelines however, could result in another update to the definition and criteria of the metabolic syndrome and possibly include ethnic and race specificity which may further complicate this issue.

3. Metabolic syndrome Within Schizophrenia

Presence of a mental illness has long been associated with increased overall mortality (20–22). Cardiovascular disease undoubtedly also contributes to excess morbidity and mortality in individuals with a serious mental illness. In patients with schizophrenia, it is estimated that approximately 34% of deaths among male patients and 31% of deaths among female patients are attributed to cardiovascular disease which is only surpassed by suicide (21,23). In general, schizophrenia is an often debilitating mental illness that affects approximately

1% of the population (24) usually manifesting not only through positive and negative symptoms, but significant cognitive dysfunction as well (25). The overall goal of treatment for schizophrenia is remission of symptoms, and for most individuals with schizophrenia, antipsychotic medications play an important role in this process. While our pharmacotherapeutic treatment choices for schizophrenia have expanded over the last few decades, pharmacologically these medications traditionally achieve their effect through blockade of the dopamine 2 receptor (26). More recently, the atypical antipsychotics (AAPs) (olanzapine, clozapine, risperidone, paliperidone, iloperidone, quetiapine, asenapine, lurasidone, aripirazole, and ziprasidone) have become the first line treatment for schizophrenia due to their differing serotonin antagonism, primarily at 5HT2A and 5HT2C, their possible association with negative symptom improvement, as well as attenuation of extrapyramidal side effects (27).

Although AAPs are effective for the treatment of schizophrenia, their use has now become common place in other mental illnesses and younger age groups as well. Most AAPs carry significant risks such as diabetes, weight gain and dyslipidemia which, as previously discussed, make up the constellation of cardiovascular risk factors outlined in the metabolic syndrome criteria (28–31). Patients taking AAPs frequently manifest early symptoms of metabolic syndrome followed by the actual development of more serious cardiac complications. The end result is up to 30 years of life lost (23,32) for those with schizophrenia. Furthermore, recent studies have suggested the standardized mortality ratio (SMR) for cardiac disease may be increasing in schizophrenia patients relative to the general population following the introduction of AAPs (33,34). These findings are particularly concerning given the known association between these medications and CVD risk factors, adding biological plausibility to the epidemiological findings. A comparison of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) participants with schizophrenia to matched controls from the National Health and Nutrition Examination Survey (NHANES III) on ten-year risk of coronary heart disease based on the Framingham Heart Study formula demonstrated an elevation in risk for coronary heart disease of 34% in males and 50% in females with schizophrenia (35). Similar elevations in cardiac risk with schizophrenia have been demonstrated in other studies (36,37) and are much higher than that reported in the Framingham Heart Study Offspring Study.

Until recently, significant weight gain with AAP use was the primary research focus involving AAP metabolic complications, and in fact, CATIE showed that over 30% of subjects gained greater than 7% of their baseline body weight with at least 18 months of AAP treatment (38). This trial also confirmed that overall men and women with schizophrenia were 85% and 137% more likely to develop metabolic syndrome, respectfully, than NHANES matched controls (9) and that “Clinical attention must be given to monitoring for this syndrome and minimizing the risks associated with antipsychotic treatment”. This work has been replicated by other groups showing that schizophrenia patients treated with AAPs have a two to four fold greater risk for metabolic syndrome compared to the general population (39). The precise explanation for this increased risk linked to AAPs remains unknown; however the body of literature regarding the risks seen with AAP use has grown substantially throughout the last decade (40). In addition, recent

guidelines based on this work have been developed in an effort to help mitigate the cardiovascular risks seen with AAP use in persons with a serious mental illness.

