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Depression, Cognitive, and Functional Outcomes of Problem Adaptation Therapy (PATH) in Older Adults with Major Depression and Mild Cognitive Deficits

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Abstract

Objectives—Antidepressants have limited efficacy in older adults with depression and cognitive impairment and psychosocial interventions have been inadequately investigated. Problem Adaptation Therapy (PATH) is a psychosocial intervention for older adults with major depression, cognitive impairment and disability.

Design—This study tests the efficacy of PATH vs. Supportive Therapy for Cognitively Impaired Older Adults (ST-CI) in reducing depression (MADRS) and disability (WHODAS-II) and improving cognitive outcomes (MMSE) over 24 weeks (12 weeks of treatment and 12 weeks post-treatment follow-up).

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Conflict of Interest Declaration

Setting—Participants were recruited through collaborating community agencies of Weill Cornell Institute of Geriatric Psychiatry. Both interventions and all research assessments were conducted at home.

Participants—Thirty-five older adults (age≥65 years) with major depression and cognitive impairment without dementia (CIND).

Interventions—PATH aims to increase emotion regulation by incorporating a problem solving approach, teaching compensatory strategies, and inviting caregiver participation. ST aims to facilitate the expression of affect, as well as promote empathy.

Measurements—Depression was measured using the Montgamery Asberg Depression Rating Scale (MADRS), disability using the World Health Organization Disability Assessments Schedule –II (WHODAS-II) and cognition using the Mini Mental State Examination (MMSE).

Results—PATH participants showed significantly greater reduction in MADRS total score (7.04 points at 24 weeks, treatment group by time interaction: $F_{[1,24.4]}$ =7.61, p=0.0108), greater improvement in MMSE total score (2.30 points at 24 weeks, treatment group by time interaction: $F_{[1,39.8]}$=13.31, p=0.0008), and greater improvement in WHODAS-II total score (2.95 points at 24 weeks, treatment group by time interaction: $F_{[1,89]}$=4.93, p=0.0290) than ST-CI participants over the 24-week period.

Conclusions—PATH participants had better depression, cognitive, and disability outcomes than ST-CI participants over 6 months. PATH may provide relief to depressed older adults with CIND who currently have limited treatment options. (Words: 284)

Clinical Trials Registration—Official Title: A Treatment for Depressed, Cognitively Impaired Elders;

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INTRODUCTION

Late-life depression and mild cognitive deficits frequently coexist in older adults (Alexopoulos, 2002; Arve *et al.*, 1999; Bhalla *et al.*, 2009; Butters *et al.*, 2000; Kohler *et al.*, 2010; Nebes *et al.*, 2003; van Ojen *et al.*, 1995; Wang and Blazer, 2015) and are associated with negative outcomes. Depression and cognitive impairment are present in 25% of adults over 85-years-old (Alexopoulos, 2002; Arve *et al.*, 1999; Bhalla *et al.*, 2009; Butters *et al.*, 2000; Kohler *et al.*, 2010; Nebes *et al.*, 2003; van Ojen *et al.*, 1995) and contribute to increased medical and psychiatric morbidity and mortality, decreased quality of life, and impairment in social and interpersonal functioning (Alexopoulos *et al.*, 2005; Cacciatore *et al.*, 1998; Ganguli *et al.*, 2002; LaMonica *et al.*, 2019; Lenze *et al.*, 2008; Reynolds *et al.*, 2001; Roberts *et al.*, 2010). Furthermore, depression in older adults with cognitive impairment correlates with more rapid cognitive decline than in cognitive impairment without depression in most (Van der Mussele *et al.*, 2014; Verdelho *et al.*, 2013) but not all (Cooper *et al.*, 2015; Palmer *et al.*, 2010) cohort studies, and is also associated with atrophy in brain regions typically affected in Alzheimer's Disease (Lee *et al.*, 2012). Given the detrimental consequences of comorbid depression and cognitive impairment in older adults,

identifying effective treatments is critical, especially in light of the increasing prevalence of both mood and cognitive changes in the aging population.

