

Problem-Solving Therapy and Supportive Therapy in Older Adults With Major Depression and Executive Dysfunction

Effect on Disability

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Context: Older patients with depression and executive dysfunction represent a population with significant disability and a high likelihood of failing pharmacotherapy.

Objectives: To examine whether problem-solving therapy (PST) reduces disability more than does supportive therapy (ST) in older patients with depression and executive dysfunction and whether this effect is mediated by improvement in depressive symptoms.

Design: Randomized controlled trial.

Setting: Weill Cornell Medical College and University of California at San Francisco.

Participants: Adults (aged >59 years) with major depression and executive dysfunction recruited between December 2002 and November 2007 and followed up for 36 weeks.

Intervention: Twelve sessions of PST modified for older depressed adults with executive impairment or ST.

Main Outcome Measure: Disability as quantified using the 12-item World Health Organization Disability Assessment Schedule II.

Results: Of 653 individuals referred to this study, 221 met the inclusion criteria and were randomized to receive PST or ST. Both PST and ST led to comparable improvement in disability in the first 6 weeks of treatment, but a more prominent reduction was noted in PST participants at weeks 9 and 12. The difference between PST and ST was greater in patients with greater cognitive impairment and more previous episodes. Reduction in disability paralleled reduction in depressive symptoms. The therapeutic advantage of PST over ST in reducing depression was, in part, due to greater reduction in disability by PST. Although disability increased during the 24 weeks after the end of treatment, the advantage of PST over ST was retained.

Conclusions: These results suggest that PST is more effective than ST in reducing disability in older patients with major depression and executive dysfunction, and its benefits were retained after the end of treatment. The clinical value of this finding is that PST may be a treatment alternative in an older patient population likely to be resistant to pharmacotherapy.

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DISABILITY IS A PRIMARY CONCERN of patients, families, clinicians, and policy makers.¹ The World Health Organization Global Burden of Disease Initiative identified unipolar depression as the leading cause of disability worldwide.² Depression accounts for 10.7% of the variance in disability and is responsible for more than 1 in 10 years lived with disability.² Longitudinal studies of community-residing adults show a strong rela-

tionship between depression and new-onset disability,³⁻⁷ with the likelihood of becoming disabled increasing with each additional symptom of depression.⁴ Moreover, as the number of depressive symptoms increases, the likelihood of recovering from a physical disability decreases.⁴ Even subsyndromal depressive symptoms are associated with disability in older persons.⁸ Similar relationships between depression and disability have been observed in psychiatric and primary care patients.⁹⁻¹³

Executive dysfunction and its underlying neurobiologic abnormalities are common in late-life depression, contribute to disability, and increase the risk of poor response to antidepressant drug therapy. Approximately 40% of elderly patients with major depression have impairment in some executive functions.^{14,15} Similarly, structural abnormalities in depressed older adults are mainly localized in frontal subcortical structures,¹⁶⁻¹⁸ whose integrity is essential for the performance of executive functions. Executive dysfunction¹⁹⁻²⁴ and its underlying white matter lesions^{16,25,26} are associated with disability in depressed adults. The relationship between executive dysfunction and disability is clinically intuitive because individuals with executive dysfunction have difficulties in goal setting, planning, initiating and sequencing behavior, and terminating behavior when their goals are accomplished.^{27,28} Finally, clinical, neuropathologic, and structural and functional neuroimaging studies suggest that executive dysfunction and its underlying pathogenesis predict slow, poor, and unstable response of geriatric depression to treatment with antidepressant agents,^{16,29-36} necessitating novel treatment development.

Responding to the need for effective treatments for geriatric depression with executive dysfunction, we elected to study a nonpharmacologic intervention.³⁷ The concept underlying the intervention was that imparting skills and enabling patients to deal with problems resulting from depressive symptoms and executive dysfunction would reduce their disability and their depressive symptoms by improving their daily experiences. Accordingly, problem-solving therapy (PST) was selected as the basis for this intervention. Originally developed as a treatment for depression,³⁸ PST relies on a learning model and imparts to patients an approach for identifying problems central to their lives and a method for selecting solutions and making concrete plans for problem resolution. It has been found effective in older adults with depression³⁹ and disability^{40,41} and in patients with schizophrenia, a disorder accompanied by executive dysfunction.^{42,43}

Areán et al⁴⁴ recently reported that modified PST is more efficacious than supportive therapy (ST) in reducing depressive symptoms and in leading to remission of geriatric depression with executive dysfunction. The PST modification used in this study retained the 5 original steps in selecting problems and action plans.⁴⁵ However, patients were oriented toward important yet simple and accessible problems. Furthermore, therapists were more directive than in the original version and provided structure on selecting triggers for action plans, sequencing actions, and terminating action on accomplishment of goals.

This study focuses on disability using an instrument that captures several aspects of function, including self-care, household and work activities, getting around, understanding and communicating, getting along with others, and participating in social activities. It tests the hypothesis that PST is more efficacious than ST in reducing disability while these treatments are offered and that the differential gains of the PST group made during treatment are retained during the subsequent 24 weeks. A second hypothesis postulated that the salutary effects of PST over ST on disability are mediated by improvement in depressive symptoms and signs. Exploratory

analysis focused on potential moderators of differences in efficacy between PST- and ST-treated individuals.

METHODS

PARTICIPANTS

This analysis used data from a randomized controlled trial that compared the efficacy of a modified version of PST with that of ST in participants recruited by Weill Cornell Medical College (Cornell) and the University of California at San Francisco (UCSF) research groups between December 2002 and November 2007. Study procedures were approved by the institutional review boards of both universities.

Individuals who responded to advertisements or who were referred by clinicians were interviewed by raters trained at each site and credentialed by the Cornell Advanced Center for Services Research. The selection criteria consisted of age 60 years or older, a Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-R)/DSM-IV⁴⁶ diagnosis of major nonpsychotic depression, a 24-item Hamilton Depression Rating Scale (HDRS)⁴⁷ score of at least 20, a Mini-Mental State Examination (MMSE)⁴⁸ score of at least 24, a Mattis Dementia Rating Scale initiation/perseveration domain (DRS-IP)⁴⁹ score of 33 or less, and a Stroop Color-Word Test score of 25 or less.⁵⁰ The DRS-IP and the Stroop were selected because they have been associated with poor response to antidepressant drug therapy^{16,29-36} and because of the simplicity of their administration. Individuals were excluded if they were receiving psychotherapy or antidepressant agents, reported intent to attempt suicide in the near future, had an Axis I psychiatric disorder or substance abuse other than unipolar depression or generalized anxiety disorder, had antisocial personality (DSM-IV), had dementia, had a history of head trauma, had an acute or severe medical illness (ie, delirium, metastatic cancer, decompensated organ failure, major surgery, recent stroke, or myocardial infarction), used drugs known to cause depression, or could not perform any activities of daily living even with assistance.

