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THE EFFECTS OF MEMORY, ATTENTION, AND EXECUTIVE DYSFUNCTION ON OUTCOMES OF DEPRESSION IN A PRIMARY CARE INTERVENTION TRIAL: THE PROSPECT STUDY

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Abstract

OBJECTIVE—To describe the influence of domains of cognition on remission and response of depression in an intervention trial among older primary care patients.

METHODS—Twenty primary care practices were randomly assigned to Usual Care or to an Intervention consisting of a depression care manager offering algorithm-based care for depression. In all, 599 adults 60 years and older with a depression diagnosis were included in these analyses. Depression severity and remission of depression were assessed by the 24-item Hamilton Depression Rating Scale. The Mini-Mental State Examination (MMSE) was our global measure of cognitive function. Verbal memory was assessed with the memory subscale of the Dementia Rating Scale. Attention was measured with the digit span from the Weschler Adult Intelligence Test. Response inhibition, one of the executive functions, was assessed with the Stroop Color-Word test.

RESULTS—The intervention was associated with improved remission and response rates regardless of cognitive impairment. Response inhibition as measured by the Stroop Color-Word test appeared to significantly modify the intervention versus usual care difference in remission and response at 4 months. Patients in the poorest performance quartile at baseline on the Stroop Color-Word test in the Intervention Condition were more likely to achieve remission of depression at 4 months than comparable patients in Usual Care (odds ratio (OR) = 17.76, 95% confidence interval (CI) [3.06, 103.1]).

CONCLUSIONS—Depressed older adults in primary care with executive dysfunction have low remission and response rates when receiving usual care but benefit from depression care management.

Keywords

Depression; treatment; primary health care; aged; cognition

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INTRODUCTION

Recent developments have called attention to a late-life depression characterized by cognitive or executive functioning deficits and psychomotor retardation (Alexopoulos et al., 1997; Alexopoulos et al., 2002). Impairment in some executive functions has been found to predict nonresponse to fluoxetine in major depression among a sample of 14 young and middle aged women who participated in a randomized, double-blind, placebo-controlled trial of the effectiveness of fluoxetine in treating major depression (Dunkin et al., 2000). Among older psychiatric patients with major depression, abnormal performance in tasks of response inhibition (Stroop Color-Word), initiation/perseveration, and other executive functions (Potter et al., 2004) appear to predict poor or delayed response to antidepressant drugs (Kalayam and Alexopoulos, 1999; Alexopoulos et al., 2004; Alexopoulos et al., 2005b) and early relapse and recurrence of major depression (Alexopoulos et al., 2000). However, an analysis of psychiatric patients in two independent intervention trials failed to replicate these findings (Butters et al., 2004). Nonetheless, there is evidence that randomized depressed elderly psychiatric patients with executive dysfunction respond favorably to problem solving therapy compared to supportive therapy (Alexopoulos et al., 2003). Memory, attention, and overall cognitive functioning have not been found to be related to relapse or recurrence of major depression among older adults (Butters et al., 2004).

In primary care, the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial found that depressed older adults in a depression care management intervention had better depression outcomes at one year regardless of baseline global cognitive status when compared to depressed older adults in usual care (Steffens et al., 2006). However, a paucity of information exists on the relationship between specific cognitive domains and the outcomes of depression for older patients in a primary care depression trial. Whether a comprehensive intervention can improve the outcomes of depression among older primary care patients with executive dysfunction remains unclear.

The PROSPECT Study (Prevention of Suicide in Primary care Elderly: Collaborative Trial) was a multisite effectiveness trial designed to assess the use of multi-component intervention on reducing major risk factors for suicide in late life, primarily depression. The PROSPECT intervention involved a depression care manager providing algorithm-based care for the elderly. Ethnically-diverse patients from community-based primary care practices were carefully screened and sampled to ensure the representativeness of the final sample.

The overall goal of this analysis was to determine the influence of specific domains of cognition on remission and response of depression to treatment among older primary care patients. Our specific aims were to: (1) examine and compare the role of specific domains of cognitive impairment on outcomes of depression in the Usual Care and in the PROSPECT Intervention arms, and (2) investigate whether cognitive status modified the intervention versus usual care difference in remission or response. We hypothesized that among depressed older primary care patients with executive dysfunction, participants receiving the comprehensive treatment intervention involving vigilant clinical attention would experience better treatment outcomes than those receiving Usual Care.