Antidepressant treatment studies in older adults with depression and cognitive impairment demonstrate poor outcomes in terms of depression, disability, and cognitive function. Antidepressants have limited efficacy in reducing depression and disability in older adults with cognitive dysfunction (Alexopoulos *et al.*, 2005; Nelson *et al.*, 2008), and their effects on cognitive outcomes are equivocal (Koenig *et al.*, 2014). Depression in older adults with cognitive impairment has a poor or slow response to antidepressants (Alexopoulos *et al.*, 2005; Sneed *et al.*, 2007) and only about 40% of older adults with depression and cognitive impairment achieve remission (Alexopoulos *et al.*, 2005). There are sparse data from rigorous clinical trials of antidepressants on improvement in disability. In clinical trials of the effects of antidepressants on cognitive outcomes, depressed (Koenig *et al.*, 2014), cognitively impaired older adults have demonstrated improvements in global cognition, episodic recall (Barch *et al.*, 2012; Mowla *et al.*, 2007), aspects of executive function (i.e., conceptualization and initiation (Barch *et al.*, 2012; Butters *et al.*, 2000), divided attention (Devanand *et al.*, 2003; Doraiswamy *et al.*, 2003; Raskin *et al.*, 2007), and verbal learning and memory (Raskin *et al.*, 2007), but these improvements were not significantly different among medicated patients, controls, and placebo responders (Culang *et al.*, 2009; Munro *et al.*, 2012; Nebes *et al.*, 2003; Portella *et al.*, 2003). The limited efficacy of antidepressants on mood, disability and cognitive outcomes in older adults with cognitive deficits highlights the need for psychosocial interventions for this population.

Existing psychosocial interventions aiming to reduce depression and disability and improve cognitive outcomes in this population are sparse despite patient preference for psychotherapeutic interventions (Luck-Sikorski *et al.*, 2017). A modified version of Problem Solving Therapy for Executive Dysfunction (PST-ED) was efficacious in reducing depression and disability over 12 week and 3 month follow-ups when compared to Supportive Therapy (ST) in older adults with mild executive dysfunction (Alexopoulos *et al.*, 2011; Arean *et al.*, 2010; Simon *et al.*, 2015). While the overall group (patients who received PST-ED and those who received ST) improved in a focal aspect of executive function (i.e., response inhibition), there was no significant improvement in other aspects of executive function, learning or memory.(Mackin *et al.*, 2014).

We developed Problem Adaptation Therapy (PATH), a home-delivered psychotherapy, to reduce depression and disability in older adults with depression and varying degrees of cognitive impairment (from mild cognitive deficits to moderate dementia). PATH aims to reduce depression and disability through emotion regulation, (i.e., by reducing negative emotions, promoting positive emotions, and decreasing the impact of patient's behavioral and functional limitations). Our first report (Kiosses *et al.*, 2015) focused on acute treatment outcomes (12 weeks) on depression and disability and PATH showed efficacy in reducing depression and disability in 74 older adults with major depression, accompanied by disability and a wide range of cognitive deficits from mild to moderate cognitive impairment.

This preliminary study focuses on the 24-week depression, cognitive and functional outcomes of PATH vs. Supportive Therapy for Cognitively Impaired Older Adults (ST-CI) in those 35 older adults who had cognitive impairment and no dementia (Tuokko *et al.*, 2001) over 24-weeks (12 weeks of treatment and 12 weeks post-treatment). We hypothesized that participants receiving PATH will have greater reduction in depression (MADRS) (Montgomery and Asberg, 1979) and disability (WHODAS-II) (Ustun, 2003) and better overall cognitive functioning (MMSE)(Folstein *et al.*, 1975) than participants receiving ST-CI over 24 weeks.

METHODS

Participants

Seventy-four participants with major depression, cognitive impairment (from mild cognitive deficits to moderate dementia) and disability were included in the original RCT designed to test the efficacy of PATH vs. ST-CI in reducing depression and disability (Kiosses *et al.*, 2015) (Figure 1). The analysis of the current study focuses on the subsample (N=35; PATH=16, ST-CI=19) of these participants, who had both major depression and cognitive impairment no dementia (CIND).

Participants were recruited through collaborating agencies of the Research Network Development Core of Weill-Cornell Institute of Geriatric Psychiatry (Westchester County, NY). The study design has been previously published (Kiosses *et al.*, 2015). Briefly, eligible participants were 65 years old or older and had a diagnosis of unipolar non-psychotic Major Depression Disorder by the Diagnostic and Statistical Manual for Mental Disorders–IV (DSM-IV) criteria, and a Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) total score of 17 or above. CIND was defined as a scaled score ≤7 on the Dementia Rating Scale (DRS) Initiation Perseveration or Memory Subscales (adjusted for age and education) (Koenig *et al.*, 2014) and no DSM-IV diagnosis of probable or possible dementia, i.e. progressive cognitive decline and functional decline at least in the past 6 months as reported by patient and/or caregiver; and significant impairment in two DRS subscales of cognitive functioning (scaled score ≤5) (adjusted for age and education) (Kiosses *et al.*, 2015).

