

A Primary Care Guide To Understanding The Interaction Between Depression And Dementia

1. OVERVIEW

Primary care physicians often diagnose depression in adult patients and this disorder may produce memory dysfunction in some older patients. Depression is a risk factor for patient non-compliance with treatment for other medical problems, including hypertension and diabetes. The primary care physician can assure older patients that treatment of depression may protect physical and cognitive health.

Depression is a common disorder in the elderly and specific groups of individuals have greater risk for developing mood disorders including persons with stroke, Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders (1), (2), (3), (4). Several key issues remain unanswered in the depression puzzle. First, do people with depression experience increased risks for developing dementia? Second, would treatment of depression earlier in life mitigate the risk of depression in later life? Third, is the neuropathological substrate that produces depression in later life similar to that of dementia? Fourth, is depression simply a preclinical manifestation of dementia? Finally, how does the neurobiology of depression enhance our understanding of the relationship between dementia and mood disorders? The complexity of these scientific questions is further complicated by the limited prospective data on depression and dementia (5).

2. LONGITUDINAL STUDIES OF DEPRESSION AND COGNITION

Few longitudinal studies define the relationship between midlife depression and later life dementia. Several studies suggest that individuals with a history of depression in midlife may experience greater risks for dementia in later life and the risk of dementia increases with the frequency of hospitalization to treat the mood disorder (42) (See Table 1). Numerous methodological problems exist in relating treatments to cognitive outcomes because depression may be caused by multiple neurological mechanisms and patients demonstrate variable adherence to treatment (3), (6).

People with mild cognitive impairment and dementia exhibit greater rates of depression than age-matched cognitively intact individuals (7). Depressive

symptoms may precede the onset of cognitive decline by several years. Memory dysfunction associated with depression, sometimes termed “pseudodementia”, may be a significant red flag for future dementia, as about 20% of these individuals exhibit permanent cognitive loss even with complete remission of depressive symptoms (8), (9). Chronic depression may produce hippocampal volume reductions in younger persons with normal cognition (8). Repeated bouts of depression that produce hospitalization may increase the risk for late-life dementia by 13% for each hospitalization (42).

Table 1

The Effect of Depression on the Risk for Developing Dementia in Normal Elders or Persons with MCI					
#	n (study size)	Age of Subject	Duration of Study	Effect of depression on risk for dementia	Ref.
1	1070	60+	1-5 yrs	↑ risk (2.94)	30
2	1357	LS	40	X2 ↑ risk; independent of vascular risks	6
3	1366	65+	10	Minor ↑ risk - (1.28)	31
4	766	65+	5	Depressive symptoms predict AD	32
5	594	78.5	10	Predementia / depressive episode ↑ risk	33
6	3346	65-84	5	↑ risk @ 2yr (1.9) and 5 yrs (1.6)	34
7	114*	65	3	↑ risk (2.6) for MCI	7
8	5781	65+	4	↑ symptoms = ↑ risk	35
9	2812	65+	12 yrs	Depressive symptoms not related to onset of dementia	36
10	4046	50+	1-25 yrs	Depressive symptoms are risk factor for late dementia	37
11	2220	65+	6 yrs	↑ risk for MCI	40
LS = 40 year longitudinal study (odds ratio) *Individuals with isolated amnesic syndromes at baseline					

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3. THE RELATIONSHIP OF DEPRESSION AND HEALTH STATUS

Depression can be linked to health status and chronic midlife depression increases the risk for hypertension (10) and morbidity from cardiac disease in later life (11). Depressed elders with cardiovascular disease, stroke, diabetes, or multiple other medical conditions exhibit worse outcomes than those individuals with normal mood. Prospective randomized studies have not been performed to measure the impact of treating depression versus placebo therapy on medical outcomes (12), (13), (14).

Depression in the setting of dementia increases the likelihood of psychiatric and behavioral disability. In contrast, treatment of depression in persons with dementia is safe and effective (1), (15).

4. NEUROPATHOLOGICAL SUBSTRATES FOR DEPRESSION AND DEMENTIA

Depression often occurs in persons with Alzheimer's disease and diffuse Lewy body disease (16), (17), (18). The neuropathological substrate for depression in aging and dementia remains unclear (19). Serotonin is produced by neurons located in the midline of the brainstem in the structure referred to as the "Raphe nuclei". Alzheimer's patients with depression have increased densities of tangles in brain stem structures (20) and reduced numbers of neurons that produce norepinephrine and serotonin (46). A central component to depression in Alzheimer's patients is apathy and anergy (21). Individuals with Alzheimer's disease and depression demonstrate increased severity of microscopic damage in the prefrontal cortices that is linked to apathetic symptoms (22). Cortical and brain stem Lewy body counts do not appear related to depression (23). Many persons with late life onset dementia have Alzheimer's disease neuropathology at death (24); however, neither the severity nor the distribution of cortical damage appears related to concurrent depressive symptoms (25). However, postmortem examination of hippocampi from individuals with AD and lifetime depression reveal higher densities of senile plaques and neurofibrillary tangles than non-depressed demented individuals (38).