Participants were assigned to receive PST or ST within each site using random numbers in blocks of 5 participants. Raters were unaware of participants' randomization status. Therapists were aware of participants' randomization status but not of the study hypotheses.

SYSTEMATIC ASSESSMENT

Diagnosis was assigned in research conferences by agreement of 2 clinician investigators after review of the clinical history, the SCID-R data, and all other research data obtained by trained interviewers. Measures were selected that have documented validity and reliability in older adults. All the instruments were rated using the clinical judgment of interviewers and clinician investigators rather than verbatim participant responses given the difficulties of older adults in accurately identifying psychiatric symptoms.⁵¹ Disability was quantified using the interviewer-administered 12-item World Health Organization Disability Assessment Schedule II (WHODAS II).⁵² The WHODAS II yields a composite score of disability after assessing the domains of understanding and communicating, getting around, self-care, getting along with others, household and work activities, and participation in society. This instrument is compatible with the international classification system; has been validated in 16 sites and 13 countries, including the United States; and has been found to be cross-culturally applicable.⁵² Its 6 domains had factor loadings ranging from 0.82 to 0.98, and its items also loaded on a general disability factor.

Severity of depression was assessed using the 24-item HDRS. Overall cognitive impairment was assessed using the MMSE. Executive functions were assessed using the DRS-IP, the Stroop Color-Word Test, the Wisconsin Card Sorting Test,⁵³ Trails B of the Trail Making Test,⁵⁴ and the Frontal Systems Behavior Scale.⁵⁵ Measures related to psychiatric disorders included age at onset of a first episode of major depression (SCID-R), neuroticism (subscale of the Neuroticism, Extroversion, Openness Scale),⁵⁶ and history of antidepressant drug use (Composite Antidepressant Treatment Intensity Scale modified to include the available antidepressant agents).⁵⁷

After baseline assessment, the HDRS and the WHODAS II were administered weekly until week 12 and again at weeks 24 and 36. Payment for transportation and arrangements, when necessary, were provided for all meetings. Compensation was offered for time spent in assessments but not in treatment sessions.

TREATMENT

Treatment was offered by 4 doctorate-level clinical psychologists and 4 licensed social workers with at least 5 years of postlicensure experience. No therapist had experience with formal PST or ST protocols. Each therapist offered both treatments after training, which consisted of a 2-day workshop and supervision of 3 PST and 3 ST training cases. Fidelity to treatment manuals was monitored by independent experts in both PST and ST who reviewed and rated 20% of randomly selected audiotaped sessions. Experts used the PST Adherence Scale to rate the quality of and adherence to PST⁵⁸ and the California Psychotherapy Assessment Scale to rate ST.⁵⁹ The average session ratings for each therapist were "excellent" in PST and ST (range, "excellent" to "exceptional"). No differences in quality of ratings were found for any therapist or for either treatment.

Problem-Solving Therapy

Twelve weekly individual PST sessions were offered according to an unpublished manual titled *Social Problem Solving Therapy for Depression and Executive Dysfunction*.⁶⁰ The first 5 weeks are devoted to training participants in the 5-step problem-solving model, and subsequent sessions enhanced PST skills. Participants are guided to set goals, propose ways to reach them, create action plans, and evaluate the accomplishment of their goals. They are also instructed to apply the problem-solving model to additional problems between sessions. In the last 2 sessions, participants create a relapse prevention plan using the PST model.

Supportive Therapy

Twelve weekly individual ST sessions were offered according to an unpublished manual titled *Manual for Supportive Therapy*.⁶¹ Supportive therapy is similar to person-centered psychotherapy, and therapists create a comfortable, nonjudgmental environment by demonstrating genuineness, empathy, and acceptance of patients without imposing any judgments on their decisions. This approach aids patients in addressing problems without direct input from therapists. Participants are encouraged to talk about their depression and any contributing life events. Therapists do not engage in any therapeutic strategy other than active listening and offering support focusing on participants' problems and concerns.

DATA ANALYSIS

All the participants who completed the baseline assessments (the intent-to-treat sample) were included in the data analyses. Profiles of pretreatment and weekly WHODAS II scores

across 12 weeks (disability during treatment) and, separately, between 12 and 36 weeks (disability after treatment) were compared for the 2 treatment groups (PST and ST) using mixed-effects models for longitudinal data to account for the repeated measurements across time. These models included time-trend parameter(s), treatment group, site, site \times treatment interaction, and time \times treatment interaction. Moderation was assessed by checking the interaction of baseline variables with treatment effects in the mixed-effects model. Mediation was assessed by examining the effects of lagged HDRS scores to predict WHODAS II scores, again using a mixed-effects regression model. For the analyses at weeks 0 to 12, the preceding week's HDRS scores were used (excluding the first week's data, which have no lagged mediator) to predict current WHODAS II scores. For the analyses at weeks 12 to 36, HDRS scores at 6, 12, and 24 weeks were used to predict WHODAS II scores at 12, 24, and 36 weeks, respectively. The 12-week outcomes were taken to be the averages of the 10-, 11-, and 12-week outcomes to (1) reduce variation and (2) reduce the effect of missing data. The mediation effect was quantified by calculating the proportion of the treatment effect explained by the mediator.⁶² The same approach was used to assess the mediation effect of the WHODAS II score on HDRS outcome. Analyses were conducted using a statistical software program (SAS, version 9.1; SAS Institute Inc, Cary, North Carolina).

RESULTS

RECRUITMENT AND DROPOUT FROM TREATMENT

Of 653 older persons screened, 279 met the selection criteria (**Figure 1**). Of these 279 individuals, 221 completed the baseline assessment and were randomized to receive PST (n=110) or ST (n=111). Of the 221 randomized participants, 201 (91.0%) completed the 12-week treatment trial. Among those who dropped out of treatment (n=20), 10 were receiving PST and 10 ST. Nevertheless, 5 of the 20 participants who dropped out of treatment completed the week 12 assessment (4 had received PST and 1 ST). In the end, 206 participants received the week 12 assessment, 173 received the week 24 assessment, and 167 received the week 36 assessment. The mean (SD) number of sessions attended was 10.5 (3.1) by the PST group and 10.7 (3.04) by the ST group (87.5% and 89.2% of all sessions, respectively). The median number of sessions for each group was 12.