Disability was defined by the presence of at least one impairment in the performance of Instrumental Activities of Daily Living (IADL) of the Philadelphia Multilevel Assessment Instrument (MAI). However, the average number of impairments in IADL in the original study was six out of nine. Participants were either not taking psychotropic drugs (i.e., including antidepressants, cholinesterase inhibitors, or memantine) or were on a stable dose of psychotropic medications for at least 6 weeks prior to entry into the study.

Exclusion criteria included: (1) any Axis I psychiatric disorder, except major depression and comorbid anxiety disorder; (2) acute or severe medical illness, e.g. delirium, metastatic cancer, decompensated cardiac, liver or kidney failure; (3) use of medications known to cause depression such as reserpine, alpha-methyl-dopa, steroids; (3) current involvement in psychotherapy; and (4) aphasia or lack of English fluency. Participants without full capacity

to consent, assessed by the Weill Cornell Capacity to Consent scale, were excluded from the study.

Written informed consent was obtained from all participants. After signing informed consent, 74 participants in the original study were randomly assigned to receive either home-delivered PATH or home-delivered ST-CI in blocks of 4.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Weill Cornell Medicine IRB.

Assessments and Instruments

The analysis focuses on the course of depression, cognition, and disability over 24 weeks (end of treatment at 12 weeks and 12 weeks follow-up). Depression severity and disability were evaluated with the MADRS and World Health Organization Disability Assessment Schedule-II (WHODAS-II) and were assessed at baseline, week 4, week 8, week 12, and week 24. The WHODAS-II assesses functioning in the areas of Understanding and Communicating, Mobility, Self-Care, Getting Along with others, Life activities (domestic responsibilities, leisure, work and school) and Participation (joining in community activities) (Ustun, 2003). Higher scores on both the MADRS and WHODAS-II indicate greater symptom severity. Cognitive impairment was assessed with the Mini Mental State Exam (MMSE) (Folstein *et al.*, 1975) total score at entry, week 12 and week 24.

Interventions

PATH and ST-CI were administered in 12 weekly sessions at the participant's residence and have been described in detail elsewhere (Kiosses *et al.*, 2015). PATH aims to increase emotion regulation by (1) incorporating a problem solving approach, (2) teaching compensatory strategies to bypass cognitive, behavioral and functional limitations, and (3) inviting caregiver participation in treatment to facilitate engagement in intervention techniques. PATH follows the process model of emotion regulation, which highlights five broad ways to reduce emotion regulation: situation selection, situation modification, attentional deployment, cognitive change, and response modulation. ST-CI was used as an attention control intervention even though it has been shown to reduce depression in this population. It is based on Carl Rogers' theories and aims to facilitate the expression of affect, as well as promote understanding and empathy (Kiosses *et al.*, 2015). ST-CI therapists were trained to refrain from using ingredients of Problem Solving Therapy (PST), Interpersonal Psychotherapy (IPT), CBT (Cognitive Behavior Therapy), or dynamic therapy. PATH and ST-CI were manualized and administered by the same licensed therapists. Therapists achieved very good to excellent treatment fidelity scores (average score ≥ 4.5 out of 5 based on PATH and ST-CI fidelity scales) with both interventions.

Statistical Analysis

Analyses included all participants with major depression and CIND (Figure 1). Initially, we compared the PATH (N=16) and the ST-CI (N=19) groups on clinical and demographic

variables at baseline, using the Wilcoxon-Mann-Whitney test for continuous variables and Fisher's exact tests for categorical variables. To evaluate potential bias due to dropout, participants with week 24 data and those who dropped out after 12 weeks of treatment were compared on demographic, baseline clinical and week 12 clinical characteristics, using similar approaches.

Treatment effects on outcomes were evaluated with mixed-effects models for longitudinal data to compare the two treatments on depression (MADRS total score) and disability (WHODAS-II total score) over 24 weeks, at 5 assessment points (entry, week 4, week 8, week 12 and week 24). We estimated mixed-effects models for longitudinal data on cognitive outcomes between PATH and ST-CI participants over 24 weeks, at 3 assessment points (entry, week 12, and week 24). The models included time, time squared when appropriate, treatment group, and time-by-treatment interaction. Finally, we evaluated whether changes in depression mediate changes in cognition by constructing a mixed-effects model to test whether the difference of depression scores between lagged and follow-up interview predicted cognitive scores at a follow-up interview. A two-tailed alpha level of 0.05 was used for each statistical test. All analyses were performed with SAS 9.2 (Cary, 2002–2004).

