Combinatorial pharmacogenomics in MDD has greatest potential utility for patients taking medications with significant gene-drug interactions

John F. Greden1, Sagar V. Parikh1, James LF, Rachel A. Daut2, and Mark H. Pollack2

1. University of Michigan Comprehensive Depression Center and Department of Psychiatry and National Network of Depression Centers, Ann Arbor, MI
2. Myriad Neuroscience, Mason, OH

BACKGROUND

• Trial-and-error prescribing is a widely employed treatment approach for major depressive disorder (MDD), despite a reduced likelihood of achieving remission following subsequent antidepressant trials.1

• The Genomics Used to Improve DEpression Decisions (GUIDED) trial was a large, randomized controlled trial that evaluated the impact of combinatorial pharmacogenomic testing on outcomes for patients with MDD and an inadequate response to ≥1 psychotropic medication.2

Objective

The present post hoc analysis assessed the relationship between number of prior medication failures at baseline and patient outcomes at week 8 in the GUIDED trial.

METHODS

GUIDED TRIAL2 AND COHORT

• All patients were diagnosed with MDD and had at least one prior failed medication trial.

• Patients were randomized to treatment as usual (TAU) or the combinatorial pharmacogenomic-informed (guided-care) arm.

• All patients received combinatorial pharmacogenomic testing. Test results were only available to clinicians at baseline for those in the guided-care arm. Patients and raters were blinded to study arm. For patients in TAU, clinicians were blinded to test results until after the week 8 visit was completed.

• Week 8 outcomes were assessed using the HAM-D17 rating scale: symptom improvement (% change from baseline), response (≥50% reduction), remission (score of ≤7)

COMBINATORIAL PHARMACOGENOMIC TESTING

• Medications were categorized based on the level of predicted gene-drug interactions (GDI) from a weighted, combinatorial algorithm based on multiple pharmacokinetic and pharmacodynamic genes:
  • ‘use as directed’ (no GDI)
  • ‘use with caution’ (moderate GDI)
  • ‘use with increased caution and with more frequent monitoring’ (significant GDI)

ANALYSIS

• This post hoc analysis included the subgroup of patients who took ≥1 medication subject to significant GDI at baseline according to the number of prior medication failures at baseline.

RESULTS

• Outcomes were significantly improved when patients were switched from taking medications with significant GDI at baseline to medications with no/ moderate GDI by week 8 compared to those who remained on medications with significant GDI.

• The bottom illustrations in Figure 1 show a clear trend in the relationship between number of prior medication failures and response.

Figure 1. Outcomes at week 8 for patients taking ≥1 medication subject to significant GDI at baseline (N=213).

Results are shown according to week 8 medication GDI and the number of prior medication failures at baseline.

SYMPTOM IMPROVEMENT

<table>
<thead>
<tr>
<th>Number of Medication Failures</th>
<th>Medications subject to Significant GDI</th>
<th>Medications subject to No/Moderate GDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=31</td>
<td>N=23</td>
<td>N=34</td>
</tr>
</tbody>
</table>

- Δ=2.72 p=0.754
- Δ=19.91 p=0.026
- Δ=19.82 p=0.010

CONCLUSION

• Patients who had <5 prior medication failures tended to have better outcomes compared to those with ≥5 medication failures, although small subsample sizes may have precluded statistical significance in this post hoc analysis. The results suggest that earlier use of pharmacogenomic testing may improve outcomes in the treatment of depressed individuals.

REFERENCES: