ORIGINAL ARTICLE

Executive Dysfunction and Long-term Outcomes of Geriatric Depression

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Background: This study investigated the relationship of executive and memory impairment to relapse, recurrence, and course of residual depressive symptoms and signs after remission of geriatric major depression.

Methods: Fifty-eight elderly subjects remitted from major depression received continuation nortriptyline treatment (plasma levels 60-150 ng/mL) for 16 weeks and then were randomly assigned to either nortriptyline maintenance therapy or placebo for up to 2 years. Diagnosis was made using the Research Diagnostic Criteria and the *DSM-IV* criteria after an interview using the Schedule for Affective Disorders and Schizophrenia. Executive dysfunction and memory were assessed with the Dementia Rating Scale, disablity and social support were rated with the Philadelphia Multiphasic Instrument, and medical burden was assessed with the Cumulative Illness Rating Scale.

Results: Abnormal initiation and perseveration scores, but not memory impairment, were associated with relapse and recurrence of geriatric depression and with fluctuations of depressive symptoms in the whole group and in subjects who never met criteria for relapse or recurrence during the follow-up period. Memory impairment, disability, medical burden, social support, and history of previous episodes did not significantly influence the outcome of depression in this sample.

Conclusions: Executive dysfunction was found to be associated with relapse and recurrence of geriatric major depression and with residual depressive symptoms. These observations, if confirmed, will aid clinicians in identifying patients in need of vigilant follow-up. The findings of this study provide the rationale for investigation of the role of specific prefrontal pathways in predisposing or perpetuating depressive syndromes or symptoms in elderly patients.

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EXECUTIVE dysfunction, including disturbances in planning, sequencing, organizing, and abstracting, has been reported in late-life depression.[1] Disorders of the basal ganglia and their prefrontal projections are often complicated by depression and result in executive dysfunction.[2,3]

Consistent with clinical observations, white matter hyperintensities have been reported in geriatric depression[4-6] and mainly occur in subcortical structures and their frontal projections. Ischemic lesions of the caudate head and the left frontal pole often lead to depression.[7] Reduced basal ganglia volumes[8,9] and changes in the activity of the caudate nucleus[10] and the frontal regions[11-15] have also been observed in depression. The basal ganglia, the prefrontal areas, the amygdala, and some paralimbic regions seem to be abnormally activated in young persons with depression.[16,17]

Recently, we reported that executive impairment predicts poor or delayed antidepressant response of geriatric major depression.[18] Hypometabolism of the rostral anterior cingulate was reported in treatment-resistant depression, while cingulate hypermetabolism was associated with favorable response[19,20]; integrity of the anterior cingulate is required for some executive functions. White matter hyperintensities were found to predict chronicity of geriatric depression[21,22] and to be correlated with executive dysfunction.[23] Finally, white matter hyperintensities were associated with low quantitative electroencephalographic coherence,[24] a measure of cerebral connectivity. Low coherence was shown to predict chronicity of late-life depression.[25]

Unlike executive dysfunction, memory impairment does not seem to influence the response to antidepressant treatment. In 2 samples of elderly subjects, memory impairment was not associated with change in depressive symptoms over time.[18,26]

Besides chronicity, adverse consequences of depression include relapse occurring within 4 to 6 months from remission, recurrence occurring after a well interval of 4 to 6 months or longer, and subsyndromal depressive symptoms.

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SUBJECTS AND METHODS

SUBJECTS

The subjects were consecutively recruited elderly psychiatric patients aged 65 years and older. They had achieved remission from major depression after treatment with the antidepressant nortriptyline at dosages resulting in plasma levels ranging from 60 to 150 ng/mL. At entry, the subjects had met Research Diagnostic Criteria (RDC)[30] and *DSM-IV* criteria[31] for unipolar major depression without psychotic features, had a score of 19 or greater on the 24-item Hamilton Depression Rating Scale (HDRS),[32] and a score of 1 (absent) on the Delusions and Hallucinations items of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS-L).[33] The subjects were considered in remission if they no longer met RDC criteria for depression and had an HDRS score of 10 or lower and a Cornell Scale[34] score of 6 or lower for 3 consecutive weeks. Cornell Scale scores of 6 and lower discriminate depressed from nondepressed elderly patients.[34]

Depressed patients were excluded if they had (1) history of other psychiatric disorders (except personality disorders) prior to their depression; (2) severe or acute medical illness (eg, metastatic cancer, brain tumors, decompensated cardiac, hepatic, or renal failure, or myocardial infarction or stroke within the 3 months preceding the study); (3) neurological disorders (eg, delirium, Parkinson disease, or multiple sclerosis); (4) conditions and drugs that may cause depression (endocrinopathies other than diabetes, lymphoma, or pancreatic cancer, or the use of steroids, β-blockers, α-methyl-dopa, clonidine, reserpine, tamoxifen, or cimetidine); or (5) Mini-Mental State Examination[35] score of less than 17. Therefore, the subjects were nondelusional depressed elderly patients with a wide range of cognitive impairment.