4. Monitoring Recommendations for AAP use in Schizophrenia

Although much of this literature contributes the risk for metabolic syndrome in the seriously mentally ill population to atypical antipsychotic use, not all clinicians agree that this is simply a medication associated side effect. Regardless of the etiology, there is consensus regarding the importance of routine monitoring for metabolic syndrome within the mental health population and several specific guidelines have been published for those receiving an atypical antipsychotic. The first of these guidelines was authored within the United States and was published on behalf of the American Diabetes Association (ADA) and the American Psychiatric Association (APA) in 2004 (41). Key to these guidelines is the routine monitoring of weight, waist circumference, blood pressure, fasting plasma glucose level, and fasting lipid profile. Table 1 is a summary of the APA/ADA monitoring guideline recommendations. In addition to these practice guidelines, several others have been published such as those supported by the United Kingdom's National Institute for Health and Clinical Excellence (NICE) and the Quality and Outcomes Framework (QOF) (42,43) as well as publications published in the Canadian Journal of Psychiatry (44,45). Finally, much work has looked at the quality of proposed guidelines for monitoring metabolic syndrome within schizophrenia which is beyond the scope of this review however several reviews are available (46,47). While there might be slight differences in the exact monitoring these various guidelines recommend; they all highlight the importance of continued monitoring and preventative care for those with a serious mental illness especially in those populations receiving AAPs.

Unfortunately the reality is that, despite clear recommendations, these guidelines are not being followed (48–51). Adherence to these guidelines has recently become a priority research area for many in an effort to document some of the health disparities related to those with a serious mental illness. In a recent meta-analysis on this topic, Mitchell and colleagues found 48 studies on the topic of metabolic monitoring in mental health (47). As part of their meta-analysis they found that across these studies, routine baseline monitoring was very low and that only blood pressure and triglyceride monitoring were occurring in more than half of patients receiving an atypical antipsychotic. More specifically weight was only monitored in 48% of patients, followed by glucose in 44%, cholesterol in 42% and lipids and glycosylated hemoglobin (HbA1c) in less than 25% of patients. Thus, while we have many different monitoring guidelines to choose from which can be used to guide the treatment of those with a serious mental illness, these recommendations are not being consistently followed. Additionally these authors examined the literature regarding monitoring changes after specific educational interventions were made for clinicians regarding these guidelines. They found that monitoring in areas like blood pressure, weight gain, glucose and lipids did increase, but that overall the rates of monitoring were still low related to glucose (56%) and lipids (29%)(47). The low use of these guidelines in clinical practice is of concern and indicates that this patient group does not receive adequate testing or monitoring for metabolic complications. Furthermore, clinicians must use this monitoring

to guide treatment of identified metabolic abnormalities with appropriate medications in order to prevent future cardiovascular consequences from the metabolic syndrome.

While monitoring for metabolic complications of AAP use continues to be an emphasized issue, the research community has continued to work towards understanding the mechanisms behind these medication side effects resulting in the identification of different biomarkers which have been proposed for their potential use in the clinic (52–56). Potentially having a biomarker for the metabolic side effects seen with AAP use would be highly desirable, as it would allow the clinician to easily measure a patients risk for metabolic syndrome before any medication is administered. This would aid in the effort to personalize mental illness pharmacotherapy and optimize treatment. While the research on various biomarkers related to the risk for weight gain and metabolic syndrome seen with AAPs is fairly expansive (56–58), no definitive recommendations have currently been translated into clinical practice and thus work within this area must continue.

5. Folic Acid Pharmacogenetics and Epigenetics

Our continued understanding of the pharmacogenomics of antipsychotic-associated metabolic syndrome has highlighted the importance of environment and nutrition in the body's ability to regulate the genome (59) though dietary folic acid intake and its pharmacogenetically regulated metabolism. Briefly, folate is a water soluble B-vitamin involved in the synthesis, repair, and methylation of DNA (60) whose effective utilization is dependent on adequate daily intake as well as genetically altered metabolism (60). Within the AldoMet cycle, the methylenetetrahydrofolate reductase (*MTHFR*) enzyme metabolizes folate to methyltetrahydrofolate (5-methyl THF) which then converts homocysteine to methionine and adenosyl methionine by methionine synthetase (*MTR*) (Figure 1). Reduced *MTHFR* activity results in hyperhomocysteinemia, which is associated with cardiovascular disease. The AldoMet cycle's final product is the universal methyl donor for several biological methylation reactions. It is these methyl groups which form the basis for epigenetic modulation of DNA processes, which is beyond the scope of this review (61).