PARTICIPANT CHARACTERISTICS

The participants' demographic and clinical characteristics are reported elsewhere.⁴⁴ Briefly, the randomized participants (n=221) had a mean (SD) age of 73.0 (7.8) years and a mean (SD) of 15.3 (2.8) years of education. Their mean (SD) test scores for depression (HDRS: 24.3 [4.3]), disability (WHODAS II: 26.6 [7.3]), and executive function (DRS-IP: 32.2 [3.7]; Stroop Color-Word Test: 22.1 [8.2]; and perseverative errors [Wisconsin Card Sorting Test]: 14.5 [9]) were in the mild to moderate severity range. Approximately 27% of participants had a history of antidepressant drug treatment. Less than 2% of participants were tak-

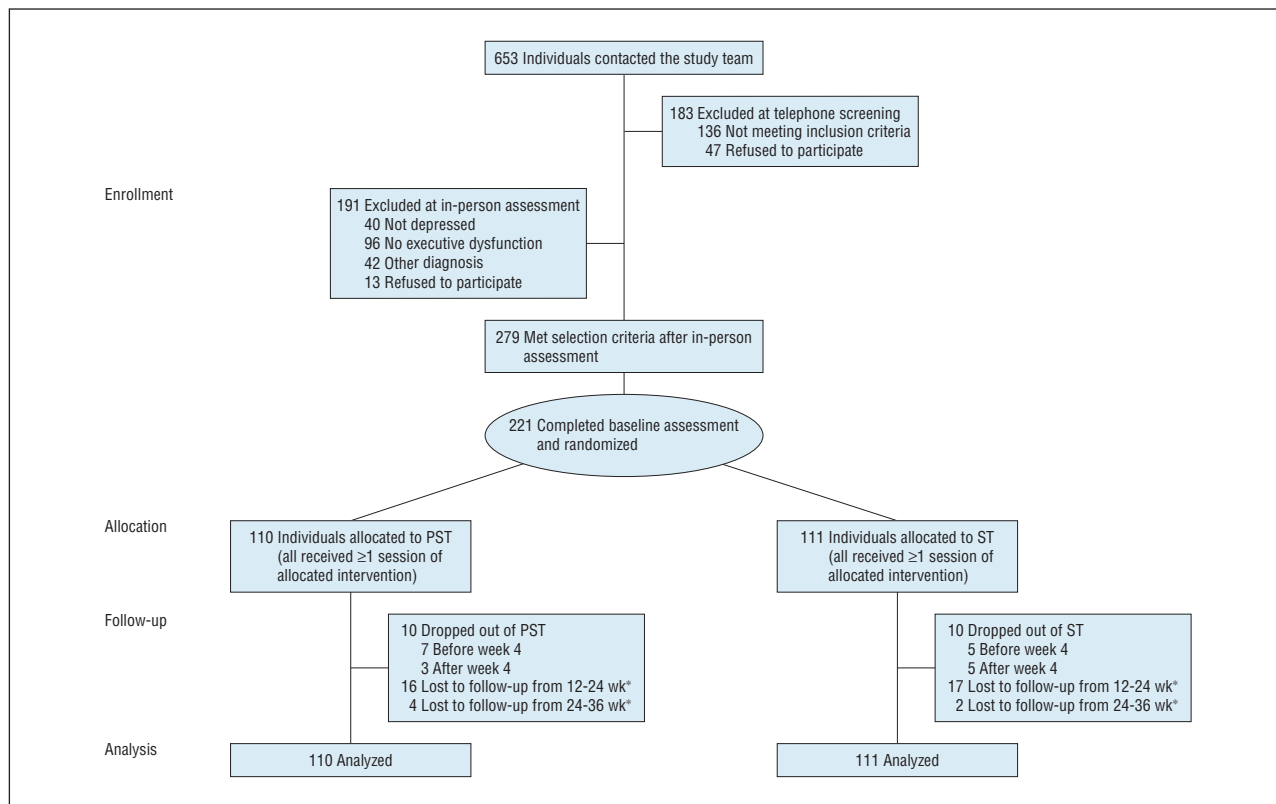


Figure 1. Flow of participants in the treatment trial. PST indicates problem-solving therapy; ST, supportive therapy. *Completed treatment.

ing benzodiazepines or sleep aids; no one was taking a cognitive enhancer. No significant differences in demographic or clinical variables were noted between the 2 treatment arms and study sites. Furthermore, no significant differences were noted in demographics, depression severity, executive function, medical burden, or disability in participants who had been taking antidepressant agents and those who had not.

OUTCOMES DURING TREATMENT (0-12 WEEKS)

Course of Disability

In a mixed-effects model consisting of treatment group (PST vs ST), time, time \times time, treatment site (Cornell vs UCSF), and treatment \times time interaction, PST participants had a significantly greater reduction in disability (total WHODAS II scores) across 12 weeks than did ST participants (**Table 1** and **Figure 2**). Treatment site (UCSF vs Cornell) did not significantly contribute to WHODAS II score variance across time. Reduction in disability was greater in the PST group than in the ST group by approximately 0.18 points per week.

Moderators of Treatment Efficacy

Problem-solving therapy was associated with a greater reduction in disability than was ST in patients with more depressive episodes and greater cognitive impairment (ie, lower MMSE scores) (**Table 2** and **Figure 3**).

Mediators of Treatment Efficacy

To examine whether depression severity mediates treatment effects on disability, a mixed-effects model was used in which depression severity (HDRS score) during each week was used as a predictor of disability (WHODAS II score) during the following week. The model consisted of treatment group (PST vs ST), site (Cornell vs UCSF), time, treatment group \times time interaction, and HDRS score. The HDRS scores predicted the effect on disability in the following week ($F_{1,1934}=27.32, P<.001$). In the whole group, for every point reduction in depression (ie, HDRS score of 1 point) at each week, there was a statistically significant reduction in disability of 0.12 points in the WHODAS II score in the following week. However, the HDRS score did not explain any of the PST vs ST treatment difference on WHODAS II scores.

To examine whether disability mediates treatment effects on depression, a mixed-effects model was used in which disability (WHODAS II score) during each week was used as a predictor of depression severity during the following week, that is, treatment group (PST vs ST), site (Cornell vs UCSF), time, time \times time, treatment group \times time interaction, and WHODAS II score. The WHODAS II scores predicted the effect on depression in the following week ($F_{1,1973}=48.66, P<.001$). In the whole group, for every point reduction in disability (ie, WHODAS II score of 1 point) at each week, there was a statistically significant reduction in depression of 0.14 points in the HDRS score in the following week. The WHODAS II score explained 10% of the PST vs ST treatment difference on HDRS score.

Table 1. Comparisons of the Course of Disability During 12 Weeks of Treatment (PST vs ST) and After Treatment Completion (Weeks 12-36) in 221 Older Adults With Major Depression and Executive Dysfunction

Variable	Estimate	t	df	P Value
Model 1: disability (WHODAS II score) during treatment (0-12 wk)				
Intercept	22.9328	26.43	238	<.001
Treatment (PST vs ST) ^a	-1.4744	-1.39	204	.17
Site ^b	1.0793	1.22	216	.23
Time ^c	0.0888	0.87	230	.39
Time × time	0.0227	2.99	194	.003
Treatment × time ^c	-0.1824	-2.51	202	.01
Model 2: disability (WHODAS II score) after treatment (12-36 wk)				
Intercept	4.3338	2.74	227	.007
Treatment	-2.1414	-2.46	178	.01
Site	0.1446	0.19	180	.85
Time	0.0642	2.15	142	.03
Baseline WHODAS II score	0.7209	13.50	185	<.001
Treatment × time	0.0134	0.31	142	.76

Abbreviations: PST, problem-solving therapy; ST, supportive therapy; WHODAS II, World Health Organization Disability Assessment Schedule II (12 items).