RESULTS

Thirty-five older adults [average age 79.2 (SD=7.6); average education 13.7 years (SD=3.0)] with major depression and CIND were included (PATH=16 vs. ST-CI=19). Out of 35 participants who entered the study, 30 (85.7%) completed the treatment (12 weeks) and 24 (80% of those who completed the treatment) completed at least one depression, disability or cognitive assessment at the 24 week timepoint. There were no significant differences between those who finished the study and those who dropped out after 12 weeks on any demographic, baseline and week 12 clinical characteristics. There were no significant differences in demographic or baseline clinical variables between participants in the two treatments (Table 1).

Depression

In a mixed-effects model consisting of treatment group, time, time squared, and treatment group by time interaction, PATH participants showed significantly greater reduction in MADRS total score than ST-CI participants over the 24-week period (treatment group by time interaction: $F_{[1,24.4]}=7.61$, p=0.0108; Cohen's D: 0.94; 95% CI=0.24–1.63)) (Figure 2). PATH participants had significantly lower depression scores at week 4 ($t_{[34.9]}=2.20$, p=0.0343), week 8 ($t_{[34.3]}=2.57$, p=0.0146), week 12 ($t_{[33.6]}=2.79$, p=0.0087) and week 24 ($t_{[30.8]}=3$, p=0.0053).

Cognitive Functioning

In a mixed-effects model consisting of treatment group, time, and treatment group by time interaction, PATH participants had significantly greater improvement in MMSE total score than ST-CI participants over the 24-week period (treatment group by time interaction: $F_{[1,39.8]}=13.31$, p=0.0008; Cohen's D:1.66, 95% CI=0.86–2.20) (Figure 3). PATH

participants had significantly better cognitive scores at week 12 ($t_{[31.9]}$=−2.10, p=0.0434) and week 24 ($t_{[63.2]}$=3.38, p=0.0012). The significant difference between PATH vs. ST-CI persisted even when we included depression severity (MADRS total score) as a covariate (treatment group by time interaction: $F_{[1,39.8]}$=13.31, p=0.0101).

Exploratory Mediation Analysis—To examine whether improvement in depression mediates improvement in cognition, a mixed-effects model was constructed in which the difference of depression scores between lagged and a follow-up interview was used as a predictor of cognitive performance (MMSE scores) at the follow-up interview. Our data and analysis did not support mediation of improvement in depression onimprovement in cognition.

Disability

In a mixed-effects model consisting of treatment group, time, and treatment group by time interaction, PATH participants had significantly greater reduction in WHODAS II total score than ST-CI participants over the 24-week period (treatment group by time interaction: $F_{[1,89]}$=4.93, p=0.0290; Cohen's D: 0.89, 95% CI=0.19–1.58). PATH participants had significantly lower disability scores at week 8 ($t_{[31.9]}$=2.40, p=0.0223), week 12 ($t_{[35.3]}$=2.73, p=0.0098) and week 24 ($t_{[72]}$=3.16, p=0.0023).

DISCUSSION

The principal findings of this study are that in older adults with major depression and cognitive impairment not dementia (CIND), PATH participants had greater reduction in depression and disability, and better overall cognitive functioning over 24 weeks. Our findings are heuristically and clinically significant because: a) antidepressants have limited efficacy in reducing depression and disability in this population; b) treatment options for improvement of cognitive outcomes are sparse; and c) psychosocial interventions for older adults with major depression and cognitive impairment are understudied. If the results are confirmed with an adequately powered randomized trial, PATH may provide relief and sustain better functional outcomes to a large number of older adults with depression who are at risk of developing dementia.

Our findings are consistent with findings from other psychotherapy studies that showed that psychotherapy reduces depression and disability in older adults with mild to moderate cognitive deficits (Wuthrich *et al.*, 2018). Problem Solving Therapy for Executive Dysfunction had greater efficacy in reducing depression and disability in older adults with major depression and mild executive dysfunction (Alexopoulos *et al.*, 2011; Arean *et al.*, 2010). The benefits were maintained for the 3 subsequent months (Alexopoulos *et al.*, 2011; Arean *et al.*, 2010). PST has also shown efficacy in reducing depression in older adults in home care, a population characterized by high prevalence of cognitively impaired patients (Gellis *et al.*, 2007).