MTHFR relies on dietary folate as well as genetic variants in determining its efficiency (62). When inadequate amounts of 5-methyl THF are available for *MTR*, homocysteine increases and s-adenosyl methionine formation is reduced, resulting in DNA hypomethylation (63,64). Thus, folic acid plays an important role in maintaining genomic stability as well as homocysteine levels (65). Genetic variation within this enzyme has also been shown to affect its efficiency. For *MTHFR*, the 677C/T variant, resulting in an alanine to valine substitution is the most prominent and produces a thermo-labile variant with reduced activity (66). The T allele is relatively common, with homozygosity occurring in up to 20% of North American and European populations (60). Individuals with a TT genotype have a 70% reduction in *MTHFR* activity, compared to the CC genotype group, while heterozygotes have a 35% reduction (67). Of the AldoMet cycle enzymes, the *MTHFR* 677TT variant is the best characterized and is most consistently associated with hyperhomocysteinemia, cardiovascular disease, metabolic syndrome and methylation status. This relationship is exaggerated by low dietary intake and reduced total body stores of folic

acid (68). Research currently points to *MTHFR* in the development of metabolic syndrome in mental health patients taking AAPs as summarized and discussed below (28,31).

Pertinent to the metabolism of homocysteine is the enzyme catechol-*O*-methyl transferase (*COMT*). Despite the lack of clarity concerning *COMT's* role in the pathogenesis of schizophrenia, it has been shown that the 158Met variant produces a more thermolabile protein resulting in reduced activity compared to the 158Val variant. Those with the Val/Val genotype have 30–50% greater activity than those with the Met/Met genotype (69). Thus, in relation to homocysteine metabolism, individuals with the *COMT* 158Val allele would have higher *COMT* activity leading to increased homocysteine concentrations, which may be exaggerated in individuals who also have *MTHFR* variants associated with hyperhomocysteinemia (70). The risks seen with the *AldoMet* variants are often exaggerated in situations of low folate exposure (71) and therefore dietary assessments as well as genetic measurements are dually important to understanding homocysteine, cardiovascular disease and the risk of metabolic syndrome within those receiving AAPs.

6. Role of Folic Acid in Atypical Antipsychotic Metabolic Syndrome

Multiple studies have demonstrated relationships between *MTHFR* gene variants and schizophrenia pathogenesis, but more recently this work has begun to focus on the role of aberrant folate metabolism as it relates to metabolic syndrome risk in the schizophrenia population using AAPs. To identify available literature associated with this topic, a pubmed search was conducted using combinations of the following words: schizophrenia, folate, metabolic syndrome, antipsychotic, pharmacogenetic, epigenetic, MTHFR, COMT and MTR. A total of 22 studies were found, 15 were excluded either because they were not conducted in humans, were conducted without reference to antipsychotic use, were reviews or did not relate to metabolic syndrome. Furthermore, references of included articles were searched for further literature sources. Table 2 is a summary of those studies on this topic that are discussed below.

The first report of this relationship included 58 subjects with schizophrenia who were receiving AAPs. It was reported that patients with schizophrenia who carried a *MTHFR* 677T allele had a 3.6 times greater risk for meeting metabolic syndrome criteria while taking an AAP ($p = 0.02$) (28). Additionally, the data showed that after controlling for waist circumference, those with the *MTHFR* 677T allele were also at increased risk for developing higher levels of insulin resistance (28). At this time, this report was the first to examine the relationship between *MTHFR* variants and metabolic syndrome risk within this population. This study was then followed up by Van Winkel and colleagues (72). While this group also found a relationship between *MTHFR* and metabolic syndrome within schizophrenia, the authors reported that the *MTHFR* 1298A>C allele instead of the 677C>T allele was related to a significant increase in risk of metabolic syndrome ($p = 0.02$). Overall these authors found that patients with the 1298C/C genotype had a 2.4 times increase risk of metabolic syndrome ($p = 0.009$) which was similar to our previously reported odds ratio of 2.54 for the 677 T variant (28,72). Van Winkel and colleagues also conducted a prospective, naturalistic 3 month follow-up study to evaluate the association between *MTHFR* 677C>T and 1298A>C variants and metabolic parameters after initiation of an AAP. In this study they