METHODS

The PROSPECT Study

The PROSPECT Study compared a primary care based intervention with usual care in improving the outcomes of depression. All study procedures were implemented with written informed consent, and the study protocols were approved by the Institutional Review Board of Cornell University, the University of Pittsburgh, and the University of Pennsylvania Schools

of Medicine. Details of the study design of the PROSPECT Study are available elsewhere (Mulsant et al., 2001; Schulberg et al., 2001; Bruce et al., 2004).

Description of Intervention Condition and Usual Care

The PROSPECT treatment algorithm and implementation including the types and proportions of treatment received over time by persons in practices randomized to the Intervention Condition or to Usual Care has been described in detail elsewhere (Bruce et al., 2004). Briefly, the intervention consisted of trained depression care managers offering guideline concordant recommendations to the primary care physicians and helping patients with adherence to treatment. Patients who refused antidepressants were offered interpersonal psychotherapy (IPT) by the depression care managers. In Usual Care, physicians were informed of their patients' depression diagnoses but no specific recommendations were given to these physicians regarding individual patients except for psychiatric emergencies.

Depression measures

Trained research assistants (Ph.D., M.A. or experienced B.A. level) assigned depression diagnoses to patients using the Structured Clinical Interview for Axis I DSM-IV Diagnoses (SCID) (Spitzer et al., 1995). Severity of depression was assessed using the 24-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Consistent with other geriatric depression studies (Lecrubier, 2002; Alexopoulos et al., 2005a), remission was defined as a (HDRS) score lower than 10. For geriatric depression, a HDRS score lower than 10 is often used because older patients often have chronic medical conditions which result in somatic symptoms and are reflected in the HDRS score. We also performed the analyses using a change in the Hamilton Depression Rating Scale (HDRS) scores $\geq 50\%$ as a marker for response to treatment.

Cognitive function measures

The Mini-Mental State Examination (MMSE) is a short standardized mental status examination that has been widely employed for clinical and research purposes (Folstein et al., 1975); (Tombaugh and McIntyre, 1992); (Crum et al., 1993). Verbal memory was assessed using a subscale of the Mattis Dementia Rating Scale (DRS) (Mattis, 1988). Immediate recall and delayed recognition were examined separately. Attention was measured with the digit span from the Wechsler Adult Intelligent Test (Wechsler, 1981). Response inhibition, one of the executive functions, was tested with the Stroop Color-Word test (Golden, 1978).

Analytic strategy

We calculated descriptive statistics for the participants to assess the representativeness of the sample. For this analysis, our sample included 599 participants who were targeted by the intervention: those with major depression or clinically significant minor depression (Bruce et al., 2004). First, we examined the domains of cognitive impairment by treatment assignment. MMSE scores were analyzed as a dichotomous variable with scores less than 24 representing cognitive impairment. For the other cognitive tests, the participants were divided into quartiles and the group of participants in the poorest quartile of performance was compared to the group in the top three quartiles of performance. For aim 1, an estimate of association (an odds ratio) along with a corresponding standard error and a p-value (two-tailed) was produced for specific domains of cognitive impairment with remission and response of depression as the outcomes at 4, 8, and 12 months (as in prior work (Bruce et al., 2004; Bogner et al., 2005)). These analyses were based on longitudinal models with random effects for clustering by patient. For all longitudinal and depression outcomes, clustering by practice and pairs of practice was negligible and did not affect the analysis, corresponding to previous results by Wells et al (Wells et al., 2000). All models were adjusted for baseline HDRS score and suicidal ideation. For aim 2, we were interested not only in whether the intervention was effective in the face of

cognitive impairment, but also in whether cognitive status modified the relationship between the two study arms and outcomes. To accomplish this aim, we introduced terms representing the interaction between presence of cognitive impairment and the two study arms into separate models for each specific domain of cognitive impairment at 4, 8, and 12 months. A priori, our primary analysis focused on the 4 month outcomes because the PROSPECT intervention intent to treat effects were statistically significant at 4 months (Bruce et al., 2004). The 8 and 12 month outcomes were therefore secondary analyses. The PROC NLMIXED macros in SAS were used to estimate the random effects models for binary outcomes. SAS version 9.1 was used to carry out analyses (SAS Institute Inc., Cary, North Carolina).

RESULTS

Study sample

The mean age of our study sample was 70.3 ± 7.9 (range 60–94). In all, 429 (71.6%) of the participants were women. The self-identified ethnic groups of the participants consisted of 419 whites (70.1%), 163 African-Americans (27.3%), and 16 American Indians, Hispanics or Asians (2.7%). Of the 599 depressed patients, 396 (66.1%) met DSM-IV criteria for major depression.