^aTreatment: 0 indicates ST; 1, PST.

^bSite: 0 indicates University of California at San Francisco; 1, Weill Cornell Medical College.

^cThe time variable was centered at 12 weeks.

OUTCOMES AFTER COMPLETION OF TREATMENT (12-36 WEEKS)

Course of Disability

To study the course of disability (WHODAS II scores) after the end of treatment, a mixed-effects analysis was performed using a model consisting of treatment group (PST vs ST), site (Cornell vs UCSF), time (12, 24, and 36 weeks), treatment × time interaction, and baseline disability. Mixed-effects models demonstrated no significant difference between the PST and ST groups in the course of disability after treatment (group × time interaction: $t_{1,142}=0.16$, $P=.66$). Participants in both groups demonstrated an increase in disability (WHODAS II scores) between 12 and 36 weeks (time: $t_{1,142}=2.15$, $P=.03$; least squares means: PST-12 weeks=21.56, 24 weeks=22.49, and 36 weeks=23.42; ST-12 weeks=23.70, 24 weeks=24.47, and 36 weeks=25.23). Treatment site (UCSF vs Cornell) did not significantly contribute to WHODAS II score variance across time (between 12 and 36 weeks) ($t_{1,180}=0.19$, $P=.86$) (**Figure 4**).

Moderators After Completion of Treatment

No demographic or clinical characteristics assessed at study entry moderated the course of disability between 12 and 36 weeks, a period in which no treatment was offered (Table 2).

Relationship Between Depression and Disability

To examine whether depression severity predicted disability after the end of treatment, we studied the relationship between depression severity (HDRS scores) at weeks 12 and 24 and disability (WHODAS II scores) at weeks 24 and 36. A mixed-effects model was constructed consisting of treatment group (PST vs ST), site

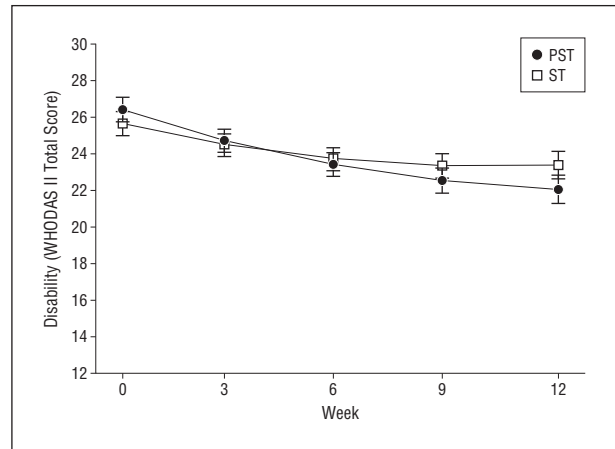


Figure 2. Mean disability (World Health Organization Disability Assessment Schedule II [WHODAS II]) scores during 12 weeks of treatment with problem-solving therapy (PST) vs supportive therapy (ST) in 221 older adults with major depression and executive dysfunction. The curves are based on the least squares means of the mixed-effects model: time + treatment + site + time × time + treatment × time (treatment × time: $t_{1,202}=0.31$, $P=.01$). Error bars represent SE.

(Cornell vs UCSF), time, and HDRS scores. The HDRS scores at weeks 12 and 24 predicted WHODAS II scores at weeks 24 and 36, respectively ($F_{1,103}=3.84$, $P=.002$). Specifically, for every point change in HDRS scores at weeks 12 and 24, there was a change of 0.18 in WHODAS II scores at weeks 24 and 36, respectively.

To examine whether disability predicted depression after the end of treatment, we studied the relationship between disability (WHODAS II scores) at weeks 12 and 24 and depression severity (HDRS scores) at weeks 24 and 36. A mixed-effects model was constructed consisting of treatment group (PST vs ST), site (Cornell vs UCSF), time, and WHODAS II scores. The WHODAS II scores at weeks 12 and 24 predicted HDRS scores at weeks 24 and 36, respectively ($F_{1,244}=54.74$, $P<.001$). Specifically, for every point change in WHODAS II

Table 2. Moderation of Problem-Solving Therapy Efficacy (vs Supportive Therapy) on Disability in 221 Older Adults With Major Depression and Executive Dysfunction

Evaluated Moderator	Value, Mean (SD)	Outcome: WHODAS II Score					
		0-12 wk			12-36 wk		
		F ^a	df	P Value	F ^a	df	P Value
Age, y	72.97 (7.74)	0.03	198	.86	1.3	145	.26
Education, y	15.24 (2.79)	2.67	195	.10	2.1	153	.15
Baseline variables							
Severity of depression (HDRS)	24.32 (4.27)	1.14	192	.29	0	158	.97
Age at depression onset, y	55.88 (22.35)	0.10	140	.75	1.39	106	.24
Depressive episodes, No.	2.23 (2.21)	4.15	153	.04	1.21	118	.27
Mini-Mental State Examination score	27.80 (1.69)	4.51	200	.04	1.44	151	.23
DRS-IP score	32.24 (3.71)	0	213	.99	0.10	160	.75
Stroop Color-Word Test score	22.03 (8.22)	0.07	201	.79	0.16	141	.69
Perseverative errors ^b	14.58 (9.12)	0	130	.97	1.08	107	.30
Trail Making Test Trails B score	137.59 (63.50)	0.01	174	.92	2.22	128	.14
Frontal Systems Behavior Scale, Clinician Rated, score	39.89 (9.04)	0.08	169	.77	0.01	140	.93
Neuroticism (NEO) score	14.98 (5.14)	1.94	192	.17	0.04	148	.85
Anxiety factor ^c	4.54 (2.00)	0	196	.99	2.27	150	.13

Abbreviations: DRS-IP, initiation/preservation scale of the Mattis Dementia Rating Scale; HDRS, Hamilton Depression Rating Scale; NEO, Neuroticism, Extroversion, Openness Scale; WHODAS II, World Health Organization Disability Assessment Schedule II.

^aEffect estimate reflecting the change in the difference between the HDRS slopes of the problem-solving therapy and supportive therapy groups when the moderator's score is increased by 1 point.

^bWisconsin Card Sorting Test.

^cSum of HDRS items: agitation, hypochondriasis, psychic anxiety, and somatic anxiety.

scores at weeks 12 and 24, there was an HDRS score change of 0.39 points at weeks 24 and 36, respectively.

