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ABSTRACT

Objective: Evaluate the clinical utility of combinatorial pharmacogenomic testing for informing medication selection among older adults who have experienced antidepressant medication failure for major depressive disorder (MDD). Design: Post hoc analysis of data from a blinded, randomized controlled trial comparing two active treatment arms. Setting: Psychiatry specialty and primary care clinics across 60 U.S. community and academic sites. Participants: Adults age 65 years or older at baseline (n = 206), diagnosed with MDD and inadequate response to at least one medication on the combinatorial pharmacogenomic test report during the current depressive episode. Intervention: Combinatorial pharmacogenomic testing to inform medication selection (guided-care), compared with treatment as usual (TAU). Outcomes: Mean percent symptom improvement, response rate, and remission rateat week 8, measured using the 17-item Hamilton Depression

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Rating Scale; medication switching; and comorbidity moderator analysis. **Results:** *At week 8, symptom improvement was not significantly different for guided-care than for TAU (Δ = 8.1%, t = 1.64, df = 187; p = 0.102); however, guided-care showed significantly improved response (Δ = 13.6%, t = 2.16, df = 187; p = 0.032) and remission (Δ = 12.7%, t = 2.49, df = 189; p = 0.014) relative to TAU. By week 8, more than twice as many patients in guided-care than in TAU were on medications predicted to have no gene-drug interactions ($\chi^2 = 19.3$, df = 2; p <0.001). Outcomes in the guided-care arm showed consistent improvement through the end of the open-design 24-week trial, indicating durability of the effect. Differences in outcomes between arms were not significantly impacted by comorbidities.* **Conclusions:** *Combinatorial pharmacogenomic test-informed medication selection improved outcomes over TAU among older adults with depression.* (Am J Geriatr Psychiatry 2020; 28:933 −945)

OBJECTIVE

Geriatric depression, which affects approximately 5% of older adults (age ≥65 years) in the United States,[1,2] places substantial burdens on function, quality of life, and healthcare resources. In 2017, 2.2% of U.S. men and 3.5% of women age 65 years or older had experienced a major depressive episode in the past year, according to the U.S. Substance Abuse and Mental Health Services Administration.[3] Although major depressive disorder (MDD) episodes are less prevalent in older adults than in younger age groups,[1] up to 15% of community-dwelling people in this age category experience clinically significant depressive symptoms, with higher rates of MDD and depressive symptomatology among those in medical settings.[1] Depression among older adults is linked with longer length of illness, more frequent MDD recurrences, and a greater risk of comorbidities.[4,5] In this population, depression is the psychiatric illness most closely associated with suicide,[6] the rate of which climbed to a high of 17.2 per 100,000 individuals in 2018.[7] A broad range of clinical and social factors adds complexity to its presentation and medical management. Therefore, diagnosis and treatment of geriatric depression warrant special focus.

Decades of investigation into the etiology of geriatric depression have implicated a likely reciprocal relationship among several age-related comorbidities,[8] including cerebrovascular disease,[9] neuroinflammation,[10] and cognitive decline and dementia.[11] These mechanisms underlie a number of coexisting conditions that can both mask and accentuate depressive symptoms, including obesity, diabetes, cardiovascular disease, and sleep disorders.[5] Social, psychological and other environmental factors also contribute meaningfully to geriatric depression; for example, the median prevalence of depression among older adults living in long-term care facilities, estimated at 10%,[12] is higher than that seen in community settings. A diagnosis of geriatric depression thus signifies the culmination of complex causal factors, both biological and environmental, that will differ among individual patients.

Making prescription decisions for older adults is similarly complicated, in large part due to increasing polypharmacy and consequent risk for drug-drug interactions, reduced medication adherence, and a greater risk of adverse events, such as falls, due to coexisting medical conditions.[13] Even so, a very recent comparison of English older-adult cohorts assessed two decades apart (1990−1993 and 2008 −2011) showed that, despite no meaningful change in the age-specific prevalence of depression, antidepressant use has more than doubled.[14] Evidence presented in several meta-analyses indicates that older adults can respond just as well to antidepressant medications as younger age groups.[15−17] Similar to younger populations, however, more than half of older adults do not achieve positive outcomes to first-line therapies of selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors.[18] Reduced antidepressant efficacy also is seen among heterogeneous study populations and individuals with executive dysfunction.[19] Whether a specific

prescribing regimen − augmenting existing medications or switching medications after dose optimization − will produce better outcomes among older adults experiencing treatment-resistant depression remains an open question.[20] As the global geriatric population increases, the need for data-driven tools to optimize prescribing decisions for older adults with treatment-resistant depression grows especially critical.