None of the specific domains of cognition were significantly correlated with assignment to the Intervention Condition versus Usual Care (all $p > 0.14$). Among depressed patients, remission and response rates for patients within specific domains of cognition, and stratified by treatment assignment, are presented in Table 1.

Remission and domains of cognitive impairment at 4 months

In pursuing our first aim, we evaluated the association of specific domains of cognition with remission (HDRS < 10) according to assignment to the Intervention Condition versus Usual Care using multiple logistic regression. The PROSPECT intervention was associated with improved remission rates across domains of cognition at 4 months. In pursuing our second aim, we studied interactions between the Intervention Condition versus Usual Care and specific domains of cognitive impairment. Response inhibition as measured by the Stroop Color-Word test appeared to significantly modify the intervention versus usual care difference in remission at 4 months (p -value for the interaction term = 0.04). Older adults in the poorest performance quartile on the Stroop Color-Word test were more likely to achieve remission (HDRS < 10) at 4 months if treated in Intervention Condition compared to Usual Care (odds ratio (OR) = 17.76, 95% confidence interval (CI) [3.06, 103.1]; Table 2).

Response and domains of cognitive impairment at 4 months

Response was defined as a change in HDRS scores $\geq 50\%$ from baseline. The analyses focusing on response paralleled the analyses of remission, and the results for response were similar to results for remission discussed previously. The interaction between the two study arms and response inhibition as measured by the Stroop Color-Word test was statistically significant at 4 months (p -value for the interaction term = 0.02). Older adults in the poorest performance quartile on the Stroop Color-Word test were more likely to achieve response (a change in HDRS scores $\geq 50\%$ from baseline) at 4 months if treated in Intervention Condition compared to Usual Care (OR = 14.86, 95% CI [3.40, 65.06]; Table 3).

Secondary analysis of 8 and 12 month outcomes

The patterns of the point estimates generally demonstrate an overall improvement in the Intervention Condition versus Usual Care across domains of cognition at 8 and 12 months. Although the interaction between the two study arms and global cognitive status as measured

by the MMSE was statistically significant at 8 months in our response analysis (p-value for the interaction term = 0.04), we did not find a statistically significant interaction in our remission analysis (p-value for the interaction term = 0.53).

DISCUSSION

The principal finding of this study was that depressed older adults in primary care with executive dysfunction have low remission and response rates when receiving usual care but benefit from collaborative care by trained depression care managers and primary care physicians at 4 months. Depressed older adults in primary care with executive dysfunction may need more intensive, individualized treatments in order to undergo depression remission or response. Consistent with the results of the IMPACT trial (Steffens et al., 2006), more favorable remission and response rates were generally noted among patients treated in the Intervention Condition, compared to Usual Care, across all domains of cognition.

Before discussing the significance of these findings, the results must be considered in the context of some potential study limitations. First, we obtained our results only from primary care sites in greater New York City, Philadelphia, and Pittsburgh whose patients may not be representative of other primary care practices. Second, selection bias is a potential limitation because, although the larger project was based on a random sample of primary care patients, the data on cognitive status and clinical remission of depression consisted of all who were selected for the larger project, agreed to participate, and had complete information. Finally, we realize that standardized measures of memory, attention, and response inhibition are fallible and may tap constructs that were not intended by the developers or implied by the labels given them.

The purpose of our analysis was to examine the role of the PROSPECT intervention on outcomes of depression in primary care with regard to specific domains of cognition. Our data are consistent with other authors who have reported that executive dysfunction is associated with worse outcomes for depression. Treatment of depression in the Usual Care practices probably consisted mainly of pharmacotherapy which is a treatment modality to which many depressed patients with executive dysfunction respond poorly (Kalayam and Alexopoulos, 1999; Alexopoulos et al., 2000; Dunkin et al., 2000; Alexopoulos et al., 2004; Potter et al., 2004; Alexopoulos et al., 2005b). Although the relationship between late-life depression, executive function, and depression course is complex and some data has failed to support a relationship between depression course and executive dysfunction (Butters et al., 2004), our results indicate that patients in Usual Care with impaired response inhibition may be at particularly high risk for poor outcomes. Depressed patients with executive dysfunction have been found to respond to problem-solving therapy modified to address the behavioral deficits resulting from depression and executive impairment (Alexopoulos et al., 2003). In our study, the Intervention Condition included frequent contact with patients, guidance, and in some cases interpersonal psychotherapy. Thus the Intervention offered behavioral interventions to which depressed, executively impaired patients have been found to respond. Depressed patients with executive dysfunction who are at risk for poor antidepressant response may require the care management provided in the Intervention Condition. Our findings require confirmation in future studies with other executive dysfunction measures.

