REPORT FROM:

The Zachary and Elizabeth M. Fisher Alzheimer's Disease Education and Resources Program at the NYU Grossman School of Medicine

In 2020-2021, with the support of the Fisher Center Foundation, we published our discovery of a new stage of eventual Alzheimer's disease that precedes the stage of Subjective Cognitive Decline, called "Psychometric Cognitive Decline." This was the first discovery and identification of normal persons with no subjective memory complaints, who eventually progress to Subjective Cognitive Decline, Mild Cognitive Impairment and the eventual dementia of Alzheimer's disease.

We recruited 60 subjects with "no cognitive decline (NCD); 47 of these subjects were followed. We collected information longitudinally, approximately every two years on these subjects, which included a psychometric test battery. This battery incorporates tests of Initial and Delayed Paragraph Recall, Initial and Delayed Paired Associates Recall, Memory for designs, Digit span Recall Forwards, Digit Span Recall Reverse, the Digit Symbol Substitution Test, and the WAIS-R Vocabulary subtest.

A Combinatorial Psychometric Deterioration Score (PDS) was computed based upon an equal weighting of these nine psychometric tests. We analyzed the subject's cognitive decline based on their Global Deterioration Scale stage. This allowed us to determine those subjects who declined, ie those who progressed to Global Deterioration Scale stage 2 (Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI), or dementia, and those who did not decline.

Thirty-six subjects declined to a GDS of > 2, indicating that they had Subjective Cognitive Decline or more advanced decline. Eleven subjects remained in GDS stage 1, indicating that they had not declined. The subjects' PDS scores were computed and it was found that the PDS was significantly lower at baseline in the future decliners than in the future non-decliners. We published this discovery of a new stage "Psychometric Cognitive Decline" (PCD), in the 30th Anniversary Research Articles issue of the journal *Dementia and Geriatric Cognitive Disorders*.

Additionally, we began our study of risk factors for this newly discovered stage of Psychometric Cognitive Decline. The mean age of the 47-subject cohort was 64.1 +/- 8.9 years; 21 subjects were

male and 36 subjects were female. Their mean level of education was 16.1 +/- 2.4 years. Upon further investigation, we determined that the future decliners had a mean age of 65.06 =/- 8.47 years and the future non-decliners had a mean age of 57.09 =/- 6.73 years. The future decliners were statistically significantly older at baseline (p=0.008).

Of the future decliners, 19 were female (52.78%) and 17 were male (47.22%). Of the future non-decliners, 7 (63.64%) were female and 4 (36.36%) were male. The future decliners had a mean educational level of 16.42 +/- years and the future non-decliners had a mean educational level of 15.45 +/1 2.21 years. There were no significant between-group differences at the time of entry into the study in terms of gender or education. We also found that, for the future decliner cohort, the mean time to decline was 3.81 +/- 1.89 years.

At the present time, age is the only clearly identifiable demographic risk factor for Psychometric Cognitive Decline. Interestingly, although we found that certain Behavioral and Psychological Symptoms of Dementia (BPSD) are a harbinger for decline of SCD persons to MCI, there was no significant different in these symptoms in our PCD or NCI cohorts.

An investigation into the role of behavioral disturbances in persons with Subjective Cognitive Decline has been completed. Seventy-three subjects with SCD, who were participants in our Alzheimer's Disease Research Center longitudinal study, with behavioral disturbance symptomatic assessments, who were 40 years of age or greater and otherwise healthy, were followed for 2.13 +/- 0.30 years. Their mean age at baseline was 66.66 +/- 8.31 years. The majority of subjects, specifically, 48 subjects, were females and 25 of the subjects were males. The mean education level of the study cohort was 15.53 +/1 2.58 years, with a range of 8 to 21 years. Subjects were divided into two categories at follow-up: (A) subjects who declined to MCI (Global Deterioration Scale stage 3), or dementia (GDS stage > 4), (n=18), and (B) subjects who remained unimpaired (GDS stage <2), (n=55).

We found that for the subjects who declined to MCI or dementia at follow-up, the great majority of subjects, 88.9%, had manifest BPSD at baseline. In contrast, we found that for those subjects who did not manifest global decline at the time of follow-up, only 54.5% of the subjects had BPSD at the time of their baseline evaluations. The differences between the occurrence of BPSD at the baseline evaluations were strongly significant (p=0.011).

