Combinatorial Pharmacogenomic Testing Improves Response and Remission for Patients Over 65 with Depression Who Have Failed At Least One Medication Trial

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BACKGROUND

- Geriatric depression affects approximately 5% of older adults (age ≥65 years) in the United States and is associated with longer length of illness, increased number of depressive episodes, a greater risk of comorbidities, and age-related changes in pharmacokinetics (i.e. reduced renal excretion).
- Challenges in medication prescribing include increased polypharmacy/drug-drug interactions, lower adherence, and higher adverse event rates.
- Combinatorial pharmacogenomic (PGx) testing may inform more precise prescribing by identifying adverse gene-drug interactions (GDI).

OBJECTIVES

- We evaluated the utility of a combinatorial PGx test in patients from the **G**enomics **U**sed to **I**mprove **DE**pression **D**ecisions (GUIDED) trial who were ≥65 years of age.

METHODS

COHORT

- The GUIDED trial was a 24-week randomized controlled trial including patients who were diagnosed with major depressive disorder (MDD). Patients were required to have a minimum of 1 prior medication failure, with an average of 3.5 failed medication trials in the cohort.
- All patients received combinatorial PGx testing and were randomized 1:1 to guided-care (test results available to inform medication selection) or treatment as usual (TAU).
- Only guided-care physicians had access to the test report before week 12.
- Patients and outcome assessment scale raters were blinded to study arm through week 8.
- Patients ≥65 years at the screening visit were included for analysis (n=206; 98 for guided-care, 108 for TAU) (Table 1).

COMBINATORIAL PGx TESTING

Significant GDI	Use with increased caution and with more frequent monitoring
Moderate GDI	Use with caution
No GDI	Use as directed

- Combinatorial PGx testing included evaluation of 8 pharmacokinetic and pharmacodynamic genes (*CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, HTR2A, SLC6A4*).
- GDI for each medication were determined based on an algorithmic assessment of individual genotypes.
- Medications were categorized according to the level of predicted GDI.

ANALYSIS

- Patient outcomes were assessed using the 17-item Hamilton Depression Rating Scale (HAM-D17):
  – Symptom Improvement: Percent decrease in HAM-D17 score from baseline
  – Response: ≥50% decrease in HAM-D17 score from baseline
  – Remission: HAM-D17 score ≤7

REFERENCES: **1.** Greden, J. F. *et al. Journal of Psychiatric Research* 111, 59–67 (2019).

RESULTS

Table 1. Baseline Characteristics

Characteristic	TAU (n=108)	Guided-Care (n=98)	Total (N=206)
Age (years)			
Mean (SD)	69.1 (4.3)	69.8 (4.5)	69.4 (4.4)
Sex			
Female, n (%)	79 (73.1)	71 (72.4)	150 (72.8)
Male, n (%)	29 (26.9)	27 (27.6)	56 (27.2)
Failed Medication Trials			
Mean (SD)	3.7 (3.2)	3.3 (2.6)	3.5 (2.9)
HAM-D17 Score			
Mean (SD)	20.2 (4.9)	19.4 (5.1)	19.8 (5.0)