In contrast, the lack of a significant interaction between global cognition, memory, or attention measures and the two study arms on depression outcomes may indicate that separate processes are involved in specific domains of cognition and depression response. Our results are consistent with other authors who failed to find a relationship between global cognition, memory, or attention measures and time-to-relapse or recurrence of major depression among older adults (Butters et al., 2004). In our study, collaborative care by trained depression care

managers and primary care physicians was as effective in promoting remission of depression in depressed older primary care patients with prominent cognitive impairment as those without prominent cognitive impairment on global cognitive, memory, or attention measures. The combination of clinical evaluation and monitoring, pharmacotherapy and in some cases interpersonal psychotherapy appears to be as effective in patients with and without global cognitive impairment, severe inattention, or memory impairment.

Identifying older primary care patients with specific domains of cognitive impairment who are at risk for not responding to standard depression treatment is important in order to identify patients who may be in need of more intensive treatments and referral. Easy to administer cognitive tests in primary care are needed to identify these patients who are at risk early in the course of treatment. Our results suggest trained depression care managers combined with algorithm-based care can attenuate the effects of executive dysfunction, and call attention to the need for assessing cognitive abilities when evaluating the effects of interventions focused on depression.

Key Points

1. Late life depression often presents in primary care in patients with cognitive impairment.
2. Identifying older primary care patients with specific domains of cognitive impairment who are at risk for not responding to standard depression treatment is important in order to identify patients who may be in need of more intensive treatments and referral.
3. Depressed older adults in primary care with executive dysfunction have low remission and response rates when receiving usual care but benefit from collaborative care by trained depression care managers and primary care physicians.
4. The combination of clinical evaluation and monitoring, pharmacotherapy and in some cases interpersonal psychotherapy appears to be as effective in patients with and without global cognitive impairment, severe inattention, or memory impairment.

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Table 1
Clinical remission and response for patients with depression affected by specific domains of cognition

Cognitive Status	Percent remission of depression (HDRS<10), (n)						Percent response (≥50 change in HDRS), n is same as for remission					
	4 month		8 month		12 month		4 month		8 month		12 month	
	Intervention	Usual Care	Intervention	Usual Care	Intervention	Usual Care	Intervention	Usual Care	Intervention	Usual Care	Intervention	Usual Care
MMSE												
	MMSE < 24	33(18)	33(21)	40(20)	50(14)	50(18)	44	33	29	50	43	22
Verbal memory DRS	MMSE ≥ 24	49(235)	35(214)	44(194)	55(203)	53(170)	43	29	47	34	53	44
	Lowest quartile	52(54)	31(49)	46(41)	55(47)	58(31)	48	24	44	37	53	42
	Highest three quartiles	52(132)	37(145)	42(135)	55(111)	51(121)	44	31	48	35	53	41
Verbal memory DRS	Lowest quartile	54(48)	32(44)	46(37)	54(37)	48(33)	50	25	37	35	46	36
	Highest three quartiles	51(137)	36(148)	43(137)	55(120)	53(118)	43	30	50	36	55	42
Attention Weschler digit span	Lowest quartile	41(37)	26(47)	34(38)	45(31)	55(29)	43	21	41	34	52	45
	Highest three quartiles	56(143)	39(147)	45(138)	57(122)	52(123)	48	33	49	36	52	40
Response Inhibition Stroop Color-Word	Lowest quartile	60(47)	26(38)	44(32)	56(43)	48(27)	60	21	43	41	47	26
	Highest three quartiles	45(134)	35(135)	42(125)	52(112)	55(109)	40	29	48	32	51	47

Notes: Data gathered from the PROSPECT study. HDRS = Hamilton Depression Rating Scale; MMSE = Mini-Mental State Examination; DRS = Mattis Dementia Rating Scale

Table 2

Odds ratios for remission for depressed patients (HDRS <10) according to specific domains of cognition