To increase protocol adherence, only subjects residing within a 45-minute drive from the hospital were selected. All subjects were required to have informants who had knowledge of the subject's history and enough contact so that they could observe changes within a week. Subjects and informants provided written informed consent.

MEASURES

The SADS-L and parts of the Structured Clinical Interview for *DSM-IV*–Patient Version[36] were initially administered when the subjects were symptomatic. Depressive symptoms were assessed using the 24-item HDRS. The HDRS was administered again after 6, 9, and 12 weeks of antidepressant treatment to ascertain remission of depression.

Baseline cognitive impairment was rated with the Mini-Mental State Examination and the Mattis Dementia Rating Scale (DRS).[37] Besides a score of overall impairment, the DRS yields subscores for impairment in (1) IP, (2) memory, (3) construction, (4) conceptualization, and (5) attention. The IP domain tests (1) verbal IP (eg, "In 1 minute, name all things that you can buy in a supermarket"); (2) alternating movements; and (3) graphomotor design (eg, reproduce *XOXO*). The memory domain consists of tests

Chronicity, relapse, and recurrence may be related events resulting from a common diathesis contributing to poor prognosis. Conversely, chronicity, relapse, and recurrence may be independent of each other, since some studies found them to have different predictors.[27]

Based on findings showing that executive dysfunction[18] as well its functional[20,25] and structural[22] imaging correlates predict chronicity of geriatric depression, this study investigated the relationship of executive dysfunction to relapse and recurrence. Deficits in initiation and perseveration (IP) were used as the index of executive dysfunction, since this measure was found to predict chronicity[18] and also is disrupted in disorders of frontal[28] and subcortical structures.[29] We tested the hypothesis that deficits in IP, but not memory impairment, predict early relapse and recurrence as well as fluctuation of depressive symptoms after remission of geriatric depression.

RESULTS

A total of 100 subjects received open acute nortriptyline treatment targeting nortriptyline plasma levels between 80 and 120 ng/mL. Of these, 5 dropped out of the study, 7 failed to tolerate nortriptyline, 28 did not achieve remission of depression (HDRS score of ≤10 for 3 consecutive weeks), and 2 died during the acute phase. Therefore, 58 depressed elderly subjects met criteria for remission and entered the continuation phase; 4 of these subjects participated in an acute treatment study as described earlier.[18] Of the 58 subjects, 1 was unavailable for follow-up; the remaining 57 subjects completed the continuation phase. The clinical characteristics of these subjects suggest that when symptomatic they had moderate to severe depression, and a wide range of cognitive impairment, medical comorbidity, disability, and social support (**Table**).

RELAPSE OF GERIATRIC DEPRESSION

Of the 57 subjects who completed the 16-week continuation treatment phase, 7 (12%) had a relapse. Relapsed subjects met RDC and *DSM-IV* criteria for major depression and had an HDRS score of 17 or greater. To test the hypothesis that IP and not memory impairment predicts relapse, a Cox proportional hazard model was constructed consisting of IP memory and age. The model was associated with relapse (likelihood ratio test = 9.72, $df = 3$, $P<.03$). However, only IP was a significant contributor (odds ratio = 0.80, 95% confidence interval [CI] = 0.66-0.98, $z = -2.2$, $P<.03$) (**Figure 1**), while memory and age were not significantly related to relapse. Relapse could not be attributed to differences in the intensity of nortriptyline treatment. The last nortriptyline plasma levels of subjects who relapsed were statistically indistinguishable from those who remained well ($t_{56} = 1.11$, $P = .28$). Post hoc analysis using univariate Cox proportional hazard models showed that the number of previous depressive episodes, medical comorbidity (CIRS-G), disability (MAI Instrumental Activities of Daily Living [IADL] index and MAI Mobility index), and poor social support (MAI index) were not significantly associated with

of orientation, verbal recall, verbal recognition, visual matching, and visual memory.

