Role of Executive Function in Late-Life Depression

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Late-onset depression has been conceptualized as a neurologic disease. This view has been supported by studies suggesting that late-onset depression is associated with cognitive impairment and neurologic comorbidity that may or may not be clinically evident when depression is first diagnosed. Findings implicating a dysfunction of frontostriatal-limbic pathways in geriatric depression have led to the depression–executive dysfunction (DED) syndrome hypothesis. Subsequent studies suggested that DED has slow, poor, or abnormal response to classical antidepressants. DED is characterized by psychomotor retardation, reduced interest in activities, impaired insight and pronounced behavioral disability. This clinical presentation begs the question whether agents that can selectively activate internal vigilance and therefore improve alertness have beneficial effects on DED. There is early evidence that psychosocial interventions aimed at improving the behavioral deficits of DED patients may also be effective in increasing remission rates and reducing depressive symptoms and disability.

(J Clin Psychiatry 2003;64[suppl 14]:18–23)

Studies of late-life depression have been useful for understanding both the mechanisms of depression and the pathophysiology of treatment response. Aging is associated with lesions or other brain abnormalities that may contribute to depression.[1–3] For this reason, late life can function as a laboratory of nature. Among depressive syndromes of late life, late-onset depression has been conceptualized as a neurologic disease. This view has been supported by studies[4–7] suggesting that late-onset depression is associated with cognitive impairment and neurologic comorbidity more often than early-onset depression. Comorbid neurologic disorders are not always clinically evident at the initial appearance of late-onset depression. Once it develops, late-onset depression may have slow or poor response to antidepressant treatment.[8]

Despite the association between late-onset depression and neurologic brain diseases or lesions, some patients with these diseases or lesions do not develop depression. This observation suggests that some brain abnormalities, but not others, contribute to depression and influence its outcome. Frontostriatal dysfunction may be one of the critical brain abnormalities contributing to late-life depression. Functional neuroimaging studies support this view[9,10] as they have demonstrated abnormal metabolism in frontal regions and the caudate nucleus during depressive states. Clinical studies[5] have shown that diseases causing frontostriatal dysfunction predispose to depression and lead to the impairment of executive functions, including disturbances in problem solving, sequencing, planning, organizing, and abstracting.[11] Moreover, geriatric depression occurring even in the absence of a diagnosable neurologic disease is often accompanied by executive dysfunction.[6]

The confluence of findings implicating a dysfunction of frontostriatal pathways in geriatric depression has led to the depression–executive dysfunction (DED) syndrome hypothesis. This hypothesis postulates that in a subgroup of elderly patients with depression, frontostriatal dysfunction caused by cerebrovascular disease or other aging-related conditions is the main predisposing factor to depression. It has been further hypothesized that DED syndrome has a distinct clinical presentation and poor long-term and short-term outcomes.

LATE-ONSET DEPRESSION

Late-onset depression is a heterogeneous syndrome that includes patients with high medical burden and neurologic disorders that may or may not be clinically evident when the depression first appears. Geriatric depression is more common in medical settings than in the community[7] and is associated with long hospital stays and substantial costs.[12,13] Depressed medical patients spend more days in bed compared with patients with other chronic diseases such as diabetes, arthritis, and hypertension without depression.[14] Compared with patients with early-onset depression, patients with late-onset depression appear to

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This article is derived from the teleconference "Optimizing Wakefulness in Patients With Fatigue and Executive Dysfunction," which was held February 10, 2003, and supported by an unrestricted educational grant from Cephalon, Inc.

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have a higher prevalence of dementing disorders, less frequent family history of mood disorders, a higher rate of dementia development on follow-up, greater impairment on neuropsychological tests, more neurosensory hearing impairment, a greater enlargement in lateral brain ventricles, and more white matter hyperintensities.[4]

Disability and psychosocial hardships often afflict patients with late-onset depression and may interact with medical and neurologic comorbidity to contribute to geriatric depression. For example, cerebrovascular and noncerebrovascular medical burden may cause cognitive dysfunction and depression,[15] and cognitive dysfunction, which contributes to disability and social isolation, may promote depression. Furthermore, when depression occurs, it may exacerbate cognitive dysfunction, medical morbidity, disability, and mortality and may promote psychosocial disruption.

