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Depression and dementias among military veterans☆

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Abstract Depression is very common throughout the course of veterans' lives, and dementia is common in late life. Previous studies suggest an association between depression and dementia in military veterans. The most likely biologic mechanisms that may link depression and dementia among military veterans include vascular disease, changes in glucocorticoid steroids and hippocampal atrophy, deposition of β-amyloid plaques, inflammatory changes, and alterations of nerve growth factors. In addition, military veterans often have depression comorbid with posttraumatic stress disorder or traumatic brain injury. Therefore, in military veterans, these hypothesized biologic pathways going from depression to dementia are more than likely influenced by trauma-related processes. Treatment strategies for depression, posttraumatic stress disorder, or traumatic brain injury could alter these pathways and as a result decrease the risk for dementia. Given the projected increase of dementia, as well as the projected increase in the older segment of the veteran population, in the future, it is critically important that we understand whether treatment for depression alone or combined with other regimens improves cognition. In this review, we summarize the principal mechanisms of this relationship and discuss treatment implications in military veterans.

Keywords: Dementia; Alzheimer's disease; Cognitive impairment; Depression; Posttraumatic stress disorder; Traumatic brain injury; Older veterans

1. Introduction

Depression is very common through the course of veterans' lives [1,2], whereas dementia is very common primarily in late life. After 65 years of age, the risk of dementia is estimated to double every 5 years [3], and among those ≥90 years, the risk is estimated to increase up to 50% [4,5]. A recent study documented that among veterans 55 years and older, patients with dysthymia and depression were more likely to develop incident dementia than those with no depression over 7 years of follow-up (Fig. 1) [2]. Although evidence linking depression to dementia has been studied in nonveterans, similar work is limited in older military veterans.

Given the current and projected growth of the older segment of the veteran population [6], a better understanding of the link between depression and risk of dementia is important, especially for possible treatment and prevention. However, there are several challenges to understanding this link. For example, major depressive disorder is common among patients with dementia, occurring in up to 20% of patients with Alzheimer disease (AD) and up to 50% of patients with vascular dementia [7–9] and, thus, disentangling which came first can be difficult. In addition, although depression and dementia are considered separate clinical entities, they share some common symptoms, such as impairment in attention and working memory, changes in sleep patterns, and a decrease in social and occupational function [10]. Moreover, the concept of "pseudodementia" highlights the

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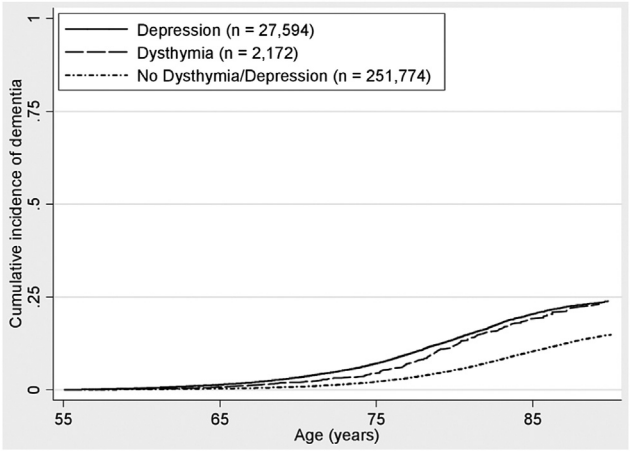

Fig. 1. Cumulative incidence of dementia by age and depression status in older veterans.

blurriness of the distinction between depression and dementia [11,12]. Thus, the interrelationship of depression and dementia is complex and sometimes indistinguishable and this complicates the ability to determine the exact relationship of depression to dementia.

In this article, we review current knowledge on the causes and sequelae that may explain the relationship between depression and risk of developing dementia in military veterans. We will primarily focus on mechanisms that may underlie the link between depression and dementia. In addition, we will discuss potential implications for screening and treatment in veteran populations.

2. Potential mechanisms

In the following section, we outline the possible biologic links between depression and the risk of dementia. Figure 2 illustrates the primary mechanisms that may link depression to risk of dementia among military veterans. Military veterans often have depression comorbid with posttraumatic stress disorder (PTSD) [13,14] or traumatic brain injury (TBI) [15,16]. Thus, in military veterans, each of the hypothesized pathways represents a mechanistic link between depression-related processes and dementia-specific neuropathology that are more than likely exacerbated by trauma-related processes. The hypothesized pathways include: (1) vascular disease; (2) changes in glucocorticoid steroids and hippocampal atrophy; (3) deposition of β-amyloid (Aβ) plaques; (4) inflammatory changes; and (5) deficits of nerve growth factors or neurotrophins.

2.1. Vascular disease

Vascular disease has the strongest evidence linking depression and dementia, and vascular risk factors are highly prevalent among veterans (>25%) [17,18]. This evidence is primarily based on the "vascular depression hypothesis" [19,20], suggesting that cerebrovascular disease predisposes, precipitates, or perpetuates some geriatric depressive syndromes [21,22]. A number of studies have reported that vascular lesions as well as structural brain changes may contribute to depression in late life [23–26]. However, whether vascular disease or vascular lesions contribute to depression or result from depression is debatable, because each condition is associated with an increased risk of developing the other [27].