Our study revealed that PATH participants had greater improvement in MMSE total scores over 24 weeks. The mean difference between treatments was 2.3 points which is 50% greater than the minimum clinically important difference for Standardized MMSE (i.e. 1.4

points) based on expert opinion- and distribution-based values recommended for dementia trials (Howard *et al.*, 2011). Even though existing psychosocial interventions for the acute treatment of late-life depression with comorbid cognitive impairment may reduce depression and disability, RCT data on cognitive outcomes are sparse. A secondary analysis of cognitive outcomes in the Alexopoulos and Arean study revealed no significant improvement on most cognitive outcomes (including memory, initiation/perseveration, learning) and small improvement in one aspect of executive functioning (response inhibition as measured by Stroop Color-word score) in both PST-ED and ST groups (Mackin *et al.*, 2014). PST-ED did not show greater improvement in any cognitive outcomes compared to ST (Joosten-Weyn Banningh *et al.*, 2011).

Our study did not evaluate PATH's mechanism of action for improvement in cognitive outcomes and our data and analysis did not support a mediating role ofdepression in the improvement of cognitive outcomes. PATH may improve cognitive functioning through stress reduction rather than mood improvement (Greenberg *et al.*, 2014; Lucassen *et al.*, 2014). Depression and mild cognitive deficits are associated with increased stress, a risk factor for dementia. PATH may strengthen the ability of patients to cope with stress and thus improve cognition. Specifically, PATH may improve cognition by improving affective regulation (reducing negative emotions and increasing positive emotions), reducing the affective reaction to stress, and allowing patients to better utilize their existing cognitive resources. Potential psychological mechanisms may include: 1) reducing emotional reactivity through regulation of negative emotions; 2) instilling hope by increasing positive emotions (Blazer, 2019; Kim *et al.*, 2019); 3) reducing vulnerability to environmental stress by helping patients bypass behavioral and functional limitations; and 4) reducing interpersonal stress between the patient and significant others by improving communication and allowing both sides a sense of increased self-efficacy. Future evaluation of potential mediators such as stress reduction, increased self-efficacy, and improvement in emotion regulation may help us better understand the mechanism through which PATH may improve cognition. Given the long timeframe of AD pathological brain mechanisms, it is unlikely that we have affected these mechanisms with psychotherapy interventions over a short-term (3–6 months) trial.

The study has several limitations. First, our study was not a randomized trial per se. It focuses on a subgroup of older adults with CIND within a larger randomized controlled trial of PATH vs. ST-CI with a variety of cognitive profiles (Kiosses *et al.*, 2015). Second, our sample size was small. Although obtaining statistically significant results on such a small sample is encouraging, a larger adequately powered efficacy study is needed to evaluate depression, disability and cognitive outcomes of PATH vs. ST-CI in this population over 24 weeks. Third, the study focuses on those participants who are willing to undergo psychotherapy, which is relatively labor-intensive. These results may not be generalizable to those who may not be motivated to engage in psychotherapeutic interventions. Fourth, our cognition measure (MMSE) is a screening instrument that may not be as sensitive as other, more sophisticated cognitive measures so these results need to be interpreted with caution.

In sum, our study revealed that PATH is efficacious in reducing depression and disability and achieving better cognitive outcomes than ST-CI in older adults with depression and cognitive

impairment without dementia. The results are encouraging that PATH may provide relief to a large group of older adults with depression and cognitive impairment at risk of developing dementia. Treatment options for depression, disability and cognition for this population are sparse. Despite the encouraging results, our findings need to be confirmed in a large randomized trial with more sensitive cognitive measures.

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Description of authors' roles