Because it often occurs in the context of social impoverishment, disability, and medical and neurologic disorders, the outcome of geriatric depression requires special consideration. My colleagues and I[8] conducted a study to examine the timetable of recovery and the role of age at illness onset, medical burden, disability, cognitive impairment, lack of social support, and poor living conditions in predicting recovery in elderly patients with major depression. The study included 63 patients older than 63 years and 23 younger patients with a DSM-III-R diagnosis of major depression. Patients were evaluated in person every 6 months and had telephone evaluations every 3 months, and the Longitudinal Follow-up Interval Examination was used to identify recovery. We observed that while the recovery rate of depressed elderly patients was similar to that in younger depressed patients, elderly patients had different predictors of recovery than younger patients. In elderly patients, antidepressant treatment, age, age at onset, and chronicity of episode predicted time to recovery; the strongest predictor of slow recovery was late age at onset. In contrast, in younger patients, the predictors to recovery were weak social support, younger age, cognitive impairment, and low intensity of antidepressant treatment. Although geriatric depression did not have a worse outcome than depression in younger adults, depressed patients with late-life first episodes might be at a higher risk for chronicity than patients with early-onset depression.

Neurologic Abnormalities in Late-Life and Late-Onset Depression

White matter hyperintensities[1–3] occurring primarily in subcortical structures and their frontal projections may contribute to late-life and especially late-onset depression. Ischemic lesions of the caudate head and the left frontal pole,[16] reduced basal ganglia volumes,[17,18] and changes in the activity of the caudate nucleus[19] and the frontal regions are common in late-life depression.[9,10,20–22] Additionally, the prefrontal areas, basal ganglia, the amygdala, and some paralimbic regions of the brain appear to be abnormally activated in young patients with depression.[23,24]

Neurologic abnormalities associated with depression contribute to executive dysfunction. Executive dysfunction has been reported to predict poor or delayed antidepressant response in geriatric patients with major depression.[25] A series of findings drew attention to the anterior cingulate cortex, a structure whose integrity is required for some executive functions. Hypometabolism of the rostral anterior cingulate has been reported in treatment-resistant depression.[26] White matter hyperintensities often influence executive functions[27] and have been found to predict chronicity in geriatric depression.[28,29] Moreover, white matter hyperintensities are associated with low quantitative electroencephalographic coherence[30] (a measure of cerebral connectivity), a dysfunction that has been shown to predict chronicity in late-life depression.[31]

DEPRESSION–EXECUTIVE DYSFUNCTION SYNDROME

Clinical Presentation of DED

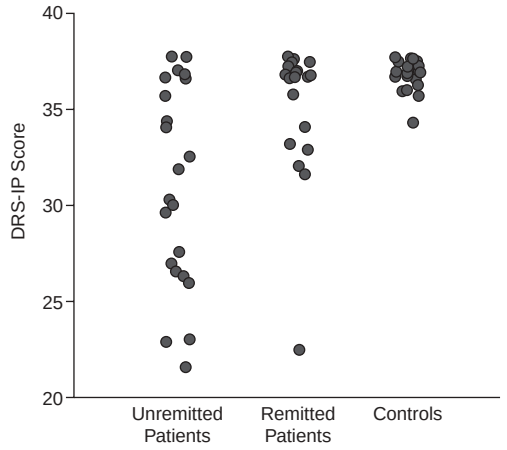
On the basis of clinical, neuropathologic, and neuroimaging findings that implicate a frontostriatal dysfunction diathesis in the development of both depression and executive dysfunction,[9,10,19–22] my colleagues and I[32] studied 126 elderly subjects with major depression in order to describe the clinical presentation of DED syndrome and its relationship to disability. We observed that patients with DED syndrome had reduced fluency, impaired visual naming, loss of interest in activities, psychomotor retardation, poor understanding of their disease, and pronounced disability. Major contributors to disability in DED syndrome patients were psychomotor retardation, depressive symptomatology, and loss of interest in activities. Suspiciousness was associated with disability independently of executive dysfunction.

An example of a patient suffering from DED syndrome might be adequately portrayed by an elderly woman with depression who awakes in the morning feeling distressed and remains in her nightgown throughout the day, despondently wandering around her house. Although she knows that she needs to brush her teeth, take a shower, get dressed, have breakfast, call her daughter, and perform other daily tasks, she fails to perform any of these tasks in an orderly fashion and consequently accomplishes very little.

