Combinatorial Pharmacogenomic Algorithm is Predictive of Citalopram and Escitalopram Metabolism in Patients with Major Depressive Disorder

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BACKGROUND

- Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) for citalopram and escitalopram dosing depend on metabolism phenotype classifications derived only from genetic variations in *CYP2C19*, likely because evidence for the contribution of other enzymes to their metabolism was limited.
- Comparatively, a combinatorial pharmacogenomic (PGx) test makes independent citalopram dosing recommendations based on a combined metabolism phenotype derived from *CYP2C19*, *CYP2D6*, and *CYP3A4*.
- We determined the validity of combinatorial PGx testing by assessing blood levels of citalopram from PGx test recommendations and *CYP2C19* phenotype classifications.

METHODS

COHORT

- The following is a subanalysis of the **G**enomics **U**sed to **I**mprove **DE**pression **D**ecisions (GUIDED) randomized, controlled trial assessing the utility of combinatorial PGx testing in depression.
- 191 out of 1,167 patients reported taking citalopram or escitalopram within 2 weeks of the screening blood draw and had citalopram blood concentrations quantified using LC-MS/MS.

COMBINATORIAL PGx TESTING

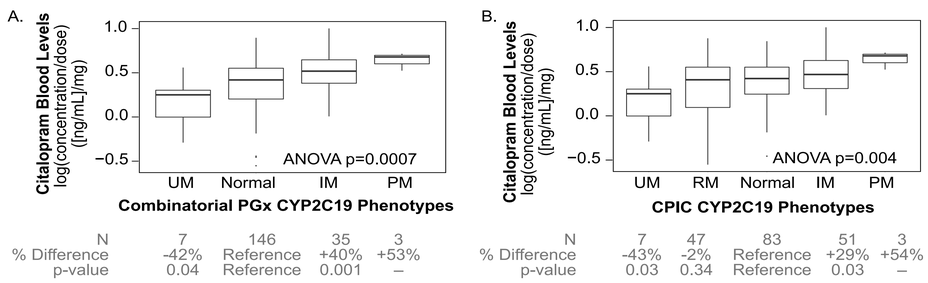
- Multiple genotypes were weighted to produce a combined phenotype.
- Medications were categorized by the severity of gene-drug interactions (GDI): none/weak, moderate, and significant.

STATISTICAL ANALYSIS

- Blood levels of citalopram were assessed according to:
  1. *CYP2C19* alone: combinatorial PGx test phenotype versus CPIC phenotype
  2. *CYP2C19* alone versus the combinatorial PGx test
  3. Multivariate analysis of *CYP2C19* alone and combinatorial PGx test.
- Analysis of covariance (ANCOVA) tests with categorical genetic variables were used to assess the relationship between blood levels and genetic variables.
- ANCOVA tests with numerically transformed genetic variables were used to compare the variability explained by the recommendations from CPIC guidelines and from the combinatorial PGx test.

RESULTS

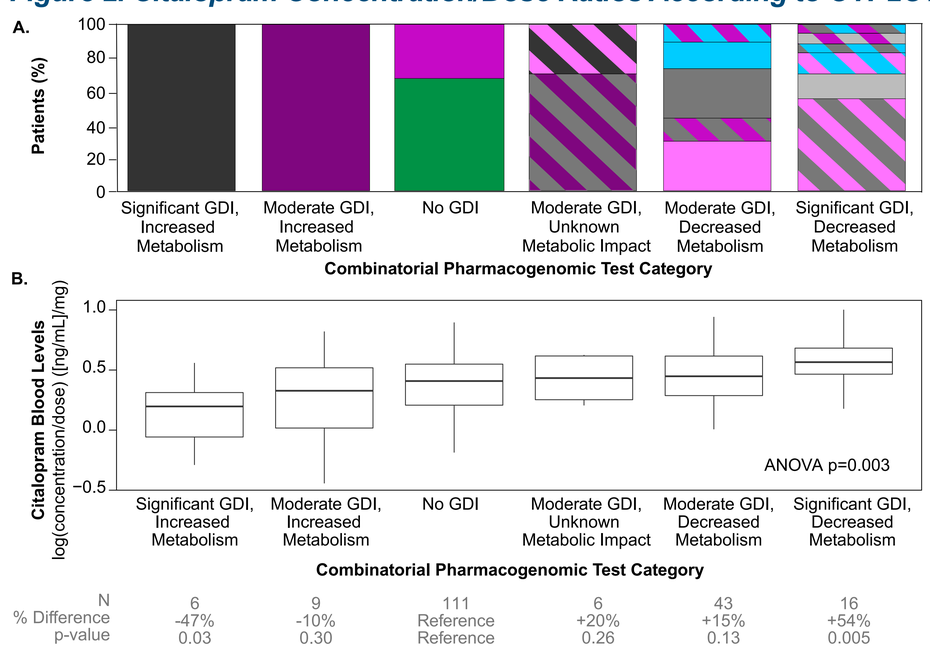
Figure 1. Citalopram Concentration/Dose Ratios According to CYP2C19 Metabolism Phenotypes

