

PSYCHIATRIC GRAND ROUNDS – JANUARY 28, 2010

- Title:** DNA-Guided Management of Psychotropic Medications: Clinical Case Studies and Pharmacogenetic Principles
- Presenter:** Gualberto Ruano, M.D., Ph.D., Director of Genetics Research, Hartford Hospital, President, Genomas, Hartford, CT
- Location:** Hartford Room, The Commons Building, 2nd Floor, The Institute of Living/Hartford Hospital, 200 Retreat Avenue, Hartford, CT 06106
- Abstract:** Major depressive disorder (MDD) is currently the leading cause of disability in North America as well as other countries and, according to the WHO, may become the second leading cause of disability worldwide (after heart disease) by the year 2020. Over the years, the elusive and highly variable nature of psychiatric disorders has led to drug therapy treatment that largely relies on empiricism to ascertain individual patient differences. This empirical approach has resulted in a high rate of refractory and adverse responses to drug therapies, rendering treatment of MDD one of the most significant challenges in psychiatry. Both published literature studies and clinical experience reveal great variability in an individual's response to psychotropic drug treatment with regard to drug metabolism, side effects and efficacy. This variability is in part attributable to genetic differences that result in slowed or accelerated oxidation of many psychotropic drugs metabolized by the cytochrome P450 (CYP450) isoenzyme system in the liver. In particular, clinically relevant variants have been identified for the isoenzymes coded by the CYP2C9, CYP2C19 and CYP2D6 genes. While the pharmacogenetic significance of CYP2C9-deficient alleles is not as prominent in psychiatry as that of CYP2D6 and CYP2C19, it is known that the gene represents a minor metabolic pathway for some antidepressants. Therefore, polymorphisms in CYP2C9 may be important in psychiatric patients deficient for other CYP450 enzymatic activities. Some of the potential consequences of polymorphic drug metabolism are extended pharmacological effect, adverse drug reactions (ADRs), lack of prodrug activation, drug toxicity, increased or decreased effective dose, metabolism by alternative deleterious pathways and exacerbated drug-drug interactions. CYP450 isoenzymes are also involved in the metabolism of endogenous substrates, including neurotransmitter amines, and have been implicated in the pathophysiology of mood disorders.

Learning Objectives: The participants will:

- Understand the clinical utility of cytochrome P450 (CYP450) genotyping in management of psychiatric drugs.
- Recognize the case presentations and patient profiles where use of CYP450 genotyping can diagnose clinically intensive side effects.
- Evaluate healthcare utilization patterns in patients with CYP450 drug metabolism deficiencies.
- Appreciate the features of next-generation multi-genotype arrays to diagnose and prevent the cardiometabolic and neuroendocrine side effects of antipsychotic drugs.

CME Questions

- **The following are differences between single nucleotide polymorphisms (SNP) arrays and gene expression arrays EXCEPT:**
 - A. The SNP arrays represent innate inherited genetic traits whereas gene expression arrays reflect solely environmental and lifestyle modifiers
 - B. The SNP arrays can be measured from blood, saliva or buccal samples whereas gene expression arrays require tissue biopsy of the involved physiological system.
 - C. The SNP arrays can sample variation in all genes whereas gene expression arrays are limited to the complement of genes expressed in a given organ or tissue.
 - D. The SNP arrays can be fully validated by pedigree analysis whereas gene expression arrays cannot.

Correct answer is A
- **The status of CYP2D6/CYP2C9/CYP2C19 combinatorial genotypes may be relevant to the following conditions EXCEPT:**
 - A. Drug Sensitivity Syndrome.
 - B. Sensitivity to environmental toxins.
 - C. Disease risk for metabolic syndrome.
 - D. Side effects to antidepressants.
 - E. Susceptibility to antipsychotic-induced metabolic syndrome.

Correct answer is C

- **The status of CYP2D6/CYP2C9/CYP2C19 combinatorial genotypes may explain all of the following EXCEPT:**
 - A. Length of hospitalization.
 - B. Age of onset of schizophrenia.
 - C. Ultra-rapid metabolizer status.
 - D. Null metabolizer status.
 - E. Anxiety towards drug utilization.

Correct answer is B

- **CYP450 metabolism information is included in the labels of the following drugs:**
 - A. Atomoxetine.
 - B. Paroxetine.
 - C. Citalopram.
 - D. Risperidone.
 - E. All of the above.

Correct answer is E

Practice Gap: Interpretation of CYP450 Genotypes and its translation to psychotropic management enables DNA-guided management of psychiatric illness. The interplay of genotyping, psychopharmacology, and clinical practice is anticipated to advance psychiatry in the near term, and requires exegesis to clinicians who may have not trained in genetics.

Reading References:

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In accordance with The Connecticut State Medical Society Faculty Disclosure requirements, Dr. Ruano has disclosed that he has the following relationship with commercial sources related to the topic or content of this CME presentation. And indicates that there will be no discussion of products being used for NON-FDA approved indications.

- Dr. Ruaño is a full time employee and shareholder of Genomas Inc. Dr. Ruaño is President and Chief Executive Officer of the company.
- Research collaborators have no commercial, financial or employment relationship with Genomas.
- Genomas Inc. has support from NIMH and NIGMS SBIR grants to develop diagnostic products for personalized medicine.
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- Genomas and Clinical Laboratory Partners have an established commercial relationship for distribution of pharmacogenetic DNA diagnostics

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Bibliography prepared by IOL Medical Library. Call 545-7276 for information.

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