Pharmacogenomic Testing to Inform Prescribing in Patients with Behavioral and Psychiatric Symptoms of Dementia (BPSD): Results from Two Small, Randomized, Controlled Trials

Julie-Anne Tanner, PhD[1]; Rachel Daut, PhD[1]; Kunbo Yu, MS[1]; James Li, MS[1]; Lindsey Burns, MBA[2]; Krystal Brown, PhD[2]; Mark Pollack, MD[1]; David S. Geldmacher, MD[3]; Giovanna Pilonieta, DDS MPH[3]; Allan Anderson, MD[4]

1. Myriad Neuroscience 2. Myriad Genetics, Inc. 3. University of Alabama at Birmingham 4. Banner Health

INTRODUCTION & OBJECTIVES

- Although antidepressants and atypical antipsychotics are often used for behavioral and psychiatric symptoms of dementia (BPSD), their limited efficacy and significant toxicity has lead to initiatives to reduce their use in this setting (Kormelinck G, et al. *BMC Psychiatry.* 2019:19;298).
- Here we present data from two small, randomized, controlled trials (RCTs) designed to test the hypothesis that combinatorial pharmacogenomic testing could aid in treatment selection for BPSD.

TRIAL DESIGN & METHODS

Inpatient RCT	Outpatient RCT
Population: Residents being treated at the Bayleigh Chase retirement community in Maryland.	**Population:** Patients from the University of Alabama at Birmingham Memory Disorders Clinic.
Eligibility: Patients were eligible if they 1) had a diagnosis of dementia with psychotic symptoms and/or behavioral disturbance and 2) their condition was severe enough to trigger a consultation with a physician. Informed consent was obtained at the screening visit from patients' legally authorized representatives.	**Eligibility:** Patients were eligible if they 1) scored <24 on the Montreal Cognitive Assessment (MoCa) or <26 on the Alabama Brief Cognitive (ABC) screen, 2) scored ≥9 on the Functional Activities Questionnaire (FAQ), and 3) their physician was considering starting/changing a psychotropic medication. Patients were also required to have a caregiver who spends at least 10 hours a week with them. Informed consent was obtained at the screening visit from patients' legally authorized representatives.
Enrollment: N=12 (target 50 patients; stopped early due to slow enrollment)	**Enrollment:** N=38 (target 100 patients; stopped early due to slow enrollment)
Randomization and Blinding: Patients were randomized 1:1 to treatment as usual (TAU) or the combinatorial pharmacogenomic-guided care arm. For patients in the guided-care arm, physicians had access to the pharmacogenomic test report at the time of the baseline visit. Physicians were blinded to the test report until after the trial for patients in the TAU arm.	
Pharmacogenomic Testing: All patients received combinatorial pharmacogenomic testing [GeneSight, Assurex Health (now Myriad Neuroscience)]. Variants in multiple pharmacokinetic and pharmacodynamic genes were assessed and a weighted combinatorial algorithm categorized medications according to the level of predicted gene-drug interactions (GDI).	
Study Assessments: Assessments were performed at baseline and weeks 2 (AEs only), 8, and 12. The primary outcome was the Nursing Home version of the Neuropsychiatric Inventory (NPI-NH), which assesses the presence and severity of BPSD across 12 domains. Side effects were evaluated using the SA-EPS and MOSES scales.	**Study Assessments:** Assessments were performed at baseline and weeks 4, 8, and 12. The primary outcome was the Neuropsychiatric Inventory questionnaire (NPI-Q), which assesses the presence and severity of BPSD across 12 domains. Side effects were evaluated using the FIBSER scale.

- A Mixed Model for Repeated Measures (MMRM) was used to evaluate the change in NPI from baseline to follow-up and included treatment, week, treatment-by-week interaction, baseline score, baseline score-by-week interaction as fixed effects.
- Changes in prescribing relative to a pre-test intended medication plan were evaluated in the outpatient RCT.