found genotype × time associations between the 1298A>C variant and measures of glucose, weight and waist circumference. Although this study did not measure the occurrence of metabolic syndrome over time, it supports their earlier results where schizophrenia patients with the 1298 C allele have genetic loading for metabolic side effects from AAPs (73).

More recently, our group has gone on to confirm our initial findings in a separate group of 237 subjects with bipolar disorder or schizophrenia who were screened for metabolic syndrome and genotyped for both *MTHFR* and *COMT* variants. In addition, subjects underwent a fairly comprehensive assessment for dietary and lifestyle factors (i.e. physical exercise, medication use, 24 hour food recount, and smoking assessment) as well as folate exposure. Overall, 41% of our subjects met metabolic syndrome criteria (n=98). There were no significant differences in age, gender, AAP exposure, or BMI between genotype groups. We found that occurrence of the metabolic syndrome was related to age, smoking and *MTHFR* 677T and *COMT* 158Val alleles ($p<0.0001$). Those with these two risk alleles (*MTHFR* 677T and *COMT* 158 Val alleles) met metabolic syndrome criteria at a much earlier age than those without these alleles (46 vs. 52 years) (31).

Additionally, studies have looked at the epigenetics of AAP-associated metabolic syndrome due to the link between folate pharmacogenetics and methylation as described above. Epigenetics is a rapidly growing field in psychiatry due to the known influence of environment on mental illness and yet, it requires cautious interpretation due to the complexities of epigenetic mechanisms and as study designs within schizophrenia continue to be defined (74). One such study investigated the role of the soluble *COMT* (COMT-s) methylation promoter status and metabolic syndrome in the peripheral blood samples from schizophrenia patients largely on atypical antipsychotics (75). This study found that *COMT* genotype was an indicator of COMT methylation status of the two CpG sites investigated ($p=0.0044$ for site 1 and $p=0.027$ for site 2). Furthermore, those homozygous for the met/met COMT genotype showed a positive correlation between CpG site methylation and metabolic syndrome (site 1: $p=0.001$ and site 2: $p=0.001$). In addition to this investigation, a different study using peripheral blood samples found that females carrying the *MTHFR* 677TT genotype had the lowest measure of global methylation, measured using the long interspersed nucleotide element-1 (LINE-1), which may help to explain the gender metabolic syndrome differences seen in schizophrenia (76). Finally, investigators have reported that global DNA methylation (using the Luminometric assay) differed based on schizophrenia onset status as well as treatment type (with AAPs users having lower levels of global of methylation) (77). Although this study did not look at metabolic indices it does begin to show that methylation status can be affected not only by antipsychotic treatment but by antipsychotic class.

Therefore, these studies provide evidence of a link between different enzymes related to folic acid metabolism and an increased risk of metabolic syndrome for patients with schizophrenia when taking an AAP. The results could possibly provide the evidence for pharmacogenetic testing of patients before starting an antipsychotic medication in an effort to reduce this risk or in addition to direct dietary and lifestyle interventions for those at greatest risk. Given that pharmacogenetic assays for *MTHFR* and its variants are

commercially available and often done within other medical specialties, the era of personalized medicine for schizophrenia may not be so far off.