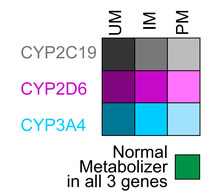


- Boxplots of the log-transformed concentration/dose ratios are shown according to *CYP2C19* phenotype assigned by the combinatorial PGx test from CPIC guidelines.
- Citalopram concentration/dose ratios were significantly different across *CYP2C19* phenotypes when the combinatorial PGx phenotype assignments were used (1A) and when CPIC assignments were used (1B).

UM, Ultrarapid Metabolizer; RM, Rapid Metabolizer; IM, Intermediate Metabolizer; PM, Poor Metabolizer

Figure 2. Citalopram Concentration/Dose Ratios According to CYP2C19 Metabolism Phenotypes





- Solid color bars in 2A indicate that the final report category was based on an individual phenotype.
- 44.5% (85/191) of patients had a variation in only one gene.
- Bars with multiple colors in 2A indicate that the final report category was informed by variations in more than one gene.
- 15.7% (30/191) of patients had an alteration in multiple genes.
- For example, 56.2% (9/16) of patients for whom citalopram was in the "significant gene-drug interaction with decreased metabolism" report category were *CYP2C19* intermediate metabolizers and *CYP2D6* poor metabolizers.
- Citalopram concentration/dose ratios were significantly different between combinatorial PGx report categories (2B).

UM, Ultrarapid Metabolizer; RM, Rapid Metabolizer; IM, Intermediate Metabolizer; PM, Poor Metabolizer

Table 1. Evaluation of individual genes and the combinatorial pharmacogenomic test to predict variance in citalopram and escitalopram blood level

Variables included in Model*	Individual Genes		Combinatorial PGx	
	F Statistic	p-value	F Statistic	p-value
Combinatorial PGx Test	—	—	13.3	0.0003
CYP2C19 Alone**	7.8	0.006	—	—
CYP2C19 Alone†	6.8	0.01	—	—
Combinatorial PGx + *CYP2C19***	2.5	0.12	7.7	0.006
Combinatorial PGx + *CYP2C19*†	0.21	0.65	6.4	0.01

*All models included patient age and smoking status *CYP2C19*
** Phenotypes assigned using CPIC guidelines
†*CYP2C19* phenotypes assigned as part of combinatorial PGx testing were used

- The combinatorial PGx test and *CYP2C19* alone were both significant predictors of citalopram blood levels.
- The F Statistic was higher for the combinatorial PGx test than for *CYP2C19* alone, showing that the combinatorial PGx test explained more variance in citalopram blood levels.
- The multivariate analyses that incorporated the PGx test and *CYP2C19* showed that only the combinatorial PGx test remained significant.

CONCLUSIONS

- *CYP2C19* phenotypes from the combinatorial PGx test more accurately reflected citalopram blood levels than those from CPIC guidelines.
- The additional impact of *CYP2D6* and *CYP3A4* contributed to the validity of the combinatorial PGx test.
- Combinatorial PGx testing allows for more patients to receive clinically actionable dosing guidance than single-gene classifications.

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