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**TITLE: RELATIONSHIP BETWEEN THE CATECHOL-O-METHYLTRANSFERASE (COMT) VAL158MET POLYMORPHISM AND ANTIPSYCHOTIC RESPONSE IN FIRST EPISODE PSYCHOSIS**

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**Abstract Type: Original Research**

**PURPOSE:** The common catechol-o-methyltransferase (COMT) Val158Met polymorphism reduces the metabolic activity of this enzyme, alters dopamine disposition in the brain, and is a pharmacogenetic candidate for studies of antipsychotic medications. This study characterized the relationship between this variant and symptom response to six weeks of antipsychotic therapy in treatment naïve patients experiencing their first episode of a major psychotic disorder.

**METHODS:** Eighty patients meeting DSM-IV criteria for schizophrenia (n=54), schizophreniform (n=1), bipolar disorder (n=19), or schizoaffective disorder (n=6) were recruited for a six week study of antipsychotic treatment. Exclusion criteria included neurological disorders, previous head injury, or substance dependence within the past six months. Subjects were predominantly antipsychotic-naïve (70%) or had less than 12 weeks lifetime exposure. At baseline, subjects underwent a 3-5 day washout if they had recently received any oral antipsychotic, antidepressant, or mood stabilizing medication. Participants were treated with an antipsychotic medication, predominantly risperidone, and evaluated for symptom improvement at baseline and follow-up. Primary treatment outcomes for this analysis were the 18 item Brief Psychiatric Rating Scale (BPRS) Total, Positive, and Negative subscale scores, which were compared across COMT Val158Met genotype groups.

**RESULTS:** Demographic (race, age, sex) characteristics and baseline global psychopathology (BPRS Total scores) did not significantly differ across diagnosis or genotype groups. COMT genotypes (Val/Val=25, Val/Met=41, Met/Met=14) were in Hardy-Weinberg Equilibrium ( $p=0.69$ ). Baseline BPRS Total, Positive, and Negative subscale scores averaged  $49\pm 9$ ,  $12\pm 7$ , and  $11\pm 6$  for the entire population and did not differ across COMT genotype groups for the study sample as a whole or when stratified by schizophrenia and schizoaffective/bipolar disorder diagnoses (all  $p's > 0.37$ ). Sixty-one patients (76%) completed the study with a mean improvement of  $10\pm 11$  points on BPRS Total scores. Clinical improvement measured by BPRS Total and subscale measures did not differ across diagnostic groups. Mean improvement scores for Val/Val, Val/Met, and Met/Met genotype groups for the BPRS Total ( $12\pm 12$ ,  $8\pm 11$ ,  $12\pm 8$ ), Positive ( $3\pm 6$ ,  $1\pm 3$ ,  $2\pm 4$ ), and Negative subscales ( $5\pm 5$ ,  $3\pm 5$ ,  $4\pm 4$ ) were not statistically different (all  $p's > 0.34$ ).

**CONCLUSIONS AND FUTURE DIRECTIONS:** COMT Val158Met genotype was not associated with response to treatment as measured by BPRS scores in this first episode psychosis population.