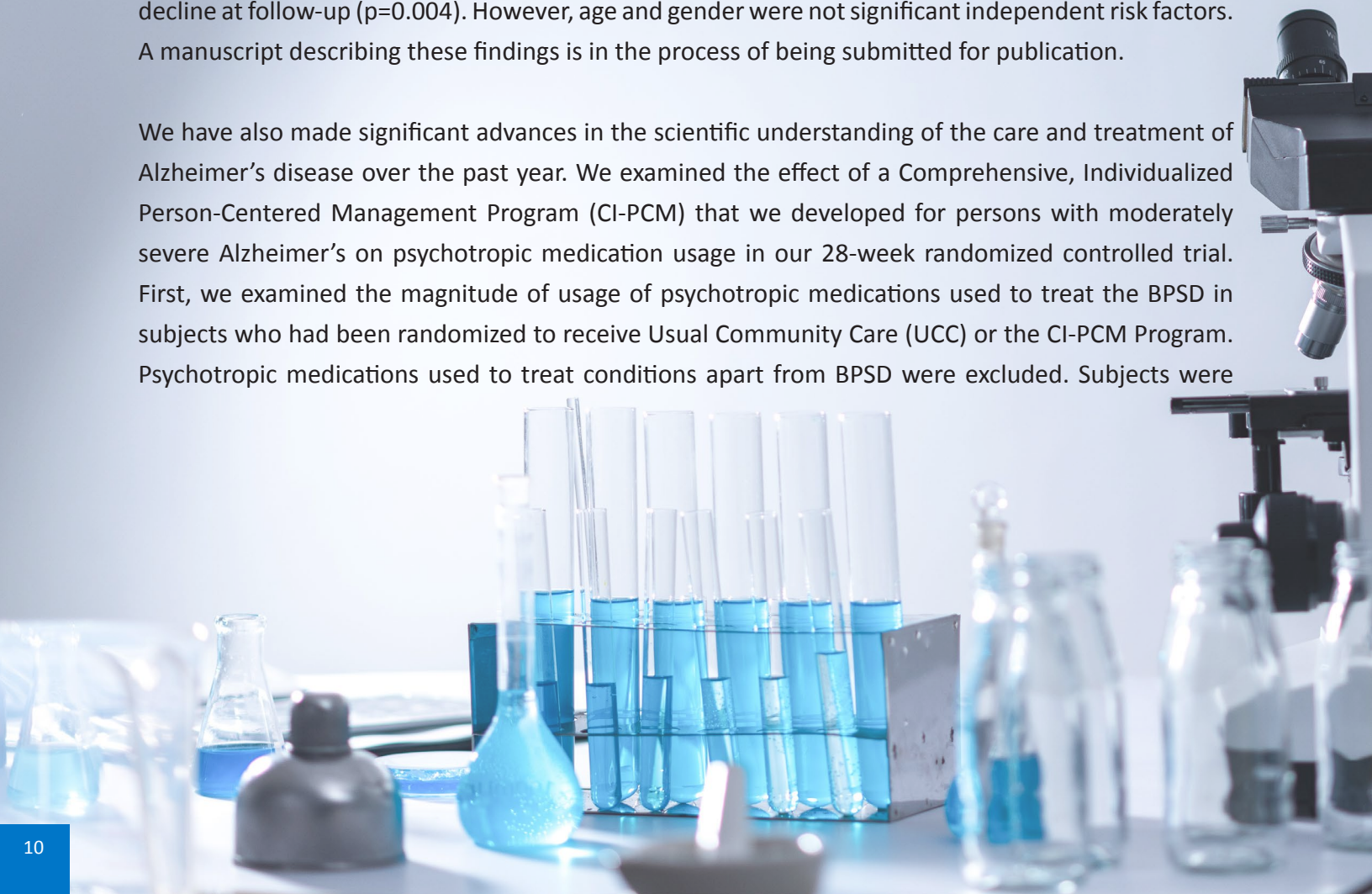
For subjects who declined at follow-up, the manifested BPSD at baseline included anxieties, other than those regarding upcoming events (66.7%), verbal outbursts (22.2%), day/night disturbance (22.2%), tearfulness (16.7%), other phobias (11.1%), suspiciousness and/or paranoia 95.6%), purposeless

activity (5.6%), physical threats and/or violence (5.6%), agitation (5.6%), and depressed mood (5.6%). For subjects who had not declined at follow-up, the manifest baseline BPSD included: anxieties other than those regarding upcoming events (43.6%), day/night disturbance (20%), tearfulness (10.9%), verbal outbursts (5.5%), suspiciousness and/or paranoia (3.6%), purposeless activity (3.6%), depressed mood (3.6%), other phobias (3.6%), inappropriate activities (1.8%), and agitation (1.8%).