Course of DED Syndrome

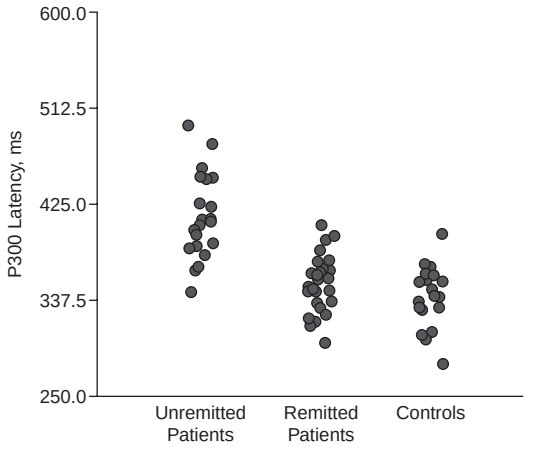
Studies[25,32–34] suggest that the course of geriatric DED syndrome is associated with early relapse and recurrence, and has poor response to antidepressant treatment. Kalayam and I[25] investigated the relationship between treatment response and clinical, neuropsychological, and electrophysiologic measures of prefrontal dysfunction in

Figure 1. Total Mattis Dementia Rating Scale Score Minus Initiation/Perseveration Subscale Scores in Patients and Controls[a]



[a]Reprinted with permission from Kalayam and Alexopoulos.[25]
Abbreviations: DRS = Dementia Rating Scale, IP = Initiation/Perseveration.

Figure 2. P300 Latency in Patients and Controls[a]



[a]Reprinted with permission from Kalayam and Alexopoulos.[25]

49 elderly patients with major depression. Subjects were examined prior to and after receiving 6 weeks of adequate antidepressant treatment and were compared with 22 healthy controls with no known psychiatric disorders. Indices of prefrontal dysfunction included the initiation/perseveration subscore of the Mattis Dementia Rating Scale and the latency of the P300 auditory evoked potential. We found that abnormal initiation/perseveration score, psychomotor retardation, and long P300 latency predicted 58% of the variance in change in depression scores from baseline to 6 weeks. Compared with patients who achieved remission with antidepressant treatment (N = 24) and compared with the 22 control subjects, patients with depression who remained symptomatic after antidepressant treatment (N = 25) had more abnormal initiation/perseveration scores (Figure 1) and longer P300 latency (Figure 2). These findings suggest that prefrontal dysfunction is associated with poor or delayed antidepressant response.

In another study, my colleagues and I[35] investigated the relationship of executive and memory impairment to relapse, recurrence, and residual depressive symptoms. In this study, 58 elderly patients who had remitted from major depression received continuation treatment of nortriptyline (increased to blood drug levels of 60–150 ng/mL) for 16 weeks. Those who remained well until the end of the continuation treatment phase were randomly assigned to receive individualized doses of nortriptyline or placebo for up to 2 years. Cognitive impairment was assessed with the Dementia Rating Scale, which includes an initiation-perseveration domain (executive functions); disability and social support were measured using the Philadelphia Multiphasic Instrument; and medical burden was assessed with the Cumulative Illness Rating Scale. Abnormal initiation-perseveration scores predicted relapse and recurrence of depression. Moreover, abnormal initiation-perseveration scores were associated with fluctuations of depressive symptoms in the group as a whole and in the subjects who never relapsed during the follow-up period of the study. Disability, medical burden, memory impairment, social support, and history of previous episodes did not influence the outcomes of depression.

In sum, the clinical picture of elderly patients with depression and executive dysfunction is one of psychomotor retardation, apathy, poor insight, disability, and severe behavioral disability. Executive dysfunction not only exacerbates the suffering of elderly patients, but also is associated with poor and unstable antidepressant response, recurrence, and relapse. These findings suggest that patients with depression and executive dysfunction are in need of a vigilant follow-up.

