Combinatorial Pharmacogenomic Algorithm is Predictive of Sertraline Metabolism in Patients with Major Depressive Disorder

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INTRODUCTION

Pharmacogenomic testing can aid in treatment selection for patients with Major Depressive Disorder (MDD) by identifying gene-drug interactions that may impact medication metabolism. The Clinical Pharmacogenetics Implemental Consortium (CPIC) provides recommendations for sertraline dosing based on genetic phenotypes for CYP2C19; however, other groups suggest that additional enzymes may be important for sertraline metabolism. Although there have been rapid advancements in this field, there is not a consensus about the approach to pharmacogenomic (PGx) testing or even which genes are relevant for many antidepressants.

Here we assessed the ability of pharmacokinetic (PK) genes in a combinatorial PGx test (weighted assessment of multiple genes) to predict meaningful variations in sertraline blood levels.

METHODS

COHORT

All patients were enrolled in the GUIDED trial – a large, patient- and rater-blinded, randomized, controlled trial that included patients diagnosed with MDD who had an inadequate response to ≥1 psychotropic medication (N=1,167).

All patients received combinational pharmacogenomic testing as part of the trial.

A subset of 124 patients reported taking sertraline within 2 weeks of the screening blood draw and had sertraline blood concentrations quantified using LC-MS/MS.

STASTICAL ANALYSIS

A combined phenotype for sertraline pharmacokinetics was generated from a weighted, combinatorial algorithm that included CYP2C19, CYP2B6, CYP3A4 to predict the level of gene-drug interactions (GDI) and change in metabolism (increase or decrease).

The ability to predict variation in sertraline blood levels (log-transformed concentration/dose ratios) was evaluated for:

- Individual gene phenotypes (CYP2C19, CYP2B6, CYP3A4)
- Combinatorial PGx combination phenotype

All data were analyzed using ANCOVA tests with log-transformed lean body weight as a covariate.

DISCUSSION

Clinically meaningful differences in sertraline blood levels were observed between phenotypes for both CYP2C19 and CYP2B6, suggesting that both enzymes are important for sertraline metabolism.

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Collectively, our findings suggest that the combinatorial PGx test may provide more clinically relevant information to inform decisions regarding sertraline compared to testing individual genes.


Table 1. A multivariate analysis evaluating the ability of individual genes and the combinatorial PGx test to predict variation in sertraline blood levels.

<table>
<thead>
<tr>
<th>Variables included in Model</th>
<th>Individual Gene</th>
<th>Combinatorial PGx Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>F Statistic</td>
<td>p-value</td>
<td>F Statistic</td>
</tr>
<tr>
<td>CYP2C19 and Combinatorial PGx</td>
<td>0.06</td>
<td>0.80</td>
</tr>
<tr>
<td>CYP2B6 and Combinatorial PGx</td>
<td>0.23</td>
<td>0.63</td>
</tr>
</tbody>
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The trends in Figure 1 are reflected in this multivariate analysis. After adjusting for all variables in the model, only the combinatorial PGx test remained a significant predictor of sertraline blood levels.

Figure 1. Sertraline blood levels across phenotypes for individual genes and the combinatorial PGx test.

Boxplots of the log-transformed concentration/dose ratios according to (A) individual CYP2C19 phenotypes, (B) individual CYP2B6 phenotypes, or (C) combinatorial PGx test phenotypes. The median (thick horizontal line) interquartile range (box) with plus/minus 1.5x interquartile range (vertical lines) are shown.

- Individually, CYP2C19 and CYP2B6 predicted blood levels with clinically meaningful differences for poor metabolizers.
- There were no differences observed in metabolizer status for CYP2A4.

- Individually, the combinatorial PGx test also predicted blood levels.
- Compared to no GDI, clinically meaningful differences (>50%) in blood levels were observed when the combinatorial PGx test predicted a significant GDI with both increased metabolism, and decreased metabolism.

- Collectively, our findings suggest that the combinatorial PGx test may provide more clinically relevant information to inform decisions regarding sertraline compared to testing individual genes.