We assessed whether disease progression was associated with the presence of individual BPSD using the Behavioral Pathology in Alzheimer's Disease Assessment Scale. There were no significant differences between the presence of individual BPSD items present at baseline in the future non-decliners or the future decliners. However, there was a significant difference in the Behavioral Pathology in Alzheimer's disease Assessment Scale total scores between the future decliners and the future non-decliners at baseline (p=0.008). In addition, the presence of the behavioral pathology categorical symptoms of Aggressivity (category D), and/or Anxieties and Phobias (category G) predicts the decline of SCD subjects to MCI or dementia (p=0.004).

After controlling for age, gender, and educational background, subjects with any BPSD were 12.88 times more likely to manifest cognitive decline at follow-up (p=0.005). We also found that subjects who had more years of education had significantly decreased odds, (OR=0.63) of having cognitive decline at follow-up (p=0.004). However, age and gender were not significant independent risk factors. A manuscript describing these findings is in the process of being submitted for publication.

We have also made significant advances in the scientific understanding of the care and treatment of Alzheimer's disease over the past year. We examined the effect of a Comprehensive, Individualized Person-Centered Management Program (CI-PCM) that we developed for persons with moderately severe Alzheimer's on psychotropic medication usage in our 28-week randomized controlled trial. First, we examined the magnitude of usage of psychotropic medications used to treat the BPSD in subjects who had been randomized to receive Usual Community Care (UCC) or the CI-PCM Program. Psychotropic medications used to treat conditions apart from BPSD were excluded. Subjects were



evaluated at baseline and at weeks 4, 12 and 28. We examined the ratio of daily psychotropic medication usage in the two groups.

Psychotropic medications were compared by examining the percent of the maximum daily dosage of each medication taken cumulatively throughout each study observation period from week 4 to week 28. At baseline, the group randomized to UCC consumed significantly more psychotropic medication than subjects randomized to the CIPCM program ($p<0.05$). Because there was a significant difference between the two groups at baseline, we analyzed psychotropic medication usage in comparison with baseline. The UCC subjects used more psychotropic medication on a per day average relative to baseline from week 4 to week 28 than the CI-PCM subjects ($p < 0.01$). The total amount of psychotropic medication take, in comparison with baseline, was significantly lower in the subjects who had been randomized to receive the CI-PCM program from weeks 4 to 28 ($p < 0.0001$).

In conclusion, the CI-PCM subjects took significantly less psychotropic medication and their BPSD symptomatology significantly improved. Psychotropic medications notably include anxiolytic medications, antidepressant medications, mood stabilizers, soporific medications, and antipsychotic medications. They are prescribed to treat BPSD, including anxiety, depression, agitation, diurnal rhythm disturbances, and psychosis. Many of these medications carry "black box warnings" indicating the need for caution in prescribing because of the possibilities of causing deleterious effects, including death. BPSD are a major cause of burden to care partners of persons living with dementia and are a frequent cause of institutionalization of AD persons. They have also been reported to cause substantial distress and decreased quality of life for both persons with dementia and their care partners (Desai AK, et al., Recognition and Management of Behavioral Disturbances in Dementia. Prim Care Companion J Clin Psychiatry. 2001; 3(3):93-109). We conclude that the CI-PCM program is a safe, highly efficacious non-pharmacologic intervention that significantly reduces both BPSD symptomatology and psychotropic medication usage in advanced AD persons.

Dr. Kenowksy served as chair of an oral research session entitled, "Dementia Care Research: Person-centered care and characteristics of care," where she presented these findings to the scientific and medial community on July 28, 2021.

In summary, over the course of the past year, we have continued to advance the understanding and treatment of Alzheimer's disease. We have also determined that the BPSD are significantly associated with subsequent cognitive decline. Future studies should investigate whether treatment of BPSD can mitigate progression.