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Risk Factors Associated with Metabolic Syndrome in Bipolar and Schizophrenia Subjects Treated With Antipsychotics: The Role of Folate Pharmacogenetics

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Introduction

In the United States, over 40% of schizophrenia and bipolar patients meet metabolic syndrome criteria, compared to 25% of the general population (1). According to NCEP-ATP II guidelines, metabolic syndrome is diagnosed when at least three of the following clinical signs are present: increased waist circumference, triglycerides, blood pressure, fasting blood sugar, and reduced high density lipoprotein (2). Metabolic syndrome may increase overall cardiovascular disease (CVD) risk above and beyond each of its individual components (3). Schizophrenia is often associated with a sedentary lifestyle and poor eating habits which may contribute to metabolic syndrome development. Genetics has also been identified as a risk factor within this population, especially in relation to atypical anti-psychotic use (4, 5).

The relationship between *MTHFR 1298A/C, and 677C/T, COMT Val158Met* variants and metabolic syndrome in schizophrenia and bipolar patients treated with antipsychotic agents has yet to be fully elucidated. Both enzymes regulate homocysteine in the Aldo Met cycle; however their mechanisms for facilitating hyperhomocysteinemia are different. For *MTHFR* in particular, studies differ regarding which variant (1298A/C or 677C/T) is more relevant to folate metabolism (6). Homocysteine is an amino acid, metabolized to either cysteine, requiring vitamin B6, or to methionine, requiring vitamin B12 and folate. Vitamin B12 and/or folate deficiencies present with elevated homocysteine (7). Links have been suggested between schizophrenia and homocysteine as well as between CVD and homocysteine (8, 9).

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Conflicts of Interest
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Hyperhomocysteinemia correlates with an increased risk of developing CVD, independent of smoking, hyperlipidemia, and hypertension (10, 11). Poor nutrition, sedentary lifestyle, smoking and coffee consumption are suggested as contributing factors linking hyperhomocysteinemia with schizophrenia and bipolar disorder (12). Studies suggest that lowering homocysteine may improve schizophrenia clinical symptoms (13). Previously our group reported a relationship between the *MTHFR* 1298A/C and 677C/T variants (rs1801131and rs1801133) and metabolic syndrome in schizophrenia (5). In general, the *MTHFR* 677TT genotype results in a 70% reduction in its metabolic capacity contributing to hyperhomocystemia (6). The relationship with aberrant homocysteine and the 1298A/C and 1317T/C variants is not as defined (6).

Also pertinent to homocysteine's metabolism is the enzyme catechol-o-methyl transferase (*COMT*), a S-adenosylmethionine (SAM) dependent methyltransferase that methylates catechol compounds including dopamine (14). The *COMT* Val158Met variant (rs4680) has been examined in relation to cognitive functioning and disease development in schizophrenia (15–17) showing a relationship with reduced cognitive function (18), although its direct genetic association with the illnesses has been weak (19). The *COMT* 158Met variant (rs4680) produces a more thermolabile protein with reduced activity (30–50%) (20). Increased *COMT* activity with the ValVal genotype has been associated with reduced dopamine levels within the frontal cortex (21). In relation to homocysteine metabolism, those 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 (14).Reduced MTHFR functioning and higher COMT functioning may explain some of the increased risk for AAP metabolic complications.

This study examined the relationship between AAP use, *MTHFR* and *COMT*, and metabolic syndrome using a cross-sectional design of bipolar disorder or schizophrenia spectrum disorder patients. Our hypothesis was that *MTHFR* 677T or 1298C alleles and the *COMT* Val allele, either independently or combined would increase metabolic syndrome incidence in individuals receiving AAPs. If such a relationship exists, future studies can be performed investigating B vitamin supplementation (primarily B1 or folic acid) to attenuate the metabolic effects of AAP use.

Materials and Methods

Subjects

Subjects met the following inclusion criteria 1) DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or bipolar disorder (type I and II), 2) Age 18–90 years; and 3) antipsychotic treatment for > 6 months. Exclusion criteria included 1) unwillingness to participate, 2) unable to give informed consent (assessed using a short questionnaire asking key questions about the study), 3) medical records documenting type II diabetes before antipsychotic use, or 4) active substance abuse diagnosis. The study protocol was approved by the University of Michigan Medical School Institutional Review Board (IRBMED).