As with other age groups, combinatorial pharmacogenomic testing holds promise for improving precision medication selection in older patients by identifying medications that have patient-specific gene-drug interactions (GDIs).[21−25] The value of assessing a combinatorial pharmacogenomic approach to prescribing in this population climbs with the risk for adverse medication reactions due to comorbidities and increasing polypharmacy. Several studies have examined the clinical utility of combinatorial pharmacogenomic testing among older adults with MDD.[26−29] However, because combinatorial pharmacogenomic tests use different algorithms to predict GDIs, one cannot apply clinical evidence supporting the utility of one test across the spectrum of available tests. Therefore, each combinatorial pharmacogenomic test requires separate evaluation.[30−32]

The **G**enomics **U**sed to **I**mprove **DE**pression **D**ecisions (GUIDED) randomized controlled trial was the largest study to date to examine the clinical utility of combinatorial pharmacogenomics among adults with MDD.[33] In this trial, response and remission rates improved significantly among patients for whom medication prescribing was informed by combinatorial pharmacogenomic testing. Clinical symptom improvement, the primary outcome, approached but did not achieve statistical significance. In the GUIDED trial, 206 (13%) patients were age 65 years or older. We sought to perform a post hoc evaluation of the clinical utility of combinatorial pharmacogenomics in these older adults with MDD.

METHODS

Combinatorial PharmacogenomicTesting

All patients underwent testing with a combinatorial pharmacogenomic test (GeneSight Psychotropic, Assurex Health, Inc., Mason, OH). The test has been described in detail previously.[34] At the time of the GUIDED trial, the test evaluated genotypes for 59 alleles and variants across eight genes: six pharmacokinetic genes involved in medication metabolism and two pharmacodynamic genes involved in medication response. (The pharmacokinetic genes and alleles were: *CYP1A2*: -3860G>A, -2467T>delT, -739T>G, -729C>T, -163C>A, 125C>G, 558C>A, 2116G>A, 2473G>A, 2499A>T, 3497G>A, 3533G>A, 5090C>T, 5166G>A, 5347C>T; *CYP2C9*: *1, *2, *3, *4, *5, *6; *CYP2C19*: *1, *2, *3, *4, *5, *6, *7, *8, *17; *CYP3A4*: *1, *13, *15A, *22; *CYP2B6*: *1, *4, *6, *9; and *CYP2D6*: *1, *2, *2A, *3, *4, *5 (gene deletion), *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41, gene duplication. The pharmacodynamic genes and alleles were: *HTR2A*: -1438 G >A; and *SLC6A4*: L, S.) The genotype for each variant or allele was factored into a weighted algorithmic assessment for each individual medication. The assessment included all tested genes implicated in pharmacokinetic and/or pharmacodynamic processes for the medication and resulted in a combined phenotype that accounted for the collective effect of alterations in all relevant genes. These combined phenotypes were applied to categorize 38 psychotropic medications in the patient report, based on the predicted level of GDIs: "use as directed" (no GDIs); "use with caution" (moderate GDIs); and "use with increased caution and with more frequent monitoring" (significant GDIs).[35]

Study Description

This was a post hoc, subgroup analysis of older-adult patients (at least 65 years of age at baseline) enrolled in the GUIDED trial, evaluating the same endpoints as did the original trial. The detailed trial design and primary analysis were published previously;[33] here, we summarize methods relevant to the current analysis. The GUIDED trial was a 24-week, patient- and rater-blinded, randomized controlled trial that evaluated the utility of combinatorial pharmacogenomic testing in guiding medication selection (guided-care) compared with treatment as usual (TAU) for adults with MDD who had at least one prior medication failure. The trial took place in primary care and psychiatry specialty clinics across 60 community and academic sites in the United States. We conducted the trial in accordance with the

principles of the Declaration of Helsinki and its amendments and with approval from the Copernicus Group independent review board (INC1-14-012). All patients provided written informed consent for participation.

Before the baseline visit, patients were randomized 1:1 to the guided-care or TAU arm. Unlike conventional pharmaceutical trials, patients in both study arms received active treatment, which was defined as standard care determined by the treating clinician. Adherence to the test results was not mandated, and no medications were prohibited. Combinatorial pharmacogenomic testing was conducted for all patients prior to the baseline visit; clinicians had access to the report at the baseline visit for patients in the guided-care arm. Medication selection was based on clinician judgment, either with (guided-care) or without (TAU) access to the combinatorial pharmacogenomic test report. All medications were FDA approved.

Patients and raters in both arms were blinded to study arm and test results. Assessments were performed at baseline and at week 4, week 8, week 12, and week 24. Clinicians for patients in the TAU arm were blinded to test results. All blinding was maintained through week 8. Sites were instructed to unblind after week 12 assessments, though unblinding may have occurred before assessments were performed. As a result, only data collected through week 8 were considered blinded.

Participants

Enrollment inclusion criteria were: diagnosis with DSM-IV-TR-defined MDD, confirmed by both the self-rated and the site-rated 16-item Quick Inventory of Depression Symptomology (QIDS-SR16 and QIDS-C16 scores ≥11 for diagnosis)[36] at screening and at baseline; and patient-reported inadequate response to at least one medication included on the combinatorial pharmacogenomic test report during the current depressive episode. Key exclusion criteria were significant short-term suicide risk; bipolar disorder; current delirium or neurocognitive disorder; psychotic disorder or psychotic symptoms during the current or a previous depressive episode; a current substance use disorder; or a significant unstable medical condition. All participants were taking at least one medication at baseline.