PURSUING THE DED SYNDROME HYPOTHESIS

The DED syndrome hypothesis is being pursued through a variety of complementary experimental approaches. First, an effort is made to clinically dissect the executive disturbances of geriatric depression and identify those most likely to occur in late life. To this end, attention and executive functioning in 40 adults with major depression were compared[36] with the attention and executive functioning of 40 healthy subjects. Four neurocognitive domains were examined: two involving the attentional processes of selective and sustained attention and two involving the higher-order executive functions of inhibitory control and focused effort. Selective attention was defined as the ability to discriminate target items from distracters;

sustained attention as the ability to perform consistently over time; inhibitory control as initiation, active switching, and inhibition of overlearned responses; and focused effort as intensity of attention such as working memory, speed of processing, and complex operations. It was observed that selective attention and sustained attention were impaired in both elderly and younger depressive groups compared with controls. In contrast, inhibitory control and sustained effort were principally impaired in geriatric subjects. The older adults with depression demonstrated the slowest psychomotor speed and the poorest performance on tasks requiring problem solving, shifting, and initiation of novel responses compared with all other subjects. These data suggest that selective attention and sustained attention appeared to be impaired in major depression regardless of age, yet inhibitory control and sustained effort appeared to be preferentially impaired in geriatric patients with late-life depression.

Cognitive neuroscience tests can also aid in the pursuit of the DED syndrome hypothesis by identifying which of the 3 neural systems—the alerting network, the orienting network, and the conflict network—are associated with antidepressant response. Neuroimaging has been conducted[37] to identify relevant neural systems, and early evidence suggests that the conflict network, associated with inhibitory control and sustained effort, is associated with time to remission, whereas abnormalities in the alerting network and the orienting network are not related to treatment response in any way.

A third avenue in the investigation of late-life depression with executive dysfunction seeks to identify the microanatomical abnormalities influencing treatment response in patients with DED syndrome. The geriatric literature has reported that a large number of elderly patients with depression have white matter abnormalities.[1–3] Theoretically, these abnormalities can cause a variety of disconnection syndromes. However, the question remains: Which of these disconnection syndromes can catalyze treatment resistance and unstable treatment response? Functional neuroimaging findings[26,38–40] have suggested that treatment resistance and increased risk for relapse are associated with hypermetabolism of ventral limbic structures (amygdala, subgenual cingulate, and posterior orbital cortex) and hypometabolism of cortical dorsal structures (lateral and dorsolateral cortex, dorsal anterior cingulate, and caudate nucleus). Based on these findings, my colleagues and I[41] postulated that microstructural white matter abnormalities "disconnecting" dorsal cortical from ventral limbic structures interfere with response to antidepressant treatment. To test this hypothesis, 13 patients aged 60 to 77 years with major depression were given open but placebo-controlled treatment with 40 mg/day (N = 8), 30 mg/day (N = 1), or 20 mg/day (N = 4) of citalopram for 12 weeks. Using diffusion tensor imaging, regions of interest lateral to the anterior cingulate along a dorsal-ventral axis were examined for white matter microanatomical abnormalities. We noted that abnormal fractional anisotropy in at least one of the regions (15 mm above the anterior commissure–posterior commissure line) was associated with slow or poor antidepressant response to citalopram.

Pharmacotherapy in DED

A fourth area of investigation stemming from the DED syndrome hypothesis could potentially lead to novel pharmacologic approaches. Agents that target some of the frontostriatal circuitry neurotransmitters such as dopamine (e.g. entacapone, D3 agonists, amantadine), acetylcholine (cholinesterase inhibitors), and endogenous opioids (naltrexone) can be used experimentally in patients with depression and executive dysfunction to investigate their effect on depressive systems and cognition.