COMMENT

The main finding of this study is that PST is more effective than ST in reducing disability in older patients with major depression and executive dysfunction. The advantage of PST over ST was most pronounced in patients with greater cognitive impairment and in those with a history of more depressive episodes, an often difficult-to-treat population. Disability increased in the PST and ST groups during the 2 years after the end of treatment, but the PST group retained the advantages made over ST made during the treatment period and experienced less disability during follow-up. The salutary effect of PST on disability in depressed, executive-impaired older adults is particularly important because such patients experience significant disability and are likely to have a poor or slow response to pharmacotherapy.^{16,29-36}

This is the first study, to our knowledge, to demonstrate that PST can reduce disability in older patients with major depression and executive dysfunction. However, we previously reported⁴⁴ that PST was superior to ST in reducing depressive symptoms and signs and in leading to higher rates of response and remission in the same sample. The benefit of PST over ST on disability was approximately the same as the benefit on depression. These findings are consistent with those of earlier studies documenting that PST benefits depressed elderly patients without cognitive impairment³⁹ and with significant medical burden.^{40,41,63} Furthermore, PST led to behavioral gains in schizophrenic patients with executive dysfunction.^{42,43}

This study has several limitations. Each therapist administered both PST and ST, a design that may have introduced a therapist bias on efficacy. An alternative design, with each therapist offering a single treatment only, would have drastically increased the sample size to control for therapist-specific effects.⁶⁴ Furthermore, a nested design does not exclude therapist bias because some therapists may assume that they offer the control treatment and view it as less efficacious. The study offered equally intensive training and certification procedures for PST and ST. Moreover, all PST and ST sessions were audio-taped, and a random 20% of sessions were reviewed by independent experts. Participants in this study had mild executive dysfunction. It is unclear whether PST is helpful in patients with severe executive dysfunction or in those with executive dysfunction as part of a dementia syndrome. Moreover, the absence of a depressed group without executive dysfunction prevents knowing whether executive dysfunction affects the efficacy of PST and ST. Finally, the sample selection process may have biased the results. Participants in the study had an average of 15 years of education, and one-fifth of those who met the selection criteria did not enter the study because of refusal or poor adherence to rating procedures. However, 91% of those who started treatment remained in treatment until the end of the 12-week period. Therefore, the results of this trial may be generalizable to educated older adults with the ability to remain in treatment. Another limitation might be the reliance on an interviewer-rated instrument for disability rather than a performance-based instrument. Performance-based instruments are time consuming and difficult to use in a study requiring frequent assessments to capture the timetable of disability change. Furthermore, performance instruments may be affected

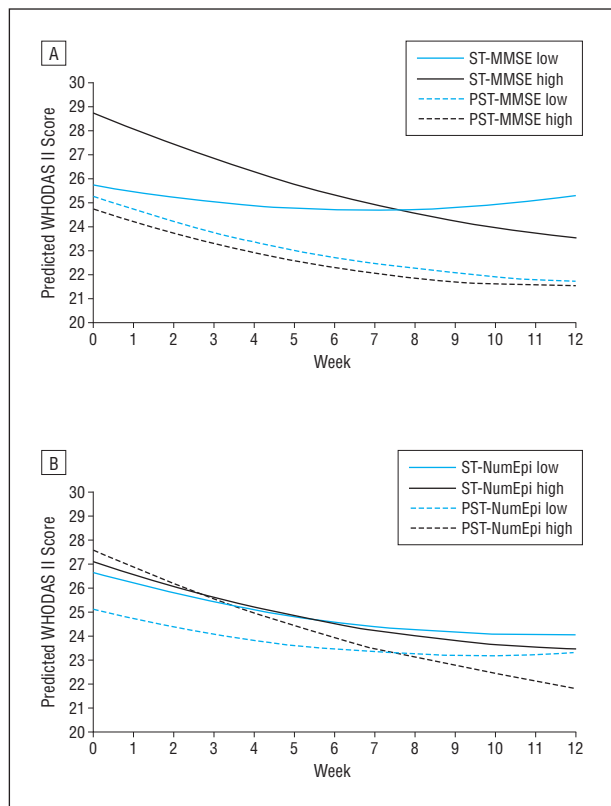


Figure 3. Moderators of problem-solving therapy (PST) efficacy (vs supportive therapy [ST]) on disability (World Health Organization Disability Assessment Schedule II [WHODAS II] scores) in 221 older adults with major depression and executive dysfunction. Mini-Mental State Examination (MMSE) scores at baseline ($F_{1,200}=4.51$, $P=.04$) (A) and number of depressive episodes (NumEpi) ($F_{1,153}=4.15$, $P=.04$) (B) moderate the effects of treatment on disability. The MMSE low and high scores are 1 SD below and above the mean, respectively (mean, 27.8; SD, 1.71); low number of depressive episodes equals 1 and high number of depressive episodes equals 4.

by the lack of energy and motivational disturbances of depression. The study paid for transportation and, when necessary, provided transportation. Therefore, its findings can be generalized only to individuals with access to treatment. Home-based care and use of telemedicine may make PST-type approaches available to an increasing number of patients.

The construct of disability is complex. Although associated with medical and psychiatric burden, disability is a distinct dimension of health with unique prognostic significance.¹⁹ In this study, disability was assessed using an interviewer-administered instrument (WHODAS II) that provides a comprehensive evaluation of disability (6 domains) associated with health conditions but not of functional states unrelated to health, for example, restriction in participation due to race, sex, religion, and socioeconomic factors. Finally, the WHODAS II treats all disorders at parity when determining the level of disability. The 12-item WHODAS II is suitable for frequent administration, and its strong psychometric properties and factor structure justify its use as a measure of global disability.^{52,65}

Participants in this study had moderate disability at entry; 27, the score approximating the mean baseline WHODAS II score of these participants, can be obtained by having severe impairment (score of 4) in 1 item, moderate impairment (score of 3) in 4 items, mild impairment

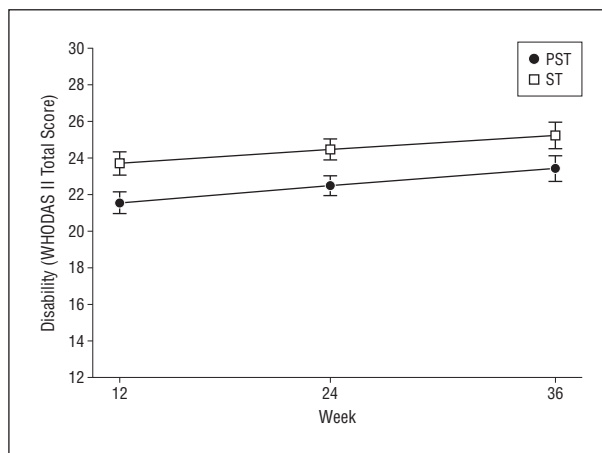


Figure 4. Mean disability (World Health Organization Disability Assessment Schedule II [WHODAS II]) scores after completion of treatment with problem-solving therapy (PST) vs supportive therapy (ST) (weeks 12-36) in 206 older adults with major depression and executive dysfunction. Curves are based on the least squares means of the mixed-effects model: time \times treatment + site + baseline WHODAS II score + treatment + time (treatment \times time: $t_{1,142}=0.31$, $P=.76$). Error bars represent SE.