Dora Kanellopoulos: Substantial contributions to interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Lisa Ravdin: Substantial contributions to interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Dimitris Kiosses: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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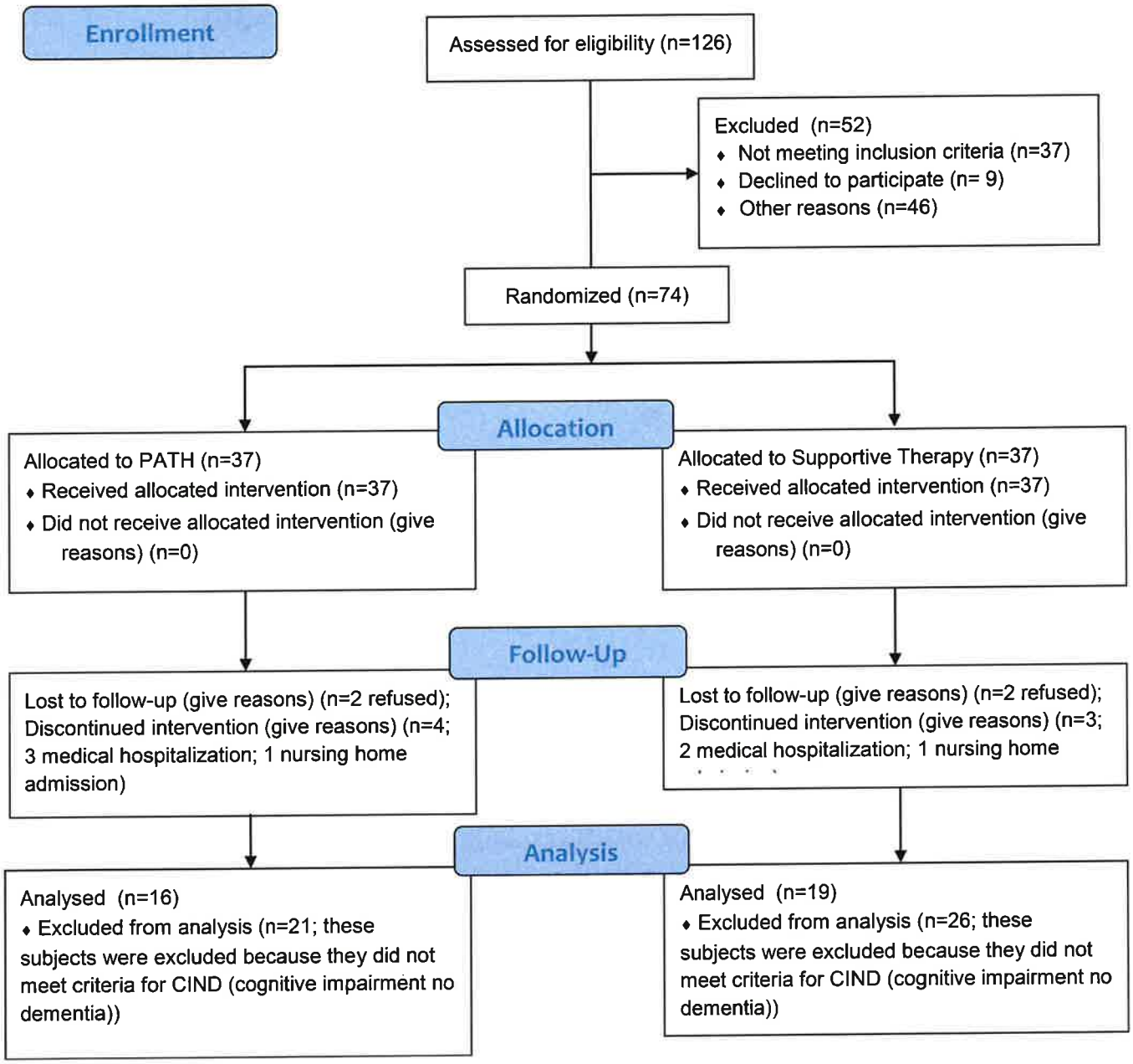