Statistical Analysis

We performed the analyses described herein with patients in the GUIDED Intent-to-Treat (ITT) cohort who were 65 years of age or older at baseline. The ITT cohort included patients who met eligibility criteria, were randomized to a study arm, and attended at least one post-baseline visit.

The protocol-defined primary efficacy measure was the 17-item Hamilton Depression Scale (HAM-D17),[37,38] administered by blinded central raters (MedAvante-ProPhase Inc., Hamilton, NJ). Patient outcomes were evaluated at week 8 relative to baseline and included *symptom improvement* (percent change in HAM-D17), *response* (≥50% decrease in HAM-D17) and *remission* (HAM-D17 ≤7).[39] We evaluated the durability of combinatorial pharmacogenomic testing utility in the guided-care arm through week 24.

We applied a mixed model for repeated measures (MMRM) to assess percent change in symptoms from baseline to week 8. For separate analyses of response and remission at week 8, we used a generalized linear mixed model. Both models included treatment, week, treatment-by-week interaction, baseline HAM-D17 score, and baseline HAM-D17 score-by-week interaction as fixed effects. An unstructured covariance structure was used to model the within-subject errors. We tested the pairwise comparisons between the two treatment arms at week 8 using a significance level of 0.05 (two-sided). Missing values were handled using the maximum likelihood method via mixed models for repeated measures for both symptom improvement and via generalized linear mixed model for the categorical variables of response and remission. We used a chi-square test to analyze whether the distribution of medication GDI severity category differed between the two study arms. Site type (academic or community), age, gender, and race (white/non-white) were added to the MMRM model as a secondary analysis.

To evaluate whether psychiatric and medical comorbidities impacted treatment outcomes, we conducted a moderator analysis, evaluating separately the total number of psychiatric and other medical comorbidities, number of cardiovascular comorbidities, and severity of comorbidities. Cardiovascular comorbidities included myocardial infarction, congestive heart failure, peripheral vascular disease, heart

disease, angina, and other cardiovascular comorbidities. The severity of comorbidities was assessed using the Charlson Comorbidity Index (CCI).[40] The severity of comorbid diseases was grouped into three categories: Mild, CCI score 1-2; Moderate, CCI score 3-4; and Severe, CCI score 5-6. Response variables included symptom improvement from baseline, response rate, and remission rate at week 8. We used the analysis of covariance method to analyze symptom improvement and a logistic regression model to analyze response and remission. The explanatory variables for both models included treatment arm, baseline HAM-D17, the variable of interest, and treatment arm-by-variable of interest. Moderator analysis for concomitant medications included number of concomitant medications, treatment, treatment-by-number of concomitant medications, and baseline HAM-D17 score.

To assess the durability of the treatment effect in the guided-care arm, we used a simple paired t test from week 8 to week 24. Because the TAU arm was unblinded after week 8 with both treating physicians and patients having access to the pharmacogenomic test reports, durability could not be evaluated for TAU through week 24.

All analyses were performed using SAS software (version 9.4) or JMP 14 (SAS Institute).

RESULTS

Cohort Description

At baseline, the ITT cohort included 206 older-adult patients (TAU, n = 108; guided-care, n = 98) (Supplementary Figure 1). Table 1 shows baseline clinical characteristics of the cohort. In both study arms, the median age was 68 years. The mean baseline HAM-D17 score, 19.8 (SD: 5.0) (severe depression), was roughly equivalent between the study arms, with approximately one-third of patients falling into each of the moderate, severe, and very severe depression categories. On average, patients across both arms had experienced three or more failed medication trials. The characteristics of comorbidities at baseline, including total number of comorbidities, number of cardiovascular comorbidities, and severity of comorbidities, also were similar between arms.

Outcomes

A total of 184 older-adult patients completed the trial through week 8 (TAU, n = 98; guided-care, n = 86). At week 8, we observed a 26.7% decrease in HAM-D17 scores in the guided-care arm, compared with an 18.7% decrease in the TAU arm (Fig. 1). This difference in mean percent symptom improvement between arms did not reach statistical significance ($\Delta = 8.1\%$, t = 1.64, df= 187; p = 0.102). The response rate at week 8 among patients in the guided-care arm (29.6%) was significantly higher than that observed in the TAU arm (16.1%) ($\Delta = 13.6\%$, t = 2.16, df=187; p = 0.032). Remission rates at week 8 also significantly favored combinatorial pharmacogenomics-guided care (20.1%) over TAU (7.4%) ($\Delta = 12.7\%$, t = 2.49, df= 189; p = 0.014). We observed no significant differences in symptom improvement, response, or remission outcomes between academic and community sites (Supplementary Table 1). The frequency of adverse drug events was 10.2% (SE = 3.1%) in TAU and 7.0% (SE = 2.7%) in guided-care; the difference between arms was not significant ($\chi^2 = 0.609$, df = 1; p = 0.435) (Supplementary Table 2).