(score of 2) in 4 items, and no impairment (score of 1) in 3 items. Disability declined in PST- and ST-treated patients. This was not surprising because PST and ST are active treatments. The mean difference in WHODAS II scores between the PST and ST groups at the end of the 12-week treatment was 2.3 points, equal to approximately 1 SD of healthy elderly individuals. However, even the PST-treated participants had mild disability (mean WHODAS II score: 21.8) at the end of the 12-week treatment phase. The remaining disability may be accounted for, in part, by the residual executive dysfunction at the end of the trial, an observation consistent with earlier literature.⁶⁶

The advantage of PST over ST emerged after week 6 of treatment, and it was retained during follow-up even though disability increased in both groups after the end of treatment. The design of this study does not permit identification of the exact mechanisms underlying the reasons and timing of PST efficacy. Indeed, there was a mild improvement in executive functions during the 12-week trial. However, change in executive functions during treatment was similar in the PST and ST arms and did not explain the PST therapeutic advantage. Another question is whether the disability measure was affected by the patients' depressive symptoms and whether change in disability mainly reflected change in reporting bias. Indeed, depression scores predicted subsequent change in disability, and disability scores predicted subsequent change in depression. However, the differential treatment effect on disability may not be fully accounted for by depression-related reporting bias. Reduction in depression did not mediate the differential effect of PST (over ST) on disability, although reduction in disability mediated the differential effect of PST (over ST) on depression. Developing skills that contribute to the individual's specific behavioral limitations is inherent in PST and seems to be consistent with the timetable of improvement in the PST group compared with the ST group. The first few weeks of PST are devoted to learning the problem-solving technique, and in the latter part of treatment, patients continue to use the PST approach alone or with the

therapist in problems with a negative effect on their lives. Therefore, the timing of PST efficacy parallels the course of PST skill development, behavioral activation, self-efficacy, and hopefulness.³⁸ Identifying the mechanisms and retaining the elements by which PST decreases disability and depression may simplify its administration and make it accessible to large numbers of patients.

Although PST led to a greater reduction in disability than did ST, both treatments reduced disability during the 12-week treatment phase. Although used as a comparison condition in this study, ST itself is a treatment with established efficacy in patients with a wide range of severity of depression.⁶⁷⁻⁷⁰ Therapeutic alliance and support are elements common to PST and ST and may have accounted for the high retention in treatment and the beneficial effect on disability and mood.⁷¹

This study noted a reciprocal relationship between disability and depression during the 12-week treatment phase and after treatment completion. This observation is consistent with findings in community-based populations. Among high-functioning elderly adults, depressive symptoms were associated with an increased risk of disability onset after adjusting for baseline sociodemographic factors, physical health, and cognitive functioning.³ Similarly, increases in disability across time predict the emergence of depressive symptoms.⁷²⁻⁷⁴

The therapeutic advantage of PST over ST on disability was not mediated by a reduction in depressive symptoms and signs. Therefore, the second hypothesis was not confirmed. However, reduction of disability mediated improvement in depressive symptoms during the 12-week treatment phase. This observation suggests that the higher efficacy of PST over ST in reducing depressive symptoms is, in part, due to a greater reduction in disability, perhaps through skill development and behavioral activation.

Although anxiety, neuroticism, and behavioral symptoms of executive dysfunction did not affect treatment efficacy, PST conferred greater benefits than did ST to patients with greater cognitive impairment and a history of numerous depressive episodes. Cognitively impaired patients with recurrent depression are difficult to treat and may require skill development in addition to the empathy and support offered by PST and ST. Observing that PST reduced disability in nondemented patients with cognitive impairment encourages studies of PST modified to address the needs of depressed patients with mild dementia.

In conclusion, the results of this study suggest that PST is effective in reducing disability in older patients with major depression and executive dysfunction. The difference between PST and ST was particularly prominent in patients with greater cognitive impairment and more previous episodes. Reduction in disability paralleled reduction in depressive symptoms. The therapeutic advantage of PST over ST in reducing depression was, in part, due to the greater reduction in disability by PST. Although disability increased during the 2 years after the end of treatment, the gains made by PST-treated patients were retained. Thus, PST may be a promising treatment for an older patient population with significant disability likely to fail antidepressant drug therapy. The next steps following these findings may include approaches aimed to sustain the effects of PST (eg, booster ses-

sions) and interventions to improve access to PST by disabled community populations (including home-based care and telemedicine).

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REFERENCES

1. Lehman AF, Alexopoulos GS, Goldman H, Jeste D, Unstun B. Mental disorders and disability: time to reevaluate the relationship? In: Kupfer DJ, First MB, Regier DA, eds. *A Research Agenda for DSM-IV*. Washington, DC: American Psychiatric Association; 2002:201-218.
2. Murray CJL, Lopez AD, eds. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability From Diseases, Injuries and Risk Factors in 1990 and Projected to 2020*. Cambridge, MA: Harvard University Press; 1996.
3. Bruce ML, Seeman TE, Merrill SS, Blazer DG. The impact of depressive symptomatology on physical disability: MacArthur Studies of Successful Aging. *Am J Public Health*. 1994;84(11):1796-1799.
4. Cronin-Stubbs D, de Leon CF, Beckett LA, Field TS, Glynn RJ, Evans DA. Six-year effect of depressive symptoms on the course of physical disability in community-living older adults. *Arch Intern Med*. 2000;160(20):3074-3080.
5. Dalle Carbonare L, Maggi S, Noale M, Giannini S, Rozzini R, Lo Cascio V, Crepaldi G; ILSA Working Group; The Italian Longitudinal Study on Aging (ILSA). Physical disability and depressive symptomatology in an elderly population: a complex relationship. *Am J Geriatr Psychiatry*. 2009;17(2):144-154.
6. Penninx BW, Guralnik JM, Ferrucci L, Simonsick EM, Deeg DJ, Wallace RB. Depressive symptoms and physical decline in community-dwelling older persons. *JAMA*. 1998;279(21):1720-1726.
7. Andreescu C, Chang CC, Mulsant BH, Ganguli M. Twelve-year depressive symptom trajectories and their predictors in a community sample of older adults. *Int Psychogeriatr*. 2008;20(2):221-236.
8. Barry LC, Allore HG, Bruce ML, Gill TM. Longitudinal association between depressive symptoms and disability burden among older persons. *J Gerontol A Biol Sci Med Sci*. 2009;64(12):1325-1332.
9. Steffens DC, Hays JC, Krishnan KR. Disability in geriatric depression. *Am J Geriatr Psychiatry*. 1999;7(1):34-40.
10. Brenes GA, Penninx BW, Judd PH, Rockwell E, Sewell DD, Wetherell JL. Anxiety, depression and disability across the lifespan. *Aging Ment Health*. 2008;12(1):158-163.
11. Sinclair PA, Lyness JM, King DA, Cox C, Caine ED. Depression and self-reported functional status in older primary care patients. *Am J Psychiatry*. 2001;158(3):416-419.
12. Lyness JM, King DA, Cox C, Yoediono Z, Caine ED. The importance of subsyndromal depression in older primary care patients: prevalence and associated functional disability. *J Am Geriatr Soc*. 1999;47(6):647-652.
13. Karp JF, Skidmore E, Lotz M, Lenze E, Dew MA, Reynolds CF III. Use of the Late-Life Function and Disability instrument to assess disability in major depression. *J Am Geriatr Soc*. 2009;57(9):1612-1619.
14. Alexopoulos GS, Kiosses DN, Klimstra S, Kalayam B, Bruce ML. Clinical presentation of the "depression-executive dysfunction syndrome" of late life. *Am J Geriatr Psychiatry*. 2002;10(1):98-106.
15. Elderkin-Thompson V, Kumar A, Bilker WB, Dunkin JJ, Mintz J, Moberg PJ, Meshulam RI, Gur RE. Neuropsychological deficits among patients with late-onset minor and major depression. *Arch Clin Neuropsychol*. 2003;18(5):529-549.
16. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Latoussakis V, Kanelopoulos D,