At baseline, medical burden was assessed with the Cumulative Illness Rating Scale, Modified Version for Geriatrics (CIRS-G).[38] The CIRS-G rates chronic medical burden from 14 organ systems. Information was obtained from medical history and physical examination, as well as the available laboratory test results. A total score was computed by adding the subscores of each organ system except the psychiatric/behavioral system. Baseline disability, social support, and physical environment were assessed with the Philadelphia Multilevel Assessment Instrument (MAI).[39]

STUDY PROCEDURES

Once the subjects achieved remission, they received controlled continuation treatment for 16 weeks. Nortriptyline was administered in a single dose at bedtime and plasma levels were obtained monthly. Nortriptyline was chosen because of its known efficacy in long-term treatment of geriatric depression.[40] The dosage was adjusted if nortriptyline plasma levels were not within 60 to 150 ng/mL. Following completion of continuation treatment, the subjects were assigned either to nortriptyline (plasma levels 60-150 ng/mL) or to placebo maintenance treatment for 2 years using random computer numbers, and were followed up under double-blind conditions. In patients randomized to placebo, transition from continuation to maintenance treatment occurred during a period of 10 weeks by reducing the daily dose by 10 mg every 1 to 2 weeks and substituting nortriptyline capsules for an increasing number of inert capsules. The subjects received their medication in 2-week supply kits that permitted dispensation of their daily dosage separately. Throughout the study, the patient visits followed a medication clinic model. No subject received formal psychotherapy.

The subjects were systematically assessed monthly during the continuation phase, every 2 weeks during the transition phase, and every 2 months during the maintenance phase. Assessment consisted of administration of the HDRS and the DRS as well as pill counts. Electrocardiograms and nortriptyline plasma levels were obtained every 2 months and, if needed, the nortriptyline dosage was adjusted to achieve nortriptyline plasma levels of 60 to 150 ng/mL.

STATISTICAL ANALYSES

Survival analysis with proportional risk hazards was used to study the relationship of the hypothesized variables to the occurrence of relapse and recurrence. Mixed-effects models were used to study the relationship of the hypothesized variables to the course of depressive symptoms over time. This analysis treats depressive symptoms and signs (total HDRS score) as a continuous variable and assesses their fluctuation over time. Concordance correlation[41] was used to evaluate the goodness-of-fit of the resultant models and determine the strength of agreement between values estimated by the model and observed values. Two-tailed α levels of significance above .05 were used.

relapse of depression in this sample. Education (years in school; $r = 0.34$, $P<.009$) and IADL impairment ($r_{55} = 0.43$, $P<.001$) were weakly correlated with IP scores. However, education and IADL index were not significantly associated with relapse of depression.

Relapse is a discrete event. Focusing on relapse alone does not offer information about the course of depressive symptoms and signs (total HDRS score) that do not meet criteria for a new depressive episode. For this reason, the course of depressive symptoms after remission of depression was studied first in all subjects who had continuation treatment, and then only in subjects who never had a relapse. When all subjects who participated in the continuation treatment phase were included, a model consisting of IP, memory, their linear and curvilinear relationship to time, and relapse (presence vs absence) had a high concordance correlation (0.77) with the observed depressive symptoms over time. However, IP ($F = 6.04$, $P<.02$), IP × time ($F = 6.26$, $P<.01$), and IP × time^2 ($F = 6.22$, $P<.01$) were the only variables significantly associated with course of depressive symptoms, while memory alone or in interaction with time had no significant relationship to depressive symptoms and signs.

A separate analysis of subjects who had no relapse during the continuation treatment phase showed that a model consisting of IP, memory, and their linear and curvilinear relationships to time had a high concordance correlation (0.73) with the observed depressive symptoms over time. However, only IP ($F = 5.40$, $P<.02$), IP × time ($F = 5.89$, $P<.02$), and IP × time^2 ($F = 5.69$, $P<.02$) were significantly associated with depressive symptoms over time (**Figure 2**), while memory alone or in interaction with its linear and curvilinear relationship to time had no significant relationship to depressive symptoms and signs.