Figure 1.
Flow Diagram of the PATH vs. ST Trial For This Analysis

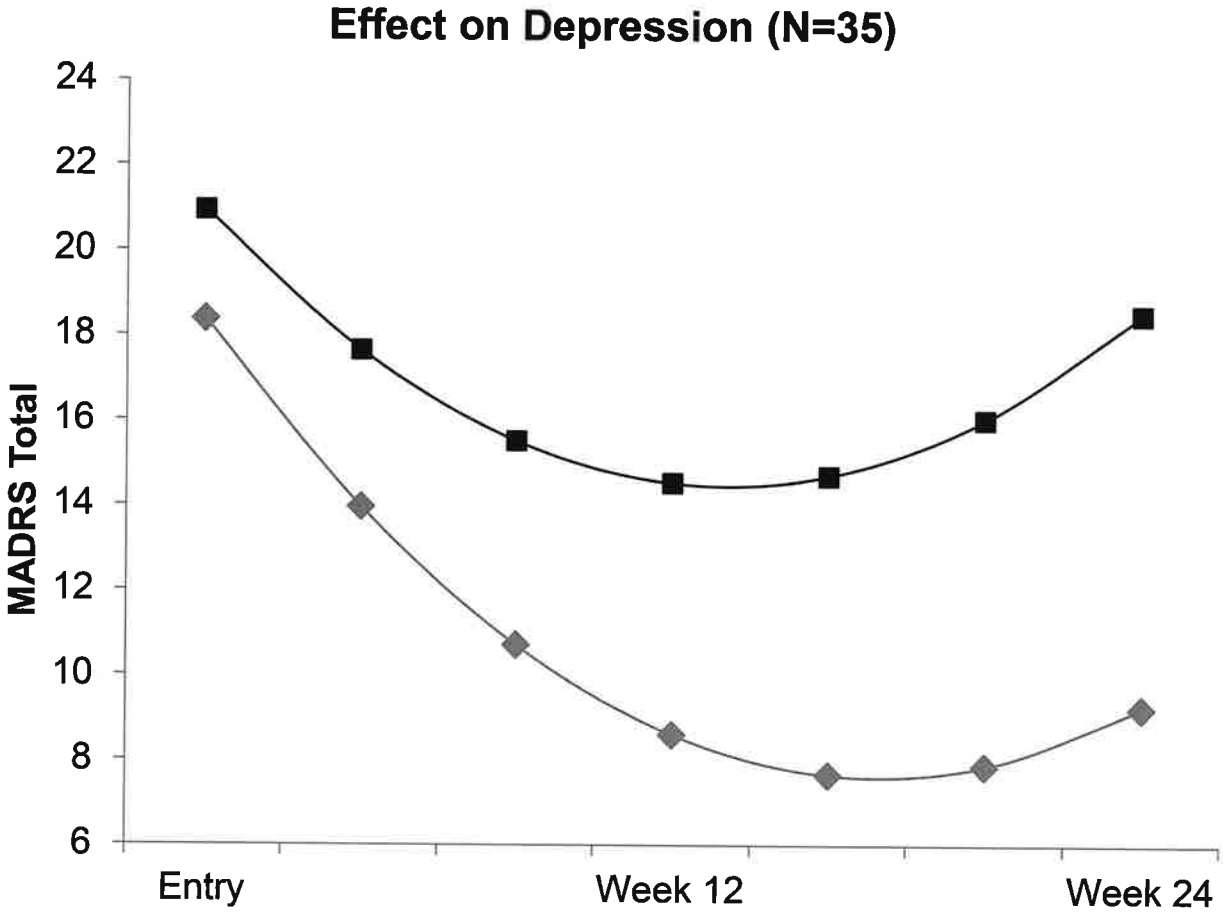

Figure 2. Course of Depression of PATH vs. ST-CI in 35 Older Adults with Major Depression and CIND.

Depression scores (MADRS Total Score) over 24 weeks of PATH (grey) versus ST-CI (black) in 35 elders (PATH=16; ST-CI=19) with major depression and CIND based on the least squares means of the mixed effects model: time + time squared + treatment + treatment x time.