- Klimstra S, Lim KO, Hoptman MJ. Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry*. 2008;165(2):238-244.
17. Gunning-Dixon FM, Hoptman MJ, Lim KO, Murphy CF, Klimstra S, Latoussakis V, Majcher-Tascio M, Hrabe J, Ardekani BA, Alexopoulos GS. Macromolecular white matter abnormalities in geriatric depression: a magnetization transfer imaging study. *Am J Geriatr Psychiatry*. 2008;16(4):255-262.
 18. Andreescu C, Butters MA, Begley A, Rajji T, Wu M, Meltzer CC, Reynolds CF III, Aizenstein H. Gray matter changes in late life depression—a structural MRI analysis. *Neuropsychopharmacology*. 2008;33(11):2566-2572.
 19. Alexopoulos GS, Vrontou C, Kakuma T, Meyers BS, Young RC, Klausner E, Clarkin J. Disability in geriatric depression. *Am J Psychiatry*. 1996;153(7):877-885.
 20. Kiosses DN, Klimstra S, Murphy C, Alexopoulos GS. Executive dysfunction and disability in elderly patients with major depression. *Am J Geriatr Psychiatry*. 2001;9(3):269-274.
 21. Kiosses DN, Alexopoulos GS, Murphy C. Symptoms of striatofrontal dysfunction contribute to disability in geriatric depression. *Int J Geriatr Psychiatry*. 2000;15(11):992-999.
 22. Moorhouse P, Song X, Rockwood K, Black S, Kertesz A, Gauthier S, Feldman H; Consortium to investigate vascular impairment of cognition. Executive dysfunction in vascular cognitive impairment in the consortium to investigate vascular impairment of cognition study. *J Neurol Sci*. 2010;288(1-2):142-146.
 23. Johnson JK, Lui LY, Yaffe K. Executive function, more than global cognition, predicts functional decline and mortality in elderly women. *J Gerontol A Biol Sci Med Sci*. 2007;62(10):1134-1141.
 24. Atkinson HH, Rosano C, Simonsick EM, Williamson JD, Davis C, Ambrosius WT, Rapp SR, Cesari M, Newman AB, Harris TB, Rubin SM, Yaffe K, Satterfield S, Kritchevsky SB; Health ABC study. Cognitive function, gait speed decline, and comorbidities: the Health, Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci*. 2007;62(8):844-850.
 25. Steffens DC, Bosworth HB, Provenzale JM, MacFall JR. Subcortical white matter lesions and functional impairment in geriatric depression. *Depress Anxiety*. 2002;15(1):23-28.
 26. Steffens DC, Pieper CF, Bosworth HB, MacFall JR, Provenzale JM, Payne ME, Carroll BJ, George LK, Krishnan KR. Biological and social predictors of long-term geriatric depression outcome. *Int Psychogeriatr*. 2005;17(1):41-56.
 27. Alexopoulos GS, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Murphy CF. Anterior cingulate dysfunction in geriatric depression. *Int J Geriatr Psychiatry*. 2008;23(4):347-355.
 28. Kiosses DN, Alexopoulos GS. IADL functions, cognitive deficits, and severity of depression: a preliminary study. *Am J Geriatr Psychiatry*. 2005;13(3):244-249.
 29. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Kalayam B, Katz R, Kanellopoulos D, Etwaroo GR, Klimstra S, Foxe JJ. Event-related potentials in an emotional go/no-go task and remission of geriatric depression. *Neuroreport*. 2007;18(3):217-221.
 30. Alexopoulos GS, Kiosses DN, Heo M, Murphy CF, Shanmugham B, Gunning-Dixon F. Executive dysfunction and the course of geriatric depression. *Biol Psychiatry*. 2005;58(3):204-210.
 31. Alexopoulos GS, Kiosses DN, Murphy C, Heo M. Executive dysfunction, heart disease burden, and remission of geriatric depression. *Neuropsychopharmacology*. 2004;29(12):2278-2284.
 32. Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, Sirey JA, Hull J. Executive dysfunction and long-term outcomes of geriatric depression. *Arch Gen Psychiatry*. 2000;57(3):285-290.
 33. Kalayam B, Alexopoulos GS. Prefrontal dysfunction and treatment response in geriatric depression. *Arch Gen Psychiatry*. 1999;56(8):713-718.
 34. Potter GG, Kittinger JD, Wagner HR, Steffens DC, Krishnan KR. Prefrontal neuropsychological predictors of treatment remission in late-life depression. *Neuropsychopharmacology*. 2004;29(12):2266-2271.
 35. Sneed JR, Culang ME, Keilp JG, Rutherford BR, Devanand DP, Roose SP. Anti-depressant medication and executive dysfunction: a deleterious interaction in late-life depression. *Am J Geriatr Psychiatry*. 2010;18(2):128-135.
 36. Sneed JR, Roose SP, Keilp JG, Krishnan KR, Alexopoulos GS, Sackeim HA. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry*. 2007;15(7):553-563.
 37. Alexopoulos GS, Raue PJ, Kanellopoulos D, Mackin S, Areán PA. Problem solving therapy for the depression-executive dysfunction syndrome of late life. *Int J Geriatr Psychiatry*. 2008;23(8):782-788.
 38. D'Zurilla TJ, Nezu AM. *Problem-Solving Therapy: A Social Competence Approach to Clinical Intervention*. New York, NY: Singer; 1999.
 39. Areán PA, Perri MG, Nezu AM, Schein RL, Christopher F, Joseph TX. Comparative effectiveness of social problem-solving therapy and reminiscence therapy as treatments for depression in older adults. *J Consult Clin Psychol*. 1993;61(6):1003-1010.
 40. Arean P, Hegel M, Vannoy S, Fan MY, Unutzer J. Effectiveness of problem-solving therapy for older, primary care patients with depression: results from the IMPACT project. *Gerontologist*. 2008;48(3):311-323.
 41. Rovner BW, Casten RJ. Preventing late-life depression in age-related macular degeneration. *Am J Geriatr Psychiatry*. 2008;16(6):454-459.
 42. Tarrrier N, Sharpe L, Beckett R, Harwood S, Baker A, Yusopoff L. A trial of two cognitive behavioural methods of treating drug-resistant residual psychotic symptoms in schizophrenic patients. II. Treatment-specific changes in coping and problem-solving skills. *Soc Psychiatry Psychiatr Epidemiol*. 1993;28(1):5-10.