To help understand the differences in outcomes between TAU and guided-care, we evaluated the continuous distribution of percent change in HAM-D17 scores from baseline to week 8 (Fig. 2). The distribution of TAU shows a generally homogeneous population, with some individuals showing modest change in in HAM-D17 score, and some showing a larger change. The distribution of changes in the guided-care arm relative to TAU showed that some patients experienced much larger improvements in HAM-D17 relative to TAU, and overall, more patients in the guided-care arm achieved clinical response ($\geq 50\%$ decrease in HAM-D17).

Predicted GDIs

We examined the distribution of predicted GDIs for medications at baseline and week 8. This assessment included patients who at baseline were taking at least one medication included on the combinatorial pharmacogenomic test report (Fig. 3). The analysis compared the medication distribution between the TAU and guided-care study arms both at baseline and at week 8. At baseline, the distribution across GDI categories did not differ significantly between

TABLE 1. Baseline Characteristics for Older-Adult Patients in the GUIDED Trial Intent-To-Treat Cohort

Characteristic	Treatment Arm		
	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)
Median	68.0	68.0	68.0
Min, Max	65, 85	65, 90	65, 90
Sex, n (%)			
Female	79 (73.1)	71 (72.4)	150 (72.8)
Male	29 (26.9)	27 (27.6)	56 (27.2)
Ethnicity, n (%)			
Hispanic or Latino	4 (3.7)	4 (4.1)	8 (3.9)
Not Hispanic or Latino	104 (96.3)	94 (95.9)	198 (96.1)
Race, n (%)			
White	99 (91.7)	89 (90.8)	188 (91.3)
Black	8 (7.4)	8 (8.2)	16 (7.8)
Asian	0	1 (1.0)	1 (0.5)
Other or Multiple	1 (0.9)	0	1 (0.5)
Depression category, n (%)			
None (HAM-D17 0-7)	0	1 (1.0)	1 (0.5)
Mild (HAM-D17 8-13)	7 (6.5)	11 (11.2)	18 (8.7)
Moderate (HAM-D17 14-18)	33 (30.6)	33 (33.7)	66 (32.0)
Severe (HAM-D17 19-22)	37 (34.3)	23 (23.5)	60 (29.1)
Very Severe (HAM-D17 ≥ 23)	31 (28.7)	30 (30.6)	61 (29.6)
Psychiatric comorbidities, n (%)			
Generalized anxiety disorder	15 (13.9)	19 (19.4)	34 (16.5)
Panic disorders/Social phobia	7 (6.5)	12 (12.2)	19 (9.2)
Post-traumatic stress disorder	3 (2.8)	5 (5.1)	8 (3.9)
Comorbidities			
Mean (SD)	10.2 (6.9)	10.0 (6.7)	10.1 (6.8)
Median	9.0	9.0	9.0
Min, Max	0.0, 45.0	1.0, 47.0	0.0, 47.0
Cardiovascular comorbidities			
Mean (SD)	0.2 (0.5)	0.2 (0.5)	0.2 (0.5)
Median	0.0	0.0	0.0
Min, Max	0.0, 3.0	0.0, 2.0	0.0, 3.0
Severity of comorbidities			
Mean (SD)	0.7 (1.0)	0.7 (1.0)	0.70 (1.0)
Median	0.0	0.0	0.0
Min, Max	0.0, 4.0	0.0, 4.0	0.0, 4.0
HAM-D17 score			
Mean (SD)	20.2 (4.9)	19.4 (5.1)	19.8 (5.0)
Median	20.0	19.0	19.5
Min, Max	8.0, 32.0	7.0, 29.0	7.0, 32.0
Failed medication trials			
Mean (SD)	3.7 (3.2)	3.3 (2.6)	3.5 (2.9)
Median	3.0	3.0	3.0
Min, Max	1.0, 23.0	1.0, 14.0	1.0, 23.0

Notes: HAM-D17: 17-item Hamilton Depression Rating Scale; SD: standard deviation; TAU: treatment as usual.

