P-953 - TREATMENT BIOMARKER: BLOOD BRAIN BARRIER (P-GP) POLYMORPHISMS PREDICT ANTIDEPRESSANT DOSE AND RESPONSE - A CANDIDATE GENE ASSOCIATION STUDY

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Overview: Pharmacokinetically important polymorphisms could guide dosing, ensuring adequate CNS bioavailability in a particular individual during a therapeutic trial. Hepatic enzyme (CYP450) polymorphisms have been extensively studied. Less work has been done on the permeability glycoprotein (P-gp) - the key efflux pump at the blood brain barrier (BBB).
Methods: An eight week prospective multi-centre candidate gene association study of 113 patients with psychiatrist diagnosed DSM-IV MDD was conducted. Subjects were treated with escitalopram (ESCIT) or venlafaxine (VEN) in a naturalistic clinical setting. Treatment outcome was assessed with the 17-item HDRS and Clinical Global Impression (CGI) Scales. Side effects were rated with a comprehensive adverse reactions scale (UKU). All response ratings were blinded to genotype. P-gp, CYP2D6, and CYP2C19 polymorphisms were assayed using microarray methodology.
Results: BBB (P-gp) polymorphisms associated with less antidepressant CNS entry were associated with need for higher medication dosage and less overall clinical improvement. Patients with higher BBB block polymorphism need 1.45 (p=0.018) times the dose of escitalopram than those with lower blood brain barrier block polymorphism. Patients with lower BBB block genotype had a 1.602 time greater reduction in depression compared to subjects with higher block polymorphisms (p=0.043). Subjects with lower BBB block and poorer metaboliser status at cytochrome P450 2D6 and 2C19 genotype were significantly more likely to respond on the HDRS (RR = 1.60, 95%CI 1.095-2.339, p=0.015).
Conclusions: This is the first study to demonstrated that P-gp polymorphisms predict antidepressant dose, and that combined P450 and P-gp polymorphisms predict antidepressant response.

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