 43. van der Gaag M, Kern RS, van den Bosch RJ, Liberman RP. A controlled trial of cognitive remediation in schizophrenia. *Schizophr Bull*. 2002;28(1):167-176.
 44. Areán PA, Raue P, Mackin RS, Kanellopoulos D, McCulloch C, Alexopoulos GS. Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction [published online ahead of print June 1, 2010]. *Am J Psychiatry*. 2010.
 45. Nezu AM, Nezu CM, Perri MG. *Problem-Solving Therapy for Depression: Theory, Research, and Clinical Guidelines*. New York, NY: John Wiley & Sons; 1989.
 46. Spitzer RL, Williams JBW, Gibbons M. *Structured Clinical Interview for Axis I DSM-IV Disorders (SCID)*. Washington, DC: American Psychiatric Association Press Inc; 1995.
 47. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
 48. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
 49. Mattis S. *Dementia Rating Scale*. Odessa, FL: Psychological Assessment Resources; 1989.
 50. Perret E. The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia*. 1974;12(3):323-330.
 51. Wetherell JL, Petkus AJ, McChesney K, Stein MB, Judd PH, Rockwell E, Sewell DD, Patterson TL. Older adults are less accurate than younger adults at identifying symptoms of anxiety and depression. *J Nerv Ment Dis*. 2009;197(8):623-626.
 52. World Health Organization. *World Health Organization Disability Assessment Schedule (WHODAS II)*. Geneva, Switzerland: WHO; 2000.
 53. Lineweaver TT, Bond MW, Thomas RG, Salmon DP. A normative study of Nelson's (1976) modified version of the Wisconsin Card Sorting Test in healthy older adults. *Clin Neuropsychol*. 1999;13(3):328-347.
 54. Reitan R, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Therapy and Clinical Interpretation*. Tucson, AZ: Neuropsychological Press; 1985.
 55. Stout JC, Ready RE, Grace J, Malloy PF, Paulsen JS. Factor analysis of the Frontal Systems Behavior Scale (FrSBe). *Assessment*. 2003;10(1):79-85.
 56. McCrae RR, John OP. An introduction to the five-factor model and its applications. *J Pers*. 1992;60(2):175-215.
 57. Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Feder M, Einhorn A, Rosendahl E. Recovery in geriatric depression. *Arch Gen Psychiatry*. 1996;53(4):305-312.
 58. Hegel MT, Dietrich AJ, Seville JL, Jordan CB. Training residents in problem-solving treatment of depression: a pilot feasibility and impact study. *Fam Med*. 2004;36(3):204-208.
 59. Marmar C, Weiss D, Gaston L. Toward the validation of the California Therapeutic Alliance Rating System. *J Consult Clin Psychol*. 1989;1:46-52.
 60. Areán PA, Raue PJ, Julian LJ. *Social Problem-Solving Therapy for Depression and Executive Dysfunction*. San Francisco, California: University of California, San Francisco; 2003.
 61. Sacks MH. *Manual for Supportive Therapy*. New York, NY: Cornell University; 2000.
 62. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. *Stat Med*. 1992;11(2):167-178.
 63. Gellis ZD, McGinty J, Horowitz A, Bruce ML, Misener E. Problem-solving therapy for late-life depression in home care: a randomized field trial. *Am J Geriatr Psychiatry*. 2007;15(11):968-978.
 64. Bhaumik DK, Roy A, Aryal S, Hur K, Duan N, Normand SL, Brown CH, Gibbons RD. Sample size determination for studies with repeated continuous outcomes. *Psychiatr Ann*. 2008;38(12):765-771.
 65. Andrews G, Kemp A, Sunderland M, Von Korff M, Ustun TB. Normative data for the 12 item WHO Disability Assessment Schedule 2.0. *PLoS One*. 2009;4(12):e8343.
 66. Murphy CF, Alexopoulos GS. Longitudinal association of initiation/perseveration and severity of geriatric depression. *Am J Geriatr Psychiatry*. 2004;12(1):50-56.
 67. Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, Leese M, McCrone P, Harris T, Moore M, Byng R, Brown G, Barthel S, Mander H, Ring A, Kelly V, Wallace V, Gabbay M, Craig T, Mann A. Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study. *Health Technol Assess*. 2009;13(22):iii-iv, ix-xi, 1-159.
 68. Freedland KE, Skala JA, Carney RM, Rubin EH, Lustman PJ, Dávila-Román VG, Steinmeyer BC, Hogue CW Jr. Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. *Arch Gen Psychiatry*. 2009;66(4):387-396.
 69. Freeman MP, Davis MF. Supportive psychotherapy for perinatal depression: preliminary data for adherence and response. *Depress Anxiety*. 2010;27(1):39-45.
 70. Brajković L, Jevtović S, Bilić V, Bras M, Loncar Z. The efficacy of a brief supportive psychodynamic therapy in treating anxious-depressive disorder in Daily Hospital. *Coll Antropol*. 2009;33(1):245-251.
 71. Oei TPS, Shuttlewood GJ. Comparison of specific and nonspecific factors in a group cognitive therapy for depression. *J Behav Ther Exp Psychiatry*. 1997;28(3):221-231.
 72. Bruce ML. Depression and disability in late life: directions for future research. *Am J Geriatr Psychiatry*. 2001;9(2):102-112.
 73. Lenze EJ, Rogers JC, Martire LM, Mulsant BH, Rollman BL, Dew MA, Schulz R, Reynolds CF III. The association of late-life depression and anxiety with physical disability: a review of the literature and prospectus for future research. *Am J Geriatr Psychiatry*. 2001;9(2):113-135.
 74. Weinberger MI, Raue PJ, Meyers BS, Bruce ML. Predictors of new onset depression in medically ill, disabled older adults at 1 year follow-up. *Am J Geriatr Psychiatry*. 2009;17(9):802-809.