- At week 8, there was an improvement in patient outcomes in the guided-care arm compared to TAU (Figure 1).
  – This was significant for response and remission.
- Outcomes in the guided-care arm showed continued improvement through week 24, indicating durability of the effect (Figure 2).
- By week 8, more than twice as many patients in the guided-care arm had switched to medications predicted by the test to have no gene-drug interactions than in TAU (p < 0.001), indicating that clinicians followed the test report recommendation (Figure 3).
  – Combinatorial PGx-guided medication selection likely drove the significant increases in response and remission rate versus TAU.
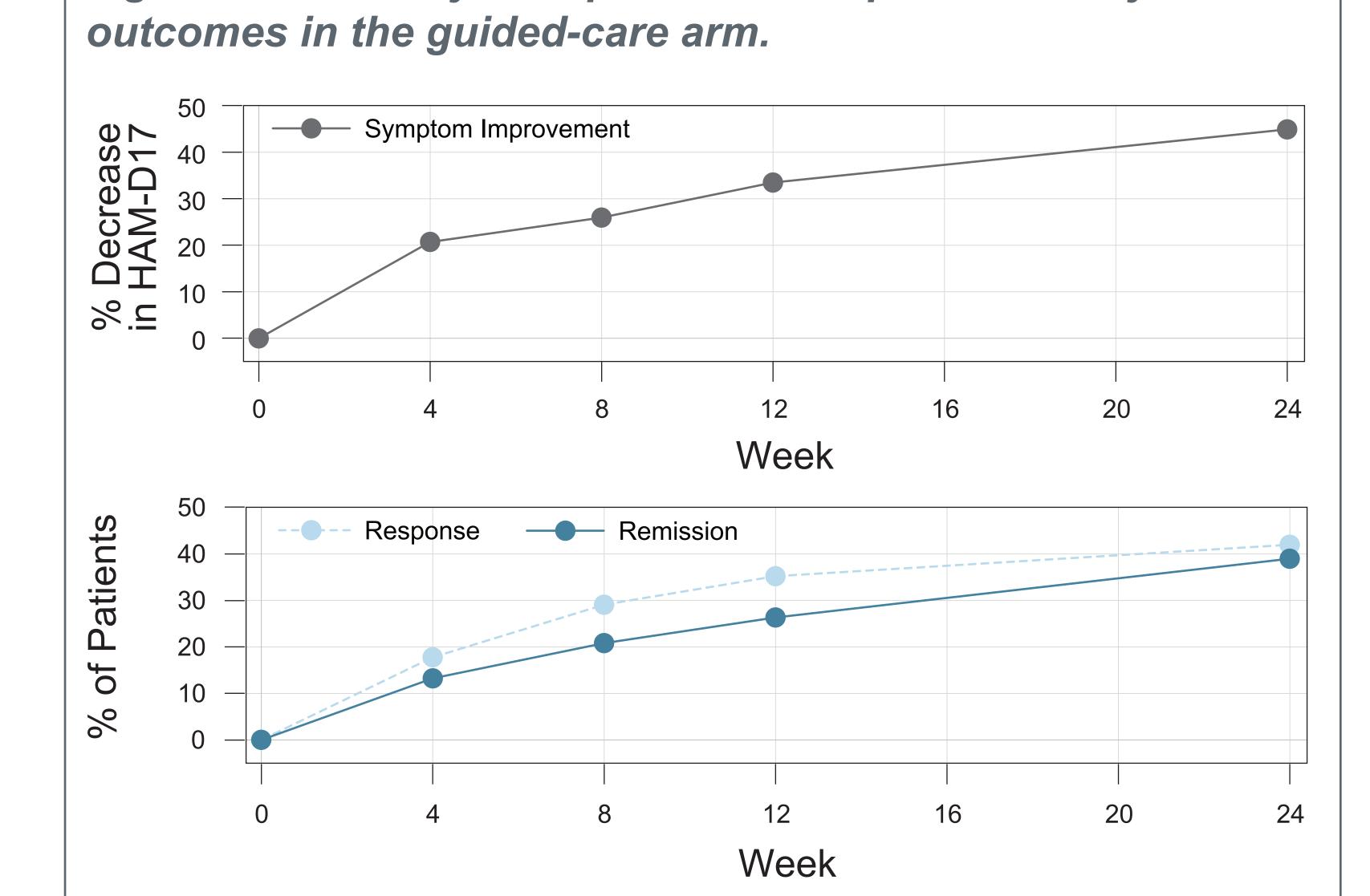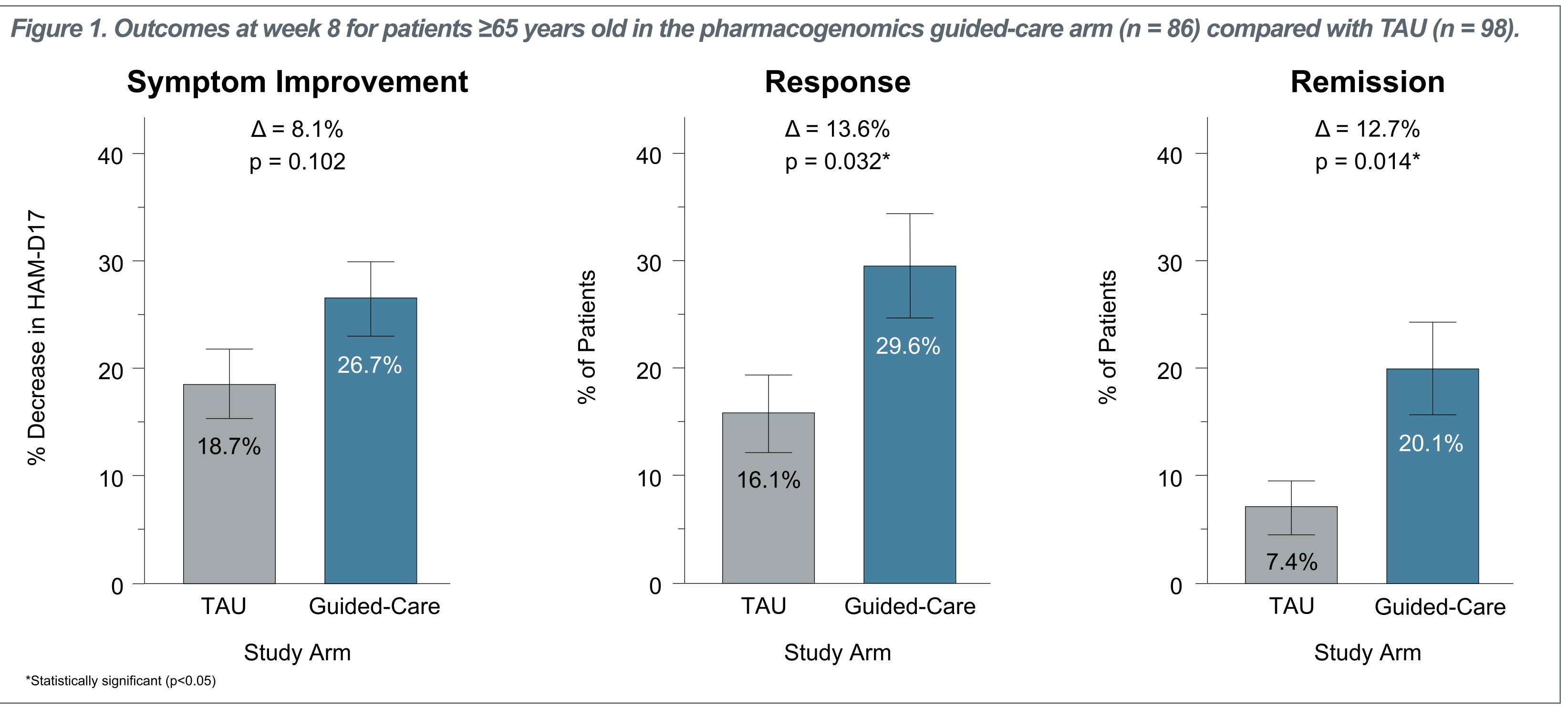
Figure 1. Outcomes at week 8 for patients ≥65 years old in the pharmacogenomics guided-care arm (n = 86) compared with TAU (n = 98).