Assessments

Subjects meeting study inclusion/exclusion criteria (from October 2008-February 2011) underwent informed consent followed by a clinical interview including an assessment of current and past medication history, smoking status (including current and past use), and ethanol intake. Subjects fasted for at least 8 hours before the visit which took place between 8 and noon. Visits were timed to be within 2 hours of the subject's usually waking time

based on appointment availability. Vital signs, as well as height, weight, and hip and waist circumference was measured for each subject and Body Mass Index (BMI) and Hip/Waist ratio was calculated. Blood was also drawn for the following fasting laboratory assessments, which were conducted by the Michigan Diabetes Research and Treatment Center (MDRTC) core laboratory: folate, vitamin B12, homocysteine, glucose, insulin, hemoglobin A1c, lipids, and leptin. Based on the results of the laboratory and clinical measurements, subjects were given a diagnosis of metabolic syndrome using the NCEP-ATP III guidelines (2), where Metabolic Syndrome is defined by any 3 of the following: 1) abdominal obesity characterized by waist circumference of >40 inches for men or >35 inches for women, 2) triglycerides ≥150 mg/dL, 3) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women, 4) blood pressure ≥130/≥85 mmHg or treatment for hypertension, or 5) fasting glucose ≥100 mg/dL or treatment of diabetes.

MTHFR and COMT genotyping

Genomic DNA was isolated from whole blood using salt precipitation (22) and genotyping was done with Pyrosequencing™ Technology for the *MTHFR* 1298A/C (rs1801131), 677C/T (rs1801133) variants and *COMT* Val158Met (rs4680) variants. Assay conditions are available upon request. Genotype calls were made blinded to participant assessments. Ambiguous calls were repeated with a consensus assessment of genotypes. Call rates were 99% for these assays.

Statistical Analysis

Differences in primarily outcomes and socio-demographic variables between study and allelic groups (*MTHFR* 1298C, 677T and *COMT* Val allele) were determined with one-way analysis of variance (ANOVA) for normally distributed variables. Subjects currently receiving olanzapine, clozapine, quetiapine, risperidone, or paliperidone were classified as receiving a weight gain associated atypical antipsychotic (WG-AAP). Ziprasidone and aripiprazole were not included due to lower weight gain liability (23). Linkage disequilibrium for gentoypes was examined using Haploview (24). Previous analyses of the *MTHFR* and *COMT* variants have shown a relationship between CVD risk and/or hyperhomocysteinemia and the *MTHFR* 677T allele in subjects with the *COMT* 158 Val allele (14). Therefore, subjects were divided by *MTHFR* 1298C, 677T or *COMT* Val allele status. Chi squared analysis was used to compare dichotomous variables by genotype groups. To examine the relationship among *MTHFR/COMT* status, folate exposure, and metabolic syndrome, a regression model was constructed using metabolic syndrome as the dependent variable and age, gender, race, smoking status, AAP use, *MTHFR and COMT* alleles, folate concentrations, and interactions as independent variables. A p-value < 0.05 was considered statistically significant.

Results

A total of 237 subjects were included (127 with schizophrenia and 110 with bipolar disorder). A total of 37 did not participate in the pharmacogenetic portion of the study. A total of 144 subjects (61%) were receiving a WG-AAPs, which were more common in the schizophrenia group (72% versus 48%, p<0.0001). Polypharmacy was common in both groups with 129 subjects (54%) receiving at least one medication in addition to their antipsychotic. The most commonly co-prescribed medications were valproic acid and antidepressants with 25% of bipolar and 14% of schizophrenia subjects receiving valproic acid and 61% of bipolar and 50% of schizophrenia subjects receiving an antidepressant. The mean age of the sample was 47.6 years (median=46) and subjects were predominately Caucasian (72%) followed by African Americans (20%). Males constituted 51% of the group and were more common in the schizophrenia group (66% versus 35%, p<0.0001).

Forty-one percent of the population met metabolic syndrome criterion which is similar to what our group and others have reported (1, 5). The schizophrenia group had a higher percentage of current cigarette smokers. Table 1 details the demographic differences seen between the groups.

Genotype distributions for *MTHFR* 677C/T and 1298A/C and *COMT* Val158Met variants were normally distributed (Hardy Weinberg p>0.1 for all) with no differences based on diagnosis or race (p>0.6 for all). The mean allele frequencies for three variants ranged from 0.25–0.45, similar to previous reports (5, 14). The genotypes for the *MTHFR* 1298 and 677 variants were in strong linkage disequilibum ($D' = 0.8$), therefore only the 677 variant was included in the final analysis as most of the folate pharmacogenetic literature has reported on this specific variant. Table 2 provides details regarding the baseline characteristics of this population by *MTHFR* 677T and *COMT* 158Val alleles. There were no differences between the different groups.