RECURRENCE OF GERIATRIC DEPRESSION

Of the 57 subjects who completed the continuation phase, 43 agreed to participate in the maintenance phase (Table) and were randomly assigned either to nortriptyline or placebo. Of the 43 subjects who entered the maintenance phase, 22 continued to receive nortriptyline and 21 were switched to placebo. A total of 15 subjects (35%) had a recurrence during the maintenance phase. Subjects treated with placebo had a higher recurrence rate (52% [n = 11])than subjects who were maintained with nortriptyline (18% [n = 4]).

To test the hypothesis that IP and not memory impairment predicts recurrence of depression, a Cox proportional hazard model was constructed consisting of the DRS subscores of IP and memory as well as age and treatment assignment. The model was associated with risk for recurrence (likelihood ratio test = 12.9, $df = 4$, $P<.02$). However, only IP (risk ratio = 0.83, 95% CI = 0.69-0.99, $z = -2.08$, $P<.04$) and treatment assignment (risk ratio = 7.25, 95% CI = 1.97-26.66, $z = -2.98$, $P<.004$) were significant predictors (Figure 1), while memory (risk ratio = 1.22, 95% CI = 0.93-1.61, $z = 1.44$, $P<.15$) and age (odds ratio = 1.07, 95% CI = 0.99-1.15, $z = 1.71$, $P<.09$) did not reach significance. Recurrence could not be attributed to differences in the intensity of nortripty-

Characteristics of Depressed Elderly Patients Who Received Continuation and Maintenance Treatment*

Variable	Continuation Treatment (n = 57)	Maintenance Treatment (n = 43)
Sex, % female	64.9	62.8
Living arrangements, %		
Lives alone	36.8	34.9
Lives with others	59.6	62.8
Nursing home	3.5	2.3
RDC subtypes, %		
Endogenous	49.1	46.5
Situational	17.5	14.0
Previous episodes, %		
0	28.9	32.4
1	48.9	45.9
2	15.6	13.5
>2	6.6	8.2
Age, y	73.6 (8.2) [60-91]	73.3 (7.6) [60-91]
Education, y	12.9 (2.9) [7-20]	13.7 (2.9) [8-20]
Severity of depression, HDRS score	25.7 (5.9) [17-38]	26.7 (6.4) [19-38]
Cognitive impairment, MMSE score	27.3 (3.7) [17-30]	28.0 (2.7) [17-30]
Medical burden, CIRS-G, score	4.7 (2.9) [0-13]	4.7 (2.8) [0-12]
Disability, MAI Mobility and IADL indices scores	20.2 (4.7) [5-24]	20.4 (5.0) [5-24]
Social support, MAI index score	62.1 (14.8) [20-97]	63.4 (14.2) [38-97]

**Data are expressed as mean (SD) [range] unless otherwise indicated. RDC indicates Research Diagnostic Criteria[30]; HDRS, 24-item Hamilton Depression Rating Scale score[32]; MMSE, Mini-Mental State Examination[35]; CIRS-G, Cumulative Illness Rating Scale, Modified Version for Geriatrics[38]; MAI, Philadelphia Multilevel Assessment Instrument[39]; and IADL, instrumental activities of daily living.*