Other novel pharmacologic approaches can rely on the observation that some depressive symptoms and sleep abnormalities such as insomnia, appetite disturbance, and short rapid eye movement sleep latency are associated with abnormal regulation of hypocretin 1 and 2 (also known as orexin A and B) in the hypothalamus. Recent studies have elucidated the neuronal pathways mediating sleep and wakefulness thorough hypocretin and other sleep- and wake-promoting neurons. The suprachiasmatic nucleus acts as an internal clock by regulating the activation of either sleep-promoting neurons (in the ventrolateral preoptic area of the hypothalamus) or wake-promoting neurons (in the tuberomamillary nucleus and lateral hypothalamus).[42] Activation of the cerebral cortex is essential for wakefulness, and is mediated by two pathways, a newly characterized projection from the hypothalamus, and the ascending reticular activating system (ARAS) arising from the brain stem. Hypocretins are recently discovered peptides, critical for maintaining normal wakefulness. Dysfunction of the hypocretin system leads to narcolepsy, a disorder with a high comorbidity of depression. Hypocretins appear to regulate monoaminergic and cholinergic components of the ARAS as well as sleep- and wake-promoter neurons in the hypothalamus. The wake-promoter neurons project to the cortex using the neurotransmitter histamine to promote arousal; whereas, sleep-promoter neurons use the neurotransmitters γ-aminobutyric acid (GABA) and galantin.[42] Two types of arousal have been proposed—stimulated vigilance (external vigilance or tense hyperarousal necessary for survival in hostile environments) and normal wakefulness (internal vigilance to cognitive and executive function). Stimulated vigilance and normal wakefulness are mediated by different pathways and neurotransmitters.[42–46] Stimulated vigilance may be mediated by dopamine, monoamines, norepinephrine, serotonin, and acetylcholine via the ARAS; whereas, internal vigilance may be mediated by the ascending histaminergic neurons arising from the hypothalamus.

One model of the normal sleep-wake cycle suggests that wake-promoter and sleep-promoter neurons inhibit each other, causing oscillation between calm wakefulness and sleep.[42] Disruption of these pathways or their neurotransmitters, therefore, would result in behavioral state instability, causing fatigue and cognitive and executive dysfunction. In fact, research has indicated that patients with narcolepsy have lost hypocretin-signaling capabilities in the hypothalamus, possibly due to damage in the lateral area of the hypothalamus.[45,46] Drugs that compensate for these disruptions act on specific neurotransmitters and have a therapeutic effect on sleepiness, fatigue,[45,47] and perhaps depression. Although stimulants (e.g., amphetamines) can treat narcolepsy and other disorders caused by malfunctioning hypocretin-signaling by activating both arousal systems, their arousal of the external vigilance system may cause motor hyperactivity and jitteriness. In contrast, modafinil can selectively activate internal vigilance at the tuberomamillary nucleus level and potentially treat narcolepsy as well as fatigue, executive function, and psychomotor retardation in elderly patients with depression without causing undesirable tense hyperarousal. Theoretically, targeting DED with modafinil and similar agents may lead to a novel therapeutic approach and elucidate some of the mechanisms of antidepressant action.

Psychotherapy in DED

As many elderly patients with depression and executive dysfunction have slow, incomplete, and unstable responses to antidepressant agents,[25,39,41] nonpharmacologic treatment may serve as an important therapeutic alternative for this population. Behavioral interventions offering coping strategies for the patients' behavioral deficits may be effective in reducing depression and disability. My colleagues and I[48] compared the efficacy of problem-solving therapy (PST) and supportive therapy (ST) in 25 elderly subjects who had major depression and executive dysfunction characterized by abnormal scores in initiation/perseveration and in a response inhibition test. Participants were all randomly assigned to receive weekly sessions of PST or ST for 12 weeks and were systematically evaluated by raters who were blind to the study hypotheses. PST was more likely than ST to lead to remission of depression ($p < .01$), fewer post-treatment depressive symptoms ($p < .002$), and less disability ($p < .001$). These findings suggest that PST may be an effective therapeutic alternative for patients with depression and executive dysfunction who respond poorly to antidepressant treatments.

CONCLUSIONS

We hypothesized that a DED syndrome exists and is characterized by distinct clinical presentation and a poor response to antidepressant treatment. These findings suggest that executive dysfunction and its contributing factors are central to the mechanisms of depression rather than mere epiphenomena. White matter abnormalities in critical areas may contribute to executive dysfunction and poor antidepressant treatment response. The clinical presentation of DED suggests that the syndrome is a target for agents that can selectively activate internal vigilance and therefore improve alertness. Further studies need to examine the mechanisms of the anti–executive dysfunction action of nonstimulant agents and specifically target patients with the DED syndrome. Psychosocial interventions that are aimed at remedying the behavioral deficits of DED may also be effective.

Drug names: citalopram (Celexa and others), modafinil (Provigil), nortriptyline (Aventyl and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, modafinil is not approved by the U.S. Food and Drug Administration for the treatment of depression with executive dysfunction.

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