Presented at AAGP on March 15-19, 2021

RESULTS

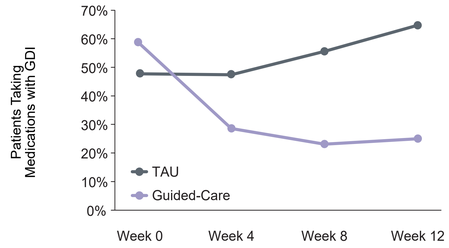
Table 1. Patient outcomes at week 12 according to treatment arm.

Measure*	Inpatient RCT			Outpatient RCT		
	TAU (N=4)	Guided-Care (N=7)	p-value	TAU (N=18)	Guided-Care (N=9)	p-value
Change in Mean NPI**	-2.1	-15.2	0.4239	-0.04	-0.51	0.5696
Subjects with AEs†	100%	85.7%	0.9688	16.7%	11.1%	1.0
Subjects with Delusion	25.0%	42.9%	0.5724	24.5%	23.6%	0.9672
Subjects with Hallucinations	0.0%	28.6%	0.9662	50.4%	45.7%	0.8243
Subjects with Agitation	100%	100%	1.0000	72.2%	76.2%	0.8495
Subjects with Depression	50.0%	14.3%	0.2545	80.5%	31.3%	0.0479
Subjects with Anxiety	50.0%	28.6%	0.5000	78.5%	82.6%	0.8165
Subjects with Elation	0.0%	0.0%	1.0000	16.7%	11.1%	1.0000
Subjects with Apathy	50.0%	57.1%	0.8243	83.6%	44.4%	0.0761
Subjects with Disinhibition	25.0%	57.1%	0.3428	45.2%	50.9%	0.8065
Subjects with Irritability	75.0%	71.4%	0.9011	78.6%	85.9%	0.6564
Subjects with Aberrant Motor	50.0%	28.6%	0.5000	55.4%	30.2%	0.3105
Subjects with Nighttime Behavior	25.0%	71.4%	0.1913	77.8%	77.8%	1.0000
Subjects with Appetite	0.0%	14.3%	0.9688	56.1%	68.4%	0.5796

*The percent of patients with a condition (i.e. depression) at week 12 was evaluated as a score >0 for the relevant domain on the NPI.
**Change in NPI from baseline to week 12. The score range varied between the NPI-NH (0-120; inpatient RCT) and NPI-Q (0-12; outpatient RCT).
† The percent of patients with AEs at week 12 was evaluated using different scales in the inpatient (SA-EPS and MOSES) and outpatient (FIBSER) RCTs.

At week 12, there were no significant differences in NPI or side effects between the guided-care arm and TAU in either RCT. However, the proportion of outpatients experiencing depression at week 12 was significantly lower in the guided-care arm versus TAU.

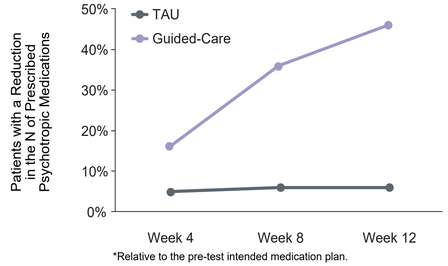
Figure 1. Prescription frequency of medications subject to gene-drug interactions in outpatient RCT.



In the outpatient RCT, the proportion of patients prescribed at least one medication subject to GDI decreased from 58.8% (pre-test) to 25.0% (week 12) in the guided-care arm.

In contrast, there was an increase in the proportion of patients in TAU taking medications subject to GDI throughout the trial.

Figure 2. Polypharmacy reduction in outpatient RCT.*



*Relative to the pre-test intended medication plan.

A significantly higher proportion of patients in the guided-care arm had a reduction in the number of prescribed psychotropic medications by week 12 compared to TAU.

CONCLUSION

- There were no observed differences in overall neuropsychiatric symptoms or side effects among inpatients or outpatients who received pharmacogenomic-guided care compared to TAU.
- It should be noted that these studies were stopped early due to slow enrollment and were likely underpowered to detect any differences.
- However, there was a significant reduction in the proportion of outpatients with depression in the guided-care arm, which is consistent with the validated use of combinatorial pharmacogenomic testing among patients with depression.
- There was also evidence that pharmacogenomic-guided care did inform prescribing, with reduced prescribing of medications subject to GDI and reduced psychotropic medication polypharmacy.