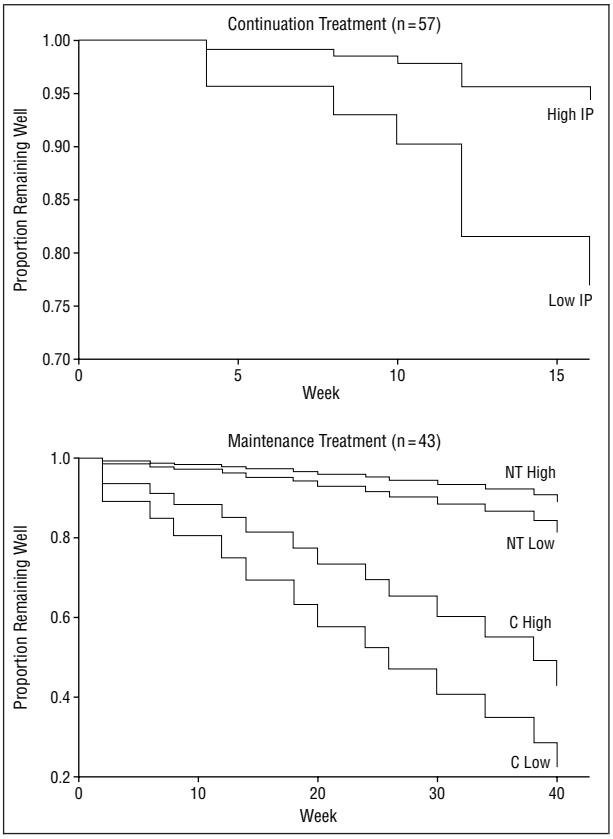

Figure 1. *Cox proportional hazard analysis of recovered depressed elderly patients who underwent continuation treatment with nortriptyline (NT) (n = 57) and subjects who received maintenance treatment with either NT or placebo (C) (n = 43). Fitted survival curves of subjects with low and high inititation and perseveration (IP) scores are shown. The cutoff for low IP was the proportion of subjects who relapsed or had a recurrence: 12% for continuation and 35% for maintenance treatment.*

line treatment. The last nortriptyline plasma levels of subjects who had a recurrence were statistically indistinguishable from those who remained well (t_{53} = 0.43, P = .68). Post hoc analysis using univariate Cox proportional hazard models showed that the number of previous depressive episodes, medical comorbidity (CIRS-G), disability (MAI Mobility index), and poor social support (MAI index) were not significantly associated with recurrence of depression. The IADL index correlated with IP scores (r_{41} = 0.55, P<.001) but IADL itself was not associated with recurrence.

The relationship of IP and memory to depressive symptoms (total HDRS score) occurring during the maintenance phase was studied using mixed-effects models. First, all patients who received nortriptyline or placebo maintenance therapy were included. A model consisting of IP, memory, their linear and curvilinear relationships to time, group membership (nortriptyline vs placebo), age, and recurrence (presence vs absence) was found to have high concordance correlation (0.68) with fluctuation of depressive symptoms during the maintenance treatment phase. Initiation and preservation (F = 13.20, P<.001), age (F = 19.76, P<.001), and time × recurrence (F = 19.25, P<.001) were the only significant predictors of the course of depressive symptoms.

Subsequent analysis focused on the subjects who did not have a recurrence during the follow-up period. A model consisting of IP, memory, group assignment (nortriptyline vs placebo), age, time, and time × group assignment was found to have high concordance correlation (r_c = 0.62) with the course of depressive symptoms. However, IP (F = 6.79, P<.009), age (F = 17.26, P<.001), and memory (F = −5.98, P<.02) were the only variables significantly associated with depressive symptoms. Unlike IP, better memory performance was associated with higher HDRS scores.

COMMENT

The principal finding of this study is that abnormal IP scores are associated with risk for relapse and recurrence and predict the course of depressive symptoms after remission of geriatric depression. These relationships may be specific to IP, since memory impairment is not related to relapse, recurrence, or fluctuations of depressive symptoms.

To our knowledge, this is the first study to identify a relationship between executive dysfunction and relapse and recurrence of geriatric depression or subthreshold depressive symptoms. This observation parallels previous reports suggesting that executive dysfunction,[18] as well as its functional[20,25] and structural[21,22] imaging correlates, is associated with chronicity of geriatric depres-

sion. Together, these findings suggest that executive dysfunction constitutes a cognitive dimension associated with poor outcomes of geriatric depression.

Memory impairment did not have a significant relationship to relapse or recurrence. Memory scores were not associated with subsyndromal depressive symptoms during the continuation phase and had an inverse relationship with the course of depressive symptoms during the maintenance phase. These observations suggest that the relationship of executive dysfunction to relapse, recurrence, and subsyndromal depressive symptoms and signs is rather specific.

A potential explanation is that pathway disruption underlying executive dysfunction confers increases the propensity of geriatric depression toward chronicity and recurrence. This conceptualization allows that clinical (such as history of recurrences) and psychosocial factors (such as poor social support) may modify the effect of this vulnerability, although no such effects were observed in this sample.

Executive dysfunction may result from disruption of the cortical-striato-pallido-thalamo-cortical (CSPTC) pathways. Five CSPTC pathways have been described. Each pathway includes a direct circuit with a net excitatory input to the cortex and an indirect circuit with a net inhibitory input.[42,43] It has been proposed that imbalance favoring the inhibitory circuit of specific CSPTC pathways may contribute to depression.[44,45] The CSPTC pathways' function is modulated by the raphe nuclei, locus ceruleus, and ventral tegmentum. Dysfunction of specific pathways can occur through vascular and degenerative processes by disrupting them directly or by damaging their connections to monoaminergic nuclei.[6,46-49]

Beyond elucidating the pathophysiology of the course of geriatric depression, our findings offer a rationale for novel psychopharmacological hypotheses. The main neurotransmitters modulating the CSTPC pathways are dopamine, acetylcholine, and enkephalin.[6,42] Therefore, studies need to investigate whether drugs influencing these neurotransmitters can prevent relapses and recurrences in elderly patients with executive dysfunction.