Cognitive Status	Quartiles of performance	Intervention Condition versus Usual Care		
		OR [CI] 4 months	OR [CI] 8 months	OR [CI] 12 months
All depressed patients				
MMSE	MMSE < 24	1.11 [0.08, 14.98]	0.81 [0.05,13.46]	1.53 [0.09,24.67]
	MMSE ≥ 24	3.93 [1.83, 8.47]	2.06 [0.95, 4.48]	1.53 [0.68, 3.43]
	Interaction p-value	p=0.36	p=0.53	p= 1.00
Verbal memory DRS memory, immediate recall	Lowest quartile	7.48 [1.43, 39.24]	1.31 [0.24, 7.03]	1.39 [0.23, 8.25]
	Highest three quartiles	3.63 [1.39, 9.45]	2.39 [0.91, 6.31]	1.50 [0.55, 4.09]
	Interaction p-value	p=0.45	p=0.54	p=0.94
Verbal memory DRS memory, delayed recall	Lowest quartile	7.57 [1.37, 41.72]	1.04 [0.18, 5.95]	1.76 [0.28, 10.84]
	Highest three quartiles	3.67 [1.40, 9.63]	2.31 [0.88, 6.07]	1.46 [0.53, 4.01]
	Interaction p-value	p=0.46	p=0.43	p=0.86
Attention Weschler digit span	Lowest quartile	3.81 [0.62, 23.19]	4.45 [0.69, 28.54]	0.80 [0.11, 5.78]
	Highest three quartiles	4.93 [1.84, 13.15]	1.90 [0.72, 5.03]	1.77 [0.64, 4.89]
	Interaction p-value	p=0.80	p=0.42	p=0.48
Response Inhibition Stroop Color-Word	Lowest quartile	17.76 [3.06, 103.1]	2.15 [0.39, 11.94]	3.00 [0.48, 18.89]
	Highest three quartiles	2.30 [0.90, 5.84]	2.03 [0.77, 5.35]	0.95 [0.35, 2.57]
	Interaction p-value	p=.04	p=0.96	p=0.28

Notes: Data gathered from the PROSPECT study. OR = Odds Ratio; CI = Confidence Interval; HDRS = Hamilton Depression Rating Scale; MMSE = Mini-Mental State Examination; DRS = Mattis Dementia Rating Scale. Odds ratios are adjusted for baseline HDRS and suicidal ideation.

Table 3

Odds ratios for response for depressed patients (Change in HDRS $\geq 50\%$) according to specific domains of cognition

Cognitive Status	Quartiles of performance	Intervention Condition versus Usual Care		
		OR [CI] 4 months	OR [CI] 8 months	OR [CI] 12 months
All depressed patients				
MMSE	Lowest quartile	2.27 [0.28,18.71]	0.19 [0.02,1.97]	4.64 [0.43,49.88]
	Highest three quartiles	2.91 [1.54, 5.52]	2.52 [1.32, 4.81]	1.94 [1.01, 3.77]
	Interaction p-value	p=0.82	p=0.04	p=0.49
Verbal memory DRS memory, immediate recall	Lowest quartile	5.16 [1.44, 18.45]	1.72 [0.47, 6.36]	2.59 [0.65, 10.31]
	Highest three quartiles	2.49 [1.16, 5.37]	2.43 [1.12, 5.27]	2.10 [0.95, 4.65]
	Interaction p-value	p=0.33	p=0.06	p=0.80
Verbal memory DRS memory, delayed recall	Lowest quartile	5.69 [1.48, 21.87]	1.08 [0.27, 4.34]	1.80 [0.41, 7.87]
	Highest three quartiles	2.42 [1.14, 5.16]	2.66 [1.24, 5.72]	2.32 [1.05, 5.10]
	Interaction p-value	p=0.27	p=0.26	p=0.77
Attention Weschler digit span	Lowest squartile	4.26 [1.03, 17.59]	1.85 [0.43, 7.92]	2.10 [0.44, 10.00]
	Highest three quartiles	2.98 [1.39, 6.37]	2.41 [1.12, 5.21]	2.17 [0.98, 4.82]
	Interaction p-value	p=0.66	p=0.73	p=0.97
Response Inhibition Stroop Color-Word	Lowest quartile	14.86 [3.40, 65.06]	1.37 [0.33, 5.72]	4.99 [1.05, 23.80]
	Highest three quartiles	2.21 [0.99, 4.90]	3.01 [1.32, 6.84]	1.34 [0.59, 3.07]
	Interaction p-value	p=0.02	p=0.35	p=0.14

Notes: Data gathered from the PROSPECT study. OR = Odds Ratio; CI = Confidence Interval; HDRS = Hamilton Depression Rating Scale; MMSE = Mini-Mental State Examination; DRS = Mattis Dementia Rating Scale. Odds ratios are adjusted for baseline HDRS and suicidal ideation.