The role of vascular brain pathology in the pathogenesis of depression remains unclear. White matter damage in the frontal cortices as manifested by MRI abnormalities appears related to risks for depression and perhaps dementia (10). White matter hyperintensities are most likely produced by hypertensive small vessel disease in regions like the centrum semiovale.

5. LINKING THE NEUROBIOLOGY OF DEPRESSION TO SUCCESSFUL COGNITIVE AGING

The neurobiology of depression in humans has been related to dysfunction of ascending catecholaminergic systems and abnormalities in cerebral cortical regions linked to regulation of mood, including the orbitofrontal cortices, subgenual prefrontal cortex and portions of the cingulate cortex. Memory deficits produced by depression may be attributable to dysregulation of serotonergic and noradrenergic innervation of the human hippocampus. Rodent models of depression are limited by issues of experimental design. Rodent models that use persistent stress to produce symptoms of depression suggest that high circulating endogenous steroids alter dendritic connections and reduce the capacity of rodent neurons to reproduce (neurogenesis) (27). Human hippocampal neurons may retain the ability to regenerate; however, this data

remains unclear. Antidepressant medications, mood stabilizing agents, such as lithium and electroshock therapy, enhance the ability of rodent neurons to reproduce. This rodent data suggests the possibility that depression may have a substantial impact on human neuronal plasticity and regeneration, while antidepressant therapy may enhance reparative or regenerative capacity in the human brain (27).

6. THERAPEUTIC CONSIDERATIONS

Treatment of depression in all adult age groups is usually safe, effective, and affordable (28), (29). Compliance remains a major problem in the treatment of depression as well as all other medical comorbidities ([Click here for more information - DETA 2514.12](#)). Treatment of depression may enhance the likelihood that other risk factors, such as psychosocial stimulation, management of hypertension, regular exercise, and others are optimally managed. Second and third generation antidepressants, such as selective serotonin reuptake inhibitors, are highly effective for older patients. Assessment and management of depression in mid and later life should be part of the primary care strategy for cognitive wellness. Prophylactic treatment of non-depressed individuals with antidepressant medications is not indicated for the prevention of dementia. Exercise training of elders may also reduce the risk of depression and dementia (43).

The role of treating depression or heart disease in the prevention of “vascular depression” remains unclear. Randomized controlled studies have not been performed to determine the benefit of blood pressure control in the reduction of risks for either depression or dementia. Such studies are unlikely as the consequence of untreated depression precludes withholding long-term antidepressant therapy. ([Click here for additional on information on the role of vascular disease in depression or dementia – 2513.12](#)).

7. RECOMMENDATION FOR PRIMARY CARE PHYSICIANS ON THE MANAGEMENT OF DEPRESSION IN OLDER PATIENTS

A randomized controlled longitudinal study will not be performed on the impact of treating depression as a preventive intervention for dementia in middle aged or older patients. Like hypertension, depression is a serious health problem that physicians are obliged to treat in order to reduce the risk for suicide and associated health problems. A meta analysis of 20 studies in eight nations demonstrated an odds ratio of 2.02 linking midlife depression to late-life dementia(41). A reasonable interpretation of this data would suggest that aggressive management of depression in midlife may reduce morbidity and

mortality in later life. A consensus opinion from the National Institute of Mental Health states that late life depression may represent an independent risk factor predisposing to dementing disorders, even when depressive symptoms occur more than ten years before the onset of dementia **(5)**. Depression screening is now recommended as a component to the annual Medicare evaluation.

The appearance of depression in an older individual who has otherwise normal cognitive function increases the likelihood that that person will develop dementia later in life **(5)**, **(8)**. Depressive symptoms may not correlate to the rate of cognitive decline over time **(39)**. These individuals should be monitored on a regular basis with cognitive testing. Aggressive management of other health problems, such as hypertension, atrial fibrillation, cardiovascular disease, etc., is warranted in these individuals. There is inadequate research data to advise patients about “increased risks for dementia” with depression and such statements can produce distress in many patients, especially those with a past history of depression. Rather, the clinician is encouraged to advise the patient of the beneficial effect of treating depression on physical health and cognitive fitness. This positive message encourages a sense of self-determination and motivates the patient towards proactive interventions that may enhance their long-term cognitive function.

RECOMMENDATIONS TO PRIMARY CARE PHYSICIANS

1. Screen older patients for depression on an annual basis.
2. Monitor cognitive function in older persons with a past history of depression.
3. Treat depression until the patient returns to baseline and sustain normal mood through antidepressant maintenance therapy.
4. Avoid chronic prescription of benzodiazepines in depressed elders.
5. Monitor compliance for antidepressant therapy.

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