arms ($\chi^2 = 1.5$, df = 2; p = 0.467). By week 8, however, this distribution had shifted significantly toward selection of medications with no predicted GDIs in the guided-care arm ($\chi^2 = 19.3$, df = 2; p <0.001) relative to TAU, indicating that clinicians in the guided-care arm had followed the recommendation of the combinatorial pharmacogenomic test report in medication selection. This also helps to explain why the guided-care arm showed significantly improved outcomes.
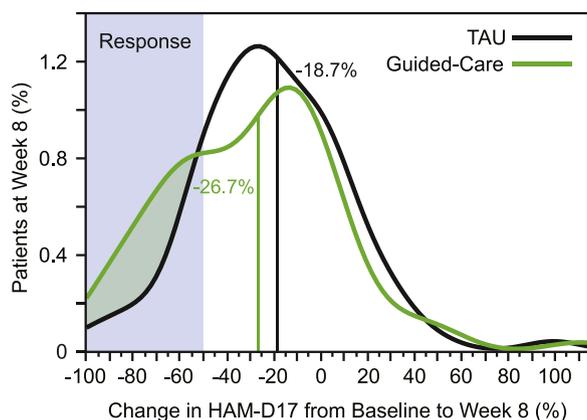
Moderation by Comorbidities and Concomitant Medications

Co-existing medical conditions and depressive symptoms/MDD can influence each other reciprocally

FIGURE 1. Patient outcomes at week 8 for older-adult patients in the pharmacogenomics-guided care arm (n = 86) compared with treatment as usual (TAU) (n = 98). Outcomes were evaluated using the 17-item Hamilton Depression Rating Scale (HAM-D17). Error bars represent standard errors (SE), as follows. For symptom improvement, TAU, SE: 3.4%; guided-care, SE: 3.6%. For response, TAU, SE: 3.7%; guided-care, SE: 5.0%. For remission, TAU, SE: 2.6%; guided-care, SE: 4.4%.
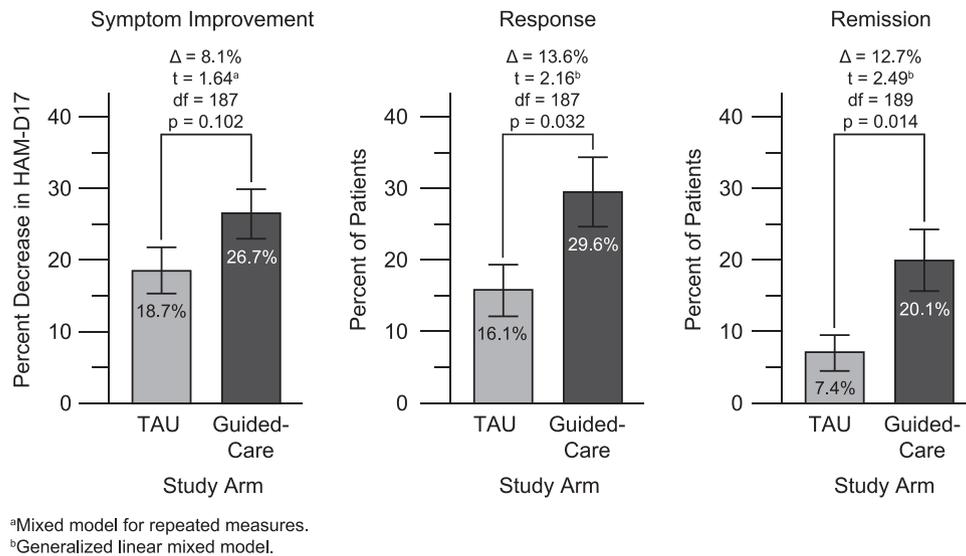
FIGURE 2. Distribution of symptom improvement at week 8 for older-adult patients in the pharmacogenomics guided care arm (n = 86) compared with treatment as usual (TAU) (n = 98). Outcomes were evaluated using the 17-item Hamilton Depression Rating Scale (HAM-D17). Mean percent change in HAM-D17 score from baseline (week 8 minus baseline) for the guided-care arm and TAU are noted by the vertical black and gray lines, respectively. The vertical shaded area indicates response, defined as ≥50% decrease in HAM-D17 score from baseline. The shaded area between curves shows the difference in response rate between TAU and guided-care.

in the older-adult population. Therefore, we performed a moderator analysis to assess the potential influence of comorbidities and concomitant medications on symptom improvement, response, and remission outcomes. Evaluation of four variables — all comorbidities, the subset of cardiovascular comorbidities, the severity of comorbidities, and concomitant medications — revealed no significant moderation factors (Table 2), indicating that the treatment effect in the guided-care arm was independent of these variables.

Durability of Combinatorial Pharmacogenomics-Guided Care Utility

To evaluate the durability of combinatorial pharmacogenomics-guided treatment results, we evaluated HAM-D17 scores in the guided-care arm at time points extending through the end of the 24-week trial. A total of 80 older-adult patients completed the trial in the guided-care arm. Figure 4 shows outcomes at weeks 4, 8, 12, and 24. Patients in the guided-care arm showed consistent increases in percent symptom improvement, response rate, and remission rate at

FIGURE 3. Distribution of medication gene-drug interaction (GDI) severity category at baseline and at week 8 for older-adult patients in the pharmacogenomics guided-care arm (n = 86) compared with treatment as usual (TAU) (n = 98). For patients taking more than one medication on the combinatorial pharmacogenomic test report, the most severe GDI category is shown. A chi-square test was used to analyze whether the distribution of medication GDI severity category differed between the two study arms. p-values were calculated for the comparisons of TAU versus guided-care at baseline ($\chi^2 = 1.5$, df = 2; p = 0.467) and TAU versus guided-care at week 8 ($\chi^2 = 19.3$, df = 2; p < 0.001).
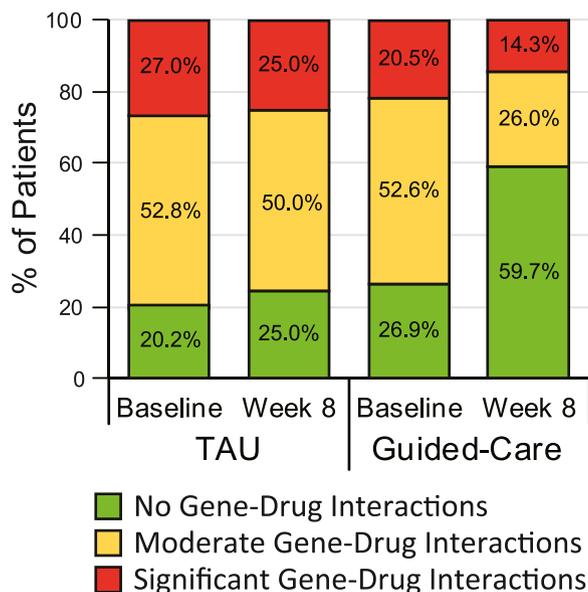
each time point. Symptom improvement from week 8 to week 24 was highly significant ($\Delta = 17.6\%$, t = 4.0, df = 83; p < 0.001; 95% CI: 8.8%-26.4%). HAM-D17 scores decreased by 43.9% (SE: 3.9%) between baseline and week 24. Additionally, 42.2% (SE: 5.6%) of patients experienced response and 39.6% (SE: 5.5%) of patients experienced remission at week 24. These represent a 43% increase in the response rate and a 97% increase in the remission rate from week 8.

We also examined outcomes through the end of week 24 for patients who were randomized to the TAU arm (Fig. 4). From week 4 to week 8 during the blinded period, this study arm showed little to no improvement across all three outcomes. Unblinding occurred after week 8 for both TAU and guided-care, at which point the trial became open-label. After unblinding, comparison between arms is not valid, as providers for patients randomized to TAU were given access to the combinatorial pharmacogenomic test report and patients were unblinded to study arm. Once unblinding occurred and providers for patients randomized to TAU had test report information, however, improvement was seen across all three outcomes through the week 24 time point.

CONCLUSIONS

Due to its complex etiology and the high prevalence of medical, neurological and psychiatric co-morbidities, geriatric depression often proves difficult to treat

TABLE 2. Moderator Analysis Evaluating the Influence of Comorbidities and Concomitant Medications on Depression Outcomes for Older-Adult Patients in the GUIDED Trial Intent-To-Treat Cohort. Outcomes were evaluated using the 17-item Hamilton Depression Rating Scale (HAM-D17). The moderator effect reflects the result of testing a null hypothesis stating that the variable's effect is consistent across the treatment-as-usual and guided-care study arms. The main effect denotes the direct effect of the variable upon outcomes of symptom improvement, response and remission.

	Moderator Effect			Main Effect			
Variable	Symptom Improvement (F, p-value)[a]	Response (F, p-value)[b]	Remission (F, p-value)[b]	Symptom Improvement (F, p-value)[a]	Response (F, p-value)[b]	Remission (F, p-value)[b]	df for All (Numerator, denominator)
Number of all comorbidities	1.26 0.264	1.91 0.169	0.55 0.460	0.35 0.552	1.99 0.160	1.55 0.214	1, 179
Number of cardiovascular comorbidities	0.36 0.549	0.56 0.456	0.00 0.978	0.67 0.414	0.00 0.982	0.40 0.527	1, 179
Severity of comorbidities[c]	0.04 0.838	0.11 0.740	0.89 0.348	1.19 0.277	0.08 0.771	0.00 0.990	1, 179
Number of concomitant medications	0.41 0.524	0.69 0.406	0.20 0.654	0.32 0.571	0.30 0.585	0.01 0.940	1, 178

[a] Analysis of covariance.
[b] Logistic regression.
[c] Severity was assessed using the Charlson Comorbidity Index.

FIGURE 4. Older-adult patient outcomes through Week 24. [A] Percent symptom improvement, [B] response rate, and [C] remission rate were evaluated for both study arms using the 17-item Hamilton Depression Rating Scale (HAM-D17). Outcomes were measured at week 4 (TAU n = 104; guided-care n = 91), week 8, (TAU n = 98; guided-care n = 86), week 12 (TAU crossover to guided-care open-label n = 88; guided-care crossover to guided-care open-label n = 81), and week 24 (TAU crossover to guided-care open-label n = 71; guided-care crossover to guided-care open-label n = 80). All blinding was maintained through week 8. Both study arms were unblinded after week 8, at which point the trial became open-label, and providers were given access to combinatorial pharmacogenomic test results for patients who were randomized to TAU. Changes in outcomes after week 8 reflect unblinding to study arm and integration of pharmacogenomic test results for patients who were randomized to both TAU and to guided-care. Therefore, comparison of study arms is not appropriate after week 8.
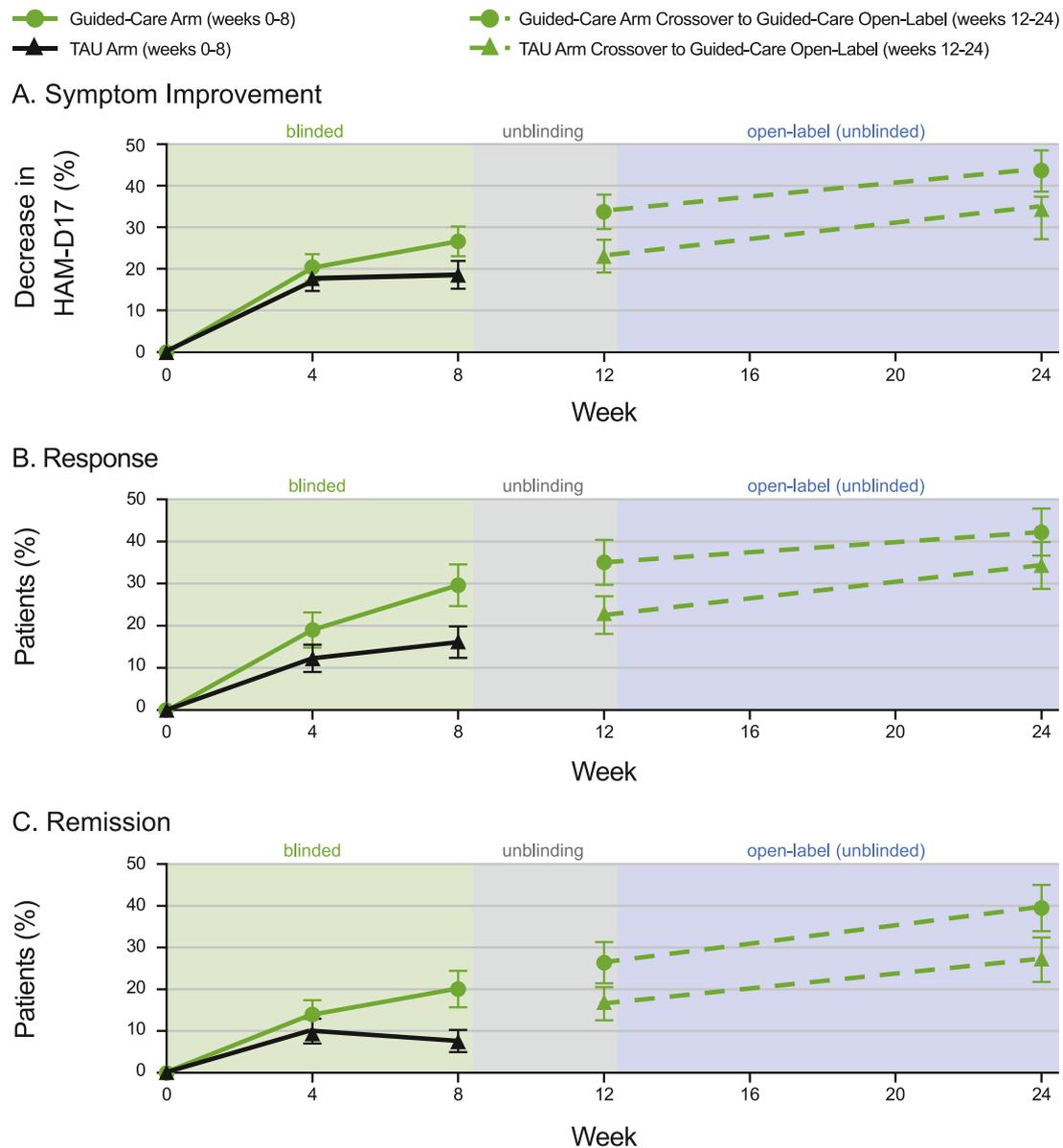
and achieving response and remission can be challenging. Our analysis explored the clinical utility of combinatorial pharmacogenomic testing to aid in medication selection for older adults who suffer with MDD.

Response (Δ = 13.6%) and remission (Δ = 12.7%) rates at week 8 emerged significantly higher in patients who received combinatorial pharmacogenomics-guided care when compared with TAU. As was seen in the all-

adult age GUIDED primary analysis cohort,[33] symptom improvement did not differ significantly between arms in older adults, although we observed a positive trend toward improvement with a magnitude greater than twice as large as seen in the full cohort (8.1% versus 3.2%).