Symptom Improvement — Δ = 8.1%, p = 0.102; TAU 18.7%, Guided-Care 26.7%
Response — Δ = 13.6%, p = 0.032*; TAU 16.1%, Guided-Care 29.6%
Remission — Δ = 12.7%, p = 0.014*; TAU 7.4%, Guided-Care 20.1%

*Statistically significant (p<0.05)

Figure 2. Durability of improvement in patients ≥65 years old outcomes in the guided-care arm.

Figure 3. Distribution of medication GDI severity category at baseline and at week 8.

TAU — Baseline: No GDI 20.2%, Moderate GDI 52.8%, Significant GDI 27.0%; Week 8: No GDI 25.0%, Moderate GDI 50.0%, Significant GDI 25.0%
Guided-Care — Baseline: No GDI 26.9%, Moderate GDI 52.6%, Significant GDI 20.5%; Week 8: No GDI 59.7%, Moderate GDI 26.0%, Significant GDI 14.3%

GDI, gene-drug interactions; TAU, treatment as usual

CONCLUSIONS

- Combinatorial PGx testing to inform medication selection improved outcomes among older adults with MDD in GUIDED.
- The marked improvements in response and remission rates in the guided-care arm support the clinical utility of the combinatorial PGx test in a population of patients who can be challenging to treat.

Currently under review for publication.