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DYSLIPIDEMIA IN PSYCHOTROPIC-TREATED PATIENTS CORRELATES WITH COMBINATORIAL CYP450 DRUG METABOLISM INDICES

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Objective: To examine the combinatorial effect of polymorphisms in the cytochrome P450 genes *CYP2C9*, *CYP2C19*, and *CYP2D6* on HDLc and LDLc for patients treated for major depressive disorder (MDD).

Method: We recruited 150 psychiatric in-patients referred to the Institute of Living who were treated for MDD with antidepressants and antipsychotics. Their DNA was genotyped to detect 34 alleles in *CYP2C9*, *CYP2C19*, and *CYP2D6* (6, 8, and 20 alleles respectively). We analyzed serum lipid values for correlations with 4 quantitative drug metabolism indices quantifying innate hepatic drug metabolism reserve and gene polymorphism: drug **metabolism reserve** *(MR)* index, drug **metabolism alteration** *(MA)* index, **allele alteration** *(AA)* index and **gene alteration** *(GA)* index. An individual with low metabolic reserve carries multiple deficient or null alleles, whereas a high metabolic reserve denotes the presence of mainly reference and/or ultra-rapid alleles. Greater alteration index values signify greater presence of non-reference alleles.

Results: After correcting for covariates, we found that individuals with lower metabolic reserve had higher LDLc (p=0.020, *MR*). Individuals with greater alteration index values also had higher LDLc values (p=0.008, *MA;* 0.046, *AA;* 0.002, *GA*). Patients with more gene alterations had significantly lower HDLc (p=0.018, *GA*). Finally, LDL/HDL values varied inversely with metabolic reserve index and directly with alteration indeces (p=0.012, *MR;* 0.038, *MA;* 0.099, *AA;* 0.008 *GA*). No individual gene alone was correlated with dyslipidemia.

Conclusions: Psychiatric inpatients treated for MDD with low innate metabolic capacity and a higher degree of allele and gene alterations have greater LDLc and lower HDLc values. Dyslipidemia is a side effect of psychotropic medications which may be exacerbated in patients with low metabolic reserve and therefore high drug plasma concentrations. The results suggest that benchmarking innate drug metabolism capacity through combinatorial CYP450 genotyping is relevant to psychotropic management and superior to single gene testing for predicting and avoiding adverse side effects.

Educational Objectives: At the conclusion of this presentation, participants will be able to *(1)* describe the prevalence and significance of CYP450 drug metabolism deficiencies, *(2)* assess the utility of CYP450 combinatorial drug metabolism indices in characterizing and individual's metabolic phenotype and *(3)* utilize combinatorial index values to improve psychotropic management.

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