These results are consistent with those seen in the all-adult age GUIDED primary analysis cohort; however, the enhanced difference between week 8 response and remission rates in the guided-care arm relative to TAU in the older-adult subset is particularly noteworthy. The significant shift toward selection of medications with no predicted GDIs in the guided-care arm at week 8 is evidence that these improved outcomes are driven, at least in part, by combinatorial pharmacogenomic test results. Baseline comorbidities, which in this older-adult population might be particularly likely to influence depression outcomes, appeared to have no significant effect. Altogether, the marked improvements in response and remission rates in the guided-care arm represent meaningful change, supporting the clinical utility of the combinatorial pharmacogenomic test among a population of patients who can be challenging to treat.

The lack of statistically significant symptom improvement among older-adult patients may result in part from the fact that there appeared to be no difference between the two arms in the percent of subjects who did not improve by week 8 (Fig. 2). The effect of the shift toward more pronounced gains and increased response appears to be somewhat offset by patients in the same arm who experienced more modest symptom improvement. This distribution shifted the mean toward moderate improvement and may explain why a much higher proportion of patients in the guided-care arm experienced response and remission compared with TAU. Reaching statistical significance in this relatively small cohort subset raises the possibility that the influence of combinatorial pharmacogenomics-guided prescribing on response and remission might be increased in this older-adult population relative to the full trial cohort.

Finally, percent symptom improvement, response rate, and remission rate in the guided-care arm showed sustained increase through the end of the 24-week trial among older-adult patients. The nearly 40% (SE: 5.5%) remission rate among older adults in the guided-care study arm is substantially increased relative to the 31.1% (SE: 2.1%) remission rate in the full, all-age GUIDED trial cohort.[33] It is possible that some physicians shared the reports with their patients after unblinding, and positive outcomes in patients who were engaged in their test results might have contributed to durability of the effect through week 24. This observation suggests the potential for longer-term durability in improved outcomes among older-adult patients who receive medications selected with the aid of combinatorial pharmacogenomic testing.

Geriatric depression is clinically heterogeneous, with a diverse range of underlying factors. Such heterogeneity may complicate interpretation of combinatorial pharmacogenomic results for older adult patients. Indeed, the low rate of remission observed in the TAU arm signifies an even greater challenge in treating geriatric depression, compared with treating MDD across the broader adult population. Increased polypharmacy in older adults may limit options for clinicians when prescribing psychotropic drug therapies,[21] due to the greater risk for adverse drug-drug interactions or other adverse clinical outcomes. Any age-related decline in pharmacokinetic system functions might increase the phenotypic variability of genotypes measured by the combinatorial pharmacogenomic test.[41] Our results indicate that, despite these challenges, combinatorial pharmacogenomic testing can markedly improve MDD outcomes in older adults.

A strength of this analysis is that it is the first of its kind, evaluating the prospective clinical utility of combinatorial pharmacogenomic testing in geriatric depression. In addition, the study design, comparing two active treatment arms, reflects a real-world scenario and thus provides more robust demonstration of the efficacy of combinatorial pharmacogenomic testing.

Limitations inherent to the primary GUIDED trial analysis also apply to this study.[33] Limitations specific to this post hoc analysis include the relatively smaller size of the older-adult subset of the GUIDED trial cohort. This reduced the power of some potential analyses, including evaluation of adverse drug events. Second, the older-adult subset also showed reduced ethnic diversity compared with the full GUIDED trial cohort. Third, several variables important in understanding geriatric depression, including polypharmacy, cognitive status, and comorbidities at time points other than baseline, were not included in the primary GUIDED study design; certainly, GDIs represent only one component of the information that

should be considered when making prescribing decisions. Although we cannot directly assess, we have no reason to suspect that the nonpharmacogenomic clinical information considered by physicians differed between the study arms. Incorporating factors other than GDIs, such as drug-drug interactions and smoking, into the test's combinatorial algorithm might produce even greater benefit, though additional clinical testing of that hypothesis would be required. Finally, although the standard clinical trial duration for U.S. Food and Drug Administration approval of depression medications is eight weeks, it can take longer to see clinical benefit in older adults. As a result, the patient outcomes at week 8 may underestimate the true benefit of pharmacogenomic testing in this older population. Although here we present outcomes data through week 24 for all older-adult patients, we emphasize the caveats of overinterpretation. The original GUIDED study was not designed to assess long-term improvement with rigorous controls. New studies in the field should evaluate such perspectives with adequate controls, since sustained remission is the ultimate aim. Future work also should evaluate pharmacogenomic testing in the context of different care settings, that is, psychiatry versus primary care and academic versus community practice.

To conclude, the improvements in clinical outcomes in this analysis support the utility of combinatorial pharmacogenomic testing in personalized medication selection for geriatric depression. As such, it holds promise as a tool to help achieve greater success in caring for older adults who have depression and who have experienced previous medication failure.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jagp.2020.05.005.

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