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

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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 TRIAL[2] 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 at baseline for those in the guided-care arm. All patients and raters were blinded to study arm and test results until after week 8.
- 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.

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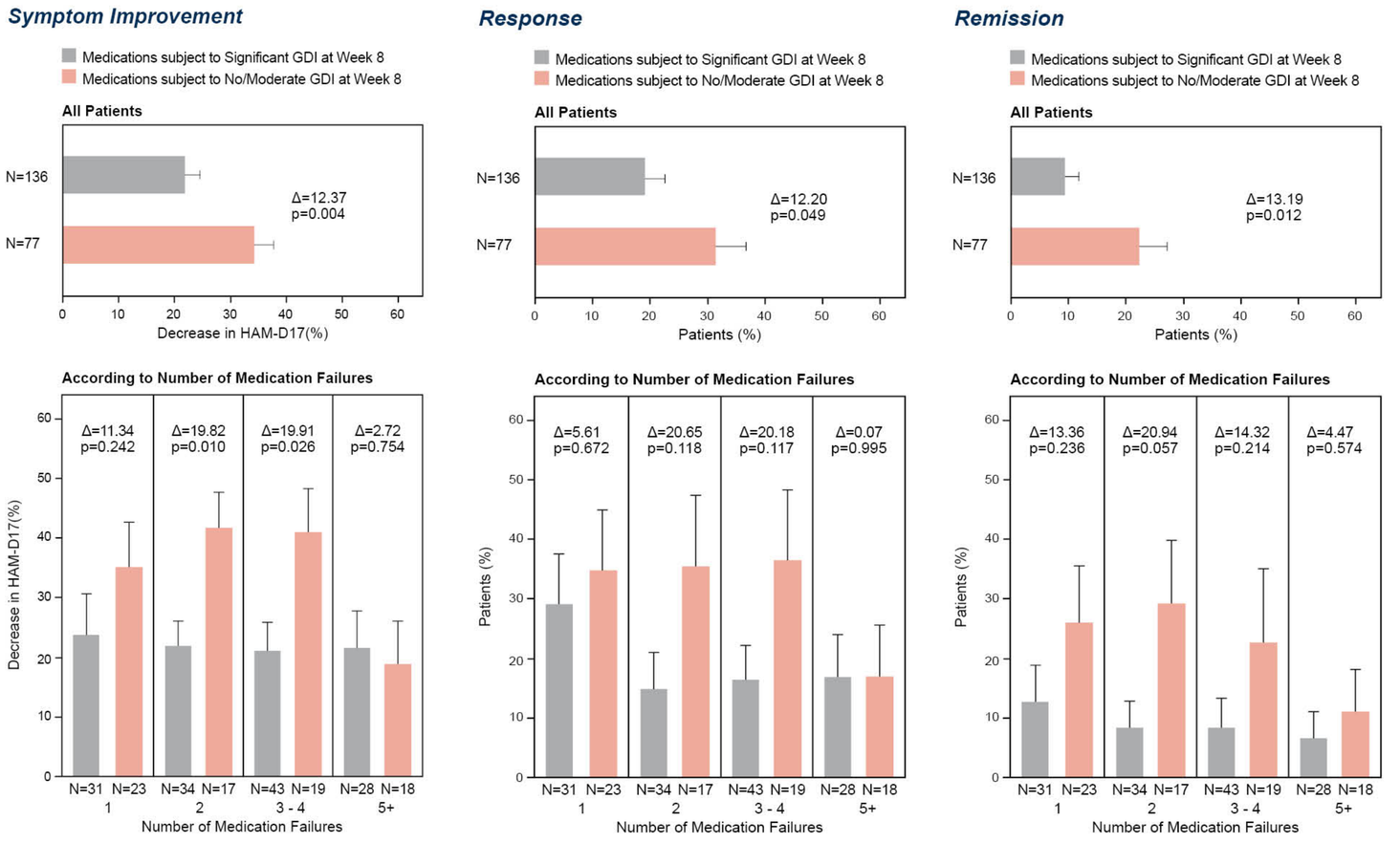
RESULTS

- 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.



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 pharmacogenetic testing may improve outcomes in the treatment of depressed individuals.

REFERENCES:

1. Rush AJ, et al. *Am J Psych.* 2006;163:1905-1917. 2. Greden JF, et al. *J Psych Res.* 2019;111:59-67.

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