Metabolic syndrome risk was not associated with psychiatric diagnosis or gender; however a trend for greater metabolic syndrome prevalence occurred in the schizophrenia group, which may be related to the higher use of WG-AAPs (Table 1). In looking at the individual laboratory values that make up the metabolic syndrome diagnosis, no differences were seen when subjects were segregated based on their *MTHFR* and *COMT* allele status. However when these values are examined for each individual subjects according to the NCEP-ATP-III Guidelines, we see that over 40% meet metabolic syndrome criteria and are at significant risk for CVD.

Within the whole group, metabolic syndrome prevalence was highly associated with age and smoking status, as well as an interaction between the *MTHFR* 677T and *COMT* 158Val alleles ($\chi^2=33.8$, $p<0.001$). After controlling for age and smoking status, the *MTHFR/COMT* interaction remained significant ($\chi^2=7.19$, $p=0.0073$) and WG-AAP use showed a trend for significance ($\chi^2=3.21$, $p=0.07$). The *MTHFR/COMT* interaction produced an odds ratio of 1.58 (95% CI=1.15–8.3) for metabolic syndrome risk. The effect of the interaction could be better seen when subjects were grouped by number of variant alleles and the mean age was examined according to presence or absence of metabolic syndrome for each group. Table 3 is an examination of the mean age for each of these groups. The mean age of subjects who were positive for metabolic syndrome decreases with increasing number of *MTHFR* 677T and *COMT* 158Val allele. This could possibly suggest that for those with each of these alleles, metabolic syndrome is occurring at a younger age (47 versus 52) compared to those who have the *MTHFR* 677CC and *COMT* 158 Met/Met genotypes.

We also examined the relationship between the number of metabolic syndrome criteria met for each subject and identified risk factors. Overall, a significant relationship was found with age, smoking, and WG-AAP use ($F(6,200)=14.54$, $p<0.0001$). However the number of metabolic syndrome criteria met was not associated with genotype or an interaction between the two ($t=1.02$, $p=0.3$), while the association with AAP use became stronger ($t=2.91$, $p=0.004$). Those receiving a WG-AAP met an average of 2.4 metabolic syndrome criteria, compared to those not receiving a WG-AAP only meeting 1.8 criteria. It could be that WG-AAP use is a greater risk factor for developing several of the risk factors associated with metabolic syndrome, but threshold of actually meeting these criteria may be more related to age, smoking, and folate pharmacogenetic variants. Thus in younger subjects WG-AAP use may precipitate metabolic syndrome, but occurrence of this syndrome may be higher in those with the *MTHFR* and *COMT* variants.

Additionally, serum homocysteine concentrations were also related to folate exposure and *MTHFR* 677T and *COMT* 158Val alleles ($F(4,206)=11.4$, $p<0.0001$). After controlling for

folate exposure, those with both the *MTHFR* 677T and *COMT* 158Val allele had the highest homocysteine concentrations (11.8 ng/ml) versus those without either of these alleles (10.5 ng/ml).

Discussion

Overall, we found that for bipolar and schizophrenia subjects receiving a WG-AAP, metabolic syndrome risk was related to age, smoking status, and *MTHFR* 677T and *COMT* 158Val alleles. For those with these alleles, metabolic syndrome risk was 1.58 times greater and was seen at an earlier age. WG-AAP use also showed a statistical trend for increasing metabolic syndrome risk, and was significantly associated with the number of metabolic syndrome criteria met. These results confirm a similar relationship previously published by our group (5). This the first time, to our knowledge, that this relationship has been reported in bipolar subjects as well as those with schizophrenia.

The study of folic acid and schizophrenia's relationship has recently gained momentum with other groups investigating folate's role in the schizophrenia symptomatology related to prefrontal cortex functioning (25–27). Folate's role in affective disorders suggests that folate metabolism related to the *MTHF*R 677 variant may play a role in disease pathology (19).

Since our first publication, other have examined folate's role in schizophrenia and AAP risk for metabolic syndrome, finding the *MTHFR* 1298A/C variant was significantly associated with metabolic syndrome development (28). While these investigations included the same *MTHFR* variants, as our current study, they did not include the *COMT* Val158Met variant which has been implicated in homocysteine regulation and folate metabolism (14). It is interesting that van Winkel er al. group did not find a *MTHFR* 677 main effect which is the focus of most *MTHFR* investigations, although they did report a linkage between the 1298 and 677 variants (28).

Folate is a water soluble B-vitamin involved in the synthesis, repair, and methylation of DNA, whose effective utilization depends on adequate daily intake and genetically altered metabolism (29). Methylenetetrahydrofolate reductase (*MTHFR*) forms methyltetrahydrofolate (5-methyl THF) from dietary folate, which converts homocysteine to methionine and adenosyl methionine by methionine synthetase (MTR) as part of the AldoMet cycle. Catechol-o-methyl transferase (*COMT*) is also involved in this cycle and the 158Val variant manifests with greater metabolic activity compared to the 158 Met allele, leading to increased homocysteine concentrations which may be exaggerated if *MTHFR* variants are also present (14). Alternations in this cycle result in hyperhomocysteinemia, and are associated with CVD (8). Interestingly, the risks seen with the *MTHFR* variants are often exaggerated in situations of low folate exposure (8), thus dietary assessments as well as genetic measurements are dually important to understanding homocysteine and WG-AAP metabolic risk within these groups.

Lastly, age and smoking were also significantly associated with metabolic syndrome risk, which has been well described within the CVD literature (2). In looking at this data, the age differences are striking and may suggest that *MTHFR* 677T and COMT 158Val variants increase metabolic syndrome risk at a younger age. In these individuals then, smoking may increase this risk and the addition of an AAP may increase this risk even further. The fact that smoking was significantly associated with metabolic syndrome risk, only underscores the importance of effective smoking cessation program for individuals with mental illness. Thus, for those with this triad of risk factors (pharmaogenetic, smoking, and age), aggressive interventions focusing on diet and exercise may help to attenuate the risk of metabolic syndrome.

Limitations

This is a cross-sectional study for the metabolic syndrome. While other genetic variants are present within the AldoMet cycle, we did not genotype all of these variants for this investigation. Additionally the polypharmacy seen in our study group may limit our ability to determine specific medication related risk factors and as such requires further study. Despite these limitations, this investigation currently is the most comprehensive assessment of AAP linked metabolic complications available in the literature and will continue to provide additional data as we continue to examine this dataset.

Conclusion

In bipolar and schizophrenia subjects treated with WG-AAPs, we found metabolic syndrome may be related to age, smoking status, and folate metabolism. Additionally the number of metabolic syndrome criteria subjects met may also be related to age, smoking, and AAP use. These data provides new insight into the role of folate in mental health and adds to currently available literature which has primarily focused on cognition in schizophrenia and depression and bipolar disease pathology. Development of future intervention trials to determine the effect of B vitamin (specifically folate) supplementation on amelioration of the AAP metabolic effects needs to be considered.

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TABLE 1

Baseline Demographic Differences Between the Schizophrenia and Bipolar Subject Groups

	Schizophrenia (n = 127)	**Bipolar Disorder (n = 110)**	***P***
Age, mean (SD), y	46.0 (11.5)	43.0 (11.9)	0.05
% White/% African American/% other	64/28/8	82/12/6	0.02
	(n = 81/36/10)	(n = 90/13/7)	
% Males	66	35	<0.0001
	(n = 84)	(n = 39)	
% Receiving AAPs	77	54	0.001
	(n = 98)	(n = 59)	
BMI, mean (SD), kg/m^2	32.7 (7.9)	32.5 (8.6)	0.86
% Meeting metabolic syndrome criteria	46	35	0.08
	(n = 58)	(n = 39)	
% Current cigarette smoker	60	34	<0.0001
	(n = 76)	(n = 37)	

Table 2

Baseline Demographic and Clinical Variables differences between the *MTHFR and COMT* groups

	***MTHFR* Genotype**		**p-value**	***COMT* Genotype**		**p-value**
	C/C (n = 126)	**T allele (n = 93)**		**Met/Met (n = 47)**	**Val allele (n = 173)**	
Mean Age ± s.d. (years)	45.1 ± 11.7	44.6 ± 11.9	0.73	44.1 ± 13.5	45.1 ± 11.3	0.59
% Caucasian/% African American	66%/27%%	77%/14%	0.22	82%/9%	68%/25%	0.06
% Males	52%	53%	0.96	54%	52%	0.77
% receiving AAPs	62%	64%	0.73	72%	60%	0.16
% current cigarette smoker	51%	48%	0.72	46%	51%	0.53
% meeting metabolic syndrome	43%	43%	0.98	40%	43%	0.72

Table 3

Subject age segregated by *MTHFR* and *COMT* alleles and metabolic syndrome diagnosis.

	Mean Age (Years ±} standard deviation)		
***MTHFR* 677 and *COMT* 158 Val alleles groups**	**Metabolic Syndrome**	**No Metabolic Syndrome**	**P value**
MTHFR CC and *COMT* Met/Met	51.9 ± 7.3	37.7 ± 15.0	0.0051
MTHFR T or COMT *Val* allele	49.0 ± 9.8	41.9 ± 12.2	0.0011
MTHFR T and *COMT* Val allele	46.7 ± 10.8	43.9 ± 11.7	0.29