7. Summary and Conclusions

It is now well known that use of the atypical antipsychotics is perhaps the most effective treatment we currently have for schizophrenia and other serious mental illnesses. Unfortunately due to their associated risk for metabolic syndrome, use of these medications may be placing these individuals at greater risk for several comorbidities, resulting in an accumulation of life years lost due to cardiovascular disease. There currently is a lack of consensus regarding the specific criteria which should be used when diagnosing metabolic syndrome within the serious mentally ill population, although some agreement does exist regarding which criteria are important and potentially place individuals at greater risk for the development of cardiovascular disease. While monitoring guidelines for the use of atypical antipsychotics and metabolic syndrome risk have been developed and widely circulated, the reality is that they are often not followed for many reasons. Although many biomarkers have been proposed for the possible prevention of metabolic syndrome seen with atypical antipsychotic use, this research has not been successfully translated into the clinic. The role of folic acid in the development of these metabolic complications is currently being investigated and current data suggests that for those with the *MTHFR* 677T and *COMT* 158Val allele, metabolic syndrome risk may be elevated or occurring at a younger age. Furthermore, evidence is beginning to show schizophrenia subjects reside in a global hypomethylation and possibly less stable genetic state. While the natural next step in this currently research is folate supplementation, ongoing work in this area is not yet available. Studies using folate supplementation in schizophrenia patients using AAPs and carrying these increased risk pharmacogenomics and epigenomic targets are needed in order to begin to translate this research into practice. Thus, at this time, educating patients and their caregivers about the importance of a balanced healthy diet with exercise as well as proper pharmacotherapeutic management of metabolic abnormalities is crucial to combating the staggering cardiovascular mortality seen within this group. For those whose diets do not include the minimum recommended daily allowance of folate, a supplement may be appropriate until such a time when conclusive data can be presented regarding the role of folic acid in the diagnosis and detection of metabolic syndrome within schizophrenia.

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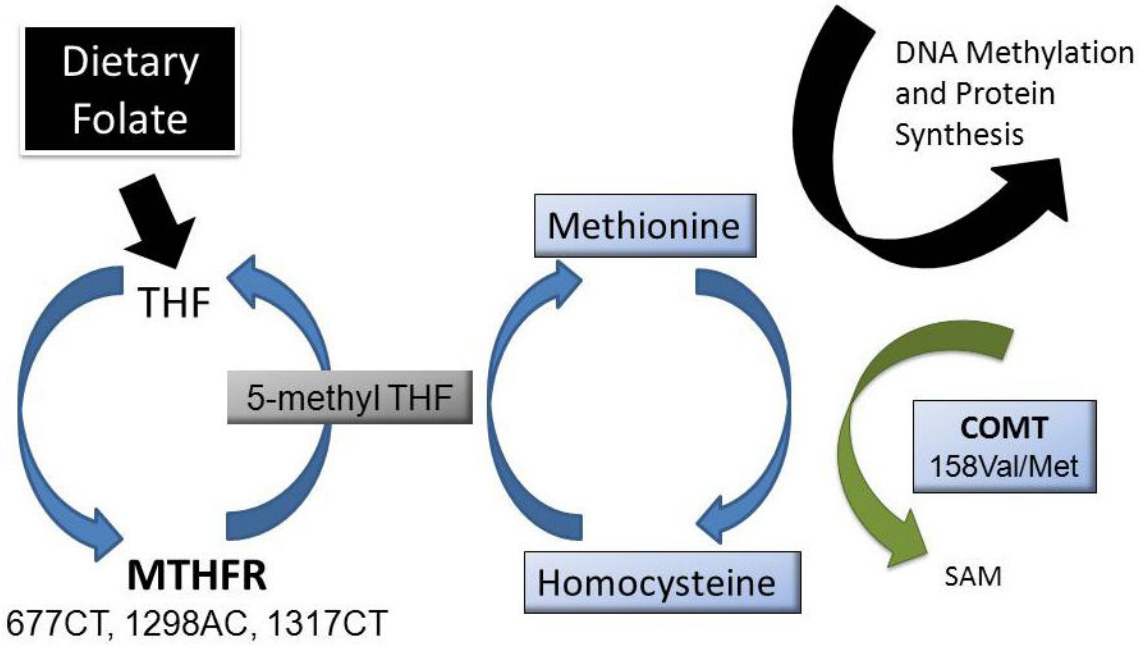

Figure 1.