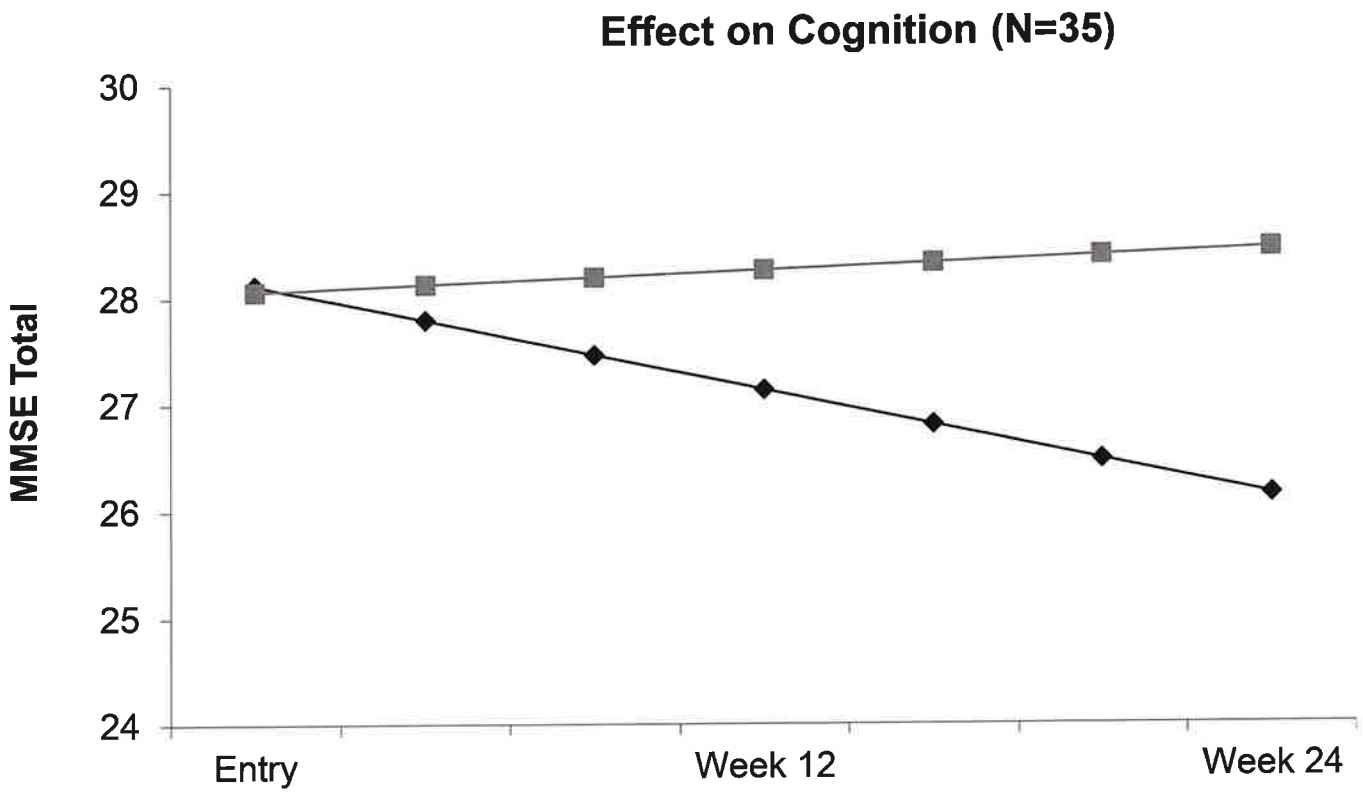

Figure 3. Course of Overall Cognitive Functioning of PATH vs. ST-CI in 35 Older Adults with Major Depression and CIND.

Overall cognitive functioning (MMSE Total scores) over 24 weeks of PATH (grey) versus ST-CI (black) in 35 Older Adults with Major Depression and CIND (PATH=16; STCI=19) based on the least squares means of the mixed effects model: time + treatment + treatment × time.

Table 1.

Demographic and Baseline Clinical Characteristics of 35 Older Adults with Major Depression and Mild Cognitive Deficits

	PATH (N=16)		ST (N=19)			
	N	Perc (%)	N	Perc (%)	Fisher's Exact (p)	
Gender					0.13	
Female	9	56.25	16	84.21		
Race and Ethnicity					0.64	
Caucasian	13	81.25	17	89.47		
African-American	3	18.75	2	10.53		
Number of Depression Episodes (>=3)	9	69.23	9	56.25	0.70	
On Antidepressants	10	62.50	11	57.89	1.00	
On Cognitive Enhancers	1	6.25	1	5.26	1.00	
					Mann-Whitney Wilcoxon	
	Mean	SD	Mean	SD	z	p
Age	77.69	7.43	80.48	7.60	−1.09	0.27
Age at Onset of Depression	53.62	25.19	56.13	26.11	−0.09	0.93
Education (years)	14.07	3.01	13.29	2.95	1.04	0.30
Attended Therapy Sessions[#]	10.56	2.94	10.95	2.99	−0.97	0.33
MADRS Total[1]	20.31	3.24	21.11	3.38	−0.63	0.53
WHODAS-12 Total[2]	30.38	8.76	32.21	3.81	−0.40	0.69
MMSE Total[3]	28.21	2.16	28.29	1.05	0.66	0.51
Charlson Total[4]	2.31	1.56	3.11	2.71	−0.76	0.45
Intensity of Antidepressant Medication Treatment[5]	2.00	1.56	2.00	1.85	−0.26	0.79

[#]90.5% of participants who completed the study had 12 therapy sessions, 6.3% had 11 sessions, and 3.2% had 10 session.

[1]Montgomery Asberg Depression Rating Scale (MADRS)

[2]World Health Organization Disability Assessment Schedule – II - 12 items

[3]Mini Mental State Exam – Total

[4]Charlson Commorbity Index

[5]Composite Antidepressant Score (CAD) – Revised.