On a clinical level, the association of executive dysfunction to relapse and recurrence may have implications for patient care. Depressed elderly patients with executive dysfunction may require frequent follow-up assessments, so that additional interventions can be instituted soon after the first depressive symptoms become evident. Education of patients and families may increase clinicians' ability to identify relapse or recurrence of depression early. Rehabilitative techniques may be used in elderly patients with remitted depression to remedy disturbances in planning, sequencing, and organizing their activities and increase their functional ability and quality of life. However, research needs to examine whether remedying disability resulting from executive dysfunction prevents relapses or recurrences, since the affective vulnerability associated with executive dysfunction may not be mediated by disability, as shown in this sample.

A limitation of this study is the rather small number of subjects who participated in the placebo-controlled nortriptyline maintenance treatment phase. Moreover, these findings cannot be generalized to treatment with selective serotonin reuptake inhibitors, the most frequently used drugs in geriatric depression. Another limitation is the use of a brief neuropsychological instrument that was designed primarily for use with dementia patients and tests some but not all executive functions. However, the DRS subscales of IP and memory used by this study seem to discriminate subcortical dementias from Alzheimer disease, a predominantly cortical dementia. Autopsy studies have shown that patients with the subcortical dementing disorders Huntington disease and supranuclear palsy perform significantly worse than patietns with Alzheimer disease on the IP subscale but better on the memory subscale of the DRS.[50] These measures correctly classified 80% of patients with Alzheimer disease and 90% of patients with Huntington disease. Similarly, high impairment in the IP subscale of the DRS and low impairment in the memory subscale characterized patients with Parkinson disease and distinguished them from those with Alzheimer disease.[51] Moreover, functional imaging studies suggest that several functions tested by the IP subscale require integrity of prefrontal circuitry. Performance of a verbal fluency task increases left dorsolateral prefrontal activity.[52] Learning a new motor sequence results in activation of the dorsal prefrontal cortex and the anterior cingulate.[53,54] Nonetheless, replication of our study with a more extensive neuropsychological battery is necessary.

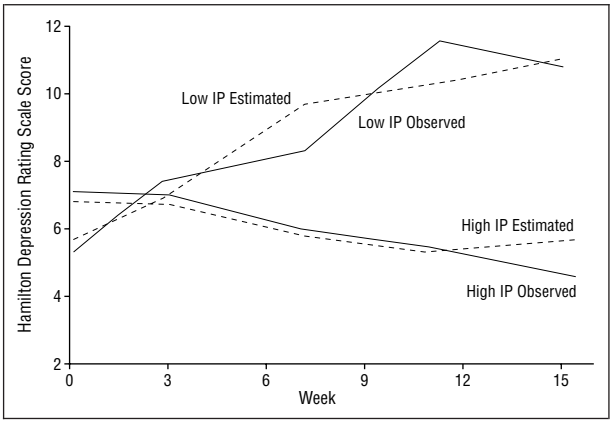

Figure 2. *Observed and estimated depressive symptoms (total Hamilton Depression Rating Scale score) in nonrelapsed patients (n = 47) with high (>30) and low (≤30) initiation and perseveration (IP) scores on the Mattis Dementia Rating Scale.*

In conclusion, this study observed that executive dysfunction constitutes a risk factor for relapse and recurrence of geriatric depression and predicts the course of depressive symptoms even in patients who do not develop a new depressive episode. The clinical value of this observation is that patients with executive impairment should be targeted for close follow-up, and should be considered for rehabilitative treatment and family counseling that may reduce their disability and family burden. The heuristic value of this finding is that it provides the basis for an empirical inquiry of the pathophysiology of relapse and recurrence. Neuropsychological and functional neuroimaging techniques may be used to describe the role of specific CSPTC pathways in modifying the course of geriatric depression. Finally, drugs influencing neurotransmission of dopamine, acetylcholine, and

enkephalin may be studied for their ability to prevent relapse and recurrence of depression in elderly patients with executive dysfunction.

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