The Aldo Met cycle converts homocysteine to methionine and is facilitated by folate and methylenetetrahydrolfate reductase (*MTHFR*). Catechol-o-methyltransferase (*COMT*) converts methionine to S-adenyl methionine (SAM), also producing homocysteine. Genetic variants within these enzymes affect their efficiency within this cycle.

Table 1

Summary of American Diabetes Association and American Psychiatric Association Monitoring Guidelines for the implementation of Atypical Antipsychotics (41)

Monitoring Parameters	Baseline	4 weeks	8 weeks	12 weeks	Annually	Every 5 years
Personal/Family History	X				X	
Weight (BMI)	X	X	X	X	X (Obtain Quarterly)	X
Waist Circumference	X				X	
Blood Pressure	X			X	X	
Fasting Plasma Glucose	X			X	X	
Fasting Lipid Profile	X			X		X

Table 2

Summary of studies for folic acid pharmacogenomics and metabolic syndrome with atypical antipsychotic use in schizophrenia.

Author	Year	Subjects	Genotype	Outcomes	Results
Ellingrod VL and colleagues	2008	58 patients with schizophrenia taking an antipsychotic for at least 12 months	*MTHFR* 677C>T *MTHFR* 1298A>C	Metabolic Syndrome HOMA-IR	*MTHFR* T allele resulted in a 3.6 times more likelihood of developing AAP associated metabolic syndrome (p = 0.02). Also, the TT genotype patients were at greater risk for insulin resistance and increasing waist circumference (p = 0.0006).
Van Winkel and colleagues	2010	518 patients with schizophrenia	*MTHFR* 677C>T *MTHFR* 1298A>C	Association between genotype and metabolic syndrome	*MTHFR* 1298 C/C genotype had a 2.4 times risk of developing metabolic syndrome (p = 0.009)
Van Winkel and colleagues	2010	155 patients with schizophrenia or schizoaffective disorder newly started on a atypical antipsychotic. Patients with diabetes or metabolic syndrome at baseline were excluded	*MTHFR* 677C>T *MTHFR* 1298A>C	Genotype × time interactions for metabolic variables (weight, waist circumference, fasting glucose, 120 minute OGTT level and lipids	No significant effect for 677C>T variant. Significant genotype × time interaction for 1298A>C and weight (p=0.006), waist (p=0.050), fasting glucose (p=0.024) and 120 minute OGTT levels (p=0.018), with a dose-response pattern with increasing C-allele loading.
Ellingrod VL and colleagues	2012	237 patients with schizophrenia and bipolar patients taking an antipsychotic for at least 6 months	*MTHFR* 677C>T *MTHFR* 1298A>C *COMT* 158Val>Met	Metabolic Syndrome	Metabolic syndrome was related to age, smoking and the *MTHFR* 677T and *COMT* 158Val alleles (χ^2=34.4, p<0.0001).
Lott SA and colleagues	2012	85 schzophrenia patients taking an atypical antipsychotic	*COMT* 158Val>Met and *COMT*-s *promoter methylation*	Genotype, promoter methylation and metabolic syndrome	Associations found between *COMT* 158MetMet genotype, COMT-S promoter methylation and metabolic syndrome
Burghardt KJ and colleagues	2012	133 patients with schizophrenia stable on an antipsychotic	*MTHFR* 677C>T and LINE-1 methylation	Genotype and global methylation measure	LINE-1 methylation lower in females carrying the *MTHFR* 677 TT genotype when controlling for serum folate
Melas PA and colleagues	2012	171 schizophrenia patients and 171 controls	*LUMA methylation, COMT-s methylation*	Disease onset, treatment type and global methylation measure	LUMA methylation related to schizophrenia onset and antipsychotic type

Abbreviations: HOMA-IR - Homeostatic Model Assessment Insulin Resistance, MTHFR –Methylenetetrahyrofolate reductase, COMT – Catechol-o-Methyl Transferase, LINE-1 long interspersed nucleotide element-1, LUMA - Luminometric assay.