The pathway connecting vascular disease to dementia through depression is probably not sequential as demonstrated in Figure 2. There are several proposed mechanisms by which previous depression could be related to subsequent vascular disease, including behavioral risk factors (e.g., smoking, inactivity), disruption of the hypothalamic–pituitary–adrenal (HPA) axis and increased cortisol related to the metabolic syndrome, development of hypertension resulting from dysregulation of normal endothelial function, and increased proinflammatory cytokines [28]. In particular, depression is a risk factor for both first-ever myocardial infarction and stroke [29]. Moreover, in veterans who have a high prevalence of comorbid mental health disorders such as depression and PTSD, there may be a greater occurrence of vascular-related disorders compared with nonveteran populations. Depression is a known risk factor for cardiovascular disease [30]. In addition, PTSD with and without other mental health diagnoses is highly associated with hypertension, dyslipidemia, and diabetes in Iraq and Afghanistan veterans [31]. Recent research has even shown that TBI, which is common in Iraq and Afghanistan veterans and highly comorbid with depression, is associated with subsequent ischemic stroke [32]. Moreover, there is strong evidence that vascular disease promotes development of depression. Risk for depression is increased greatly after myocardial infarction and stroke [27]. In particular, magnetic resonance imaging studies have shown robust associations between ischemic brain lesions and depression or depressive symptoms in older adults [33,34]. Longitudinal studies provide evidence that large cortical white matter lesions and severe subcortical white matter grade are significant risk factors for developing depressive symptoms [34]. These white matter changes have been found to predate and predict late-life depression [34,35].

The "vascular-depression-dementia hypothesis" is also supported by findings that indicate that vascular disease contributes to the clinical manifestation of dementia symptoms [36,37]. Ischemic damage, largely in the frontostriatal brain regions, may lead to significant cognitive deficits [38]. Finally, the ischemic damage to frontostriatal brain regions may explain the executive function, psychomotor slowing, and resistance to treatment common in late-life depression [28,38,39], which suggests that ischemic structural changes in the brain are a common etiologic factor of both the depression and the related cognitive impairment.

2.2. Changes in glucocorticoid steroids and hippocampal atrophy

Another proposed link between depression and dementia may be through the increased production of cortisol resulting

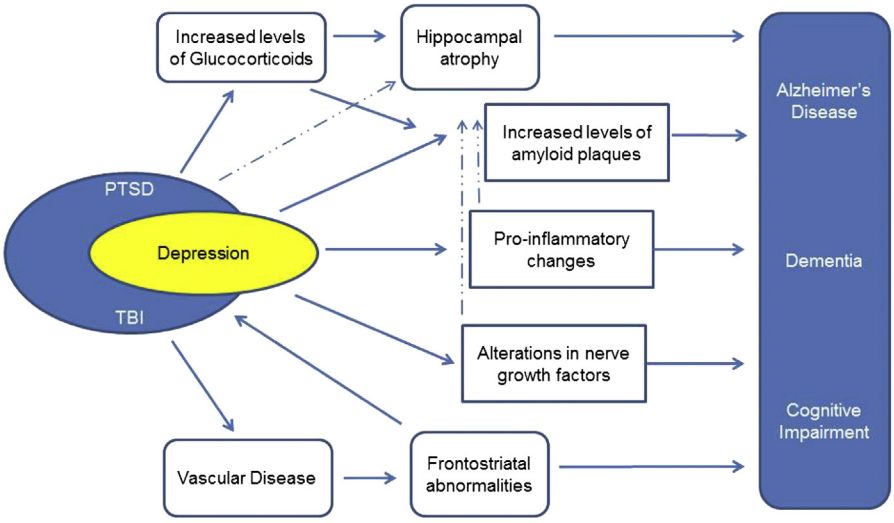

Fig. 2. Mechanisms linking depression and dementia. PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

in hippocampal atrophy. In this pathway, the HPA axis is activated by depression and depressive symptoms that increase the production of glucocorticoids. This escalation of glucocorticoids leads to damage in the hippocampus as well as down-regulation of glucocorticoid receptors (Figure 2). The net effect is impaired negative feedback to the HPA axis and chronic elevation of adrenal glucocorticoids (or "glucocorticoid cascade" [40]), ultimately resulting in a vicious cycle with hippocampus atrophy and cognitive deficits [28,41]. Impairment in glucocorticoid metabolism (e.g., increased cortisol bioavailability) has been documented in patients with depression [42] and patients with dementia [43]. Additionally, atrophy of the hippocampus is one of the early brain changes in AD [44], and reduced hippocampal volume has been found in patients with depression [45–47]. Furthermore, PTSD was associated with smaller hippocampal volume and deficits in short-term memory in 26 Vietnam combat veterans compared with 22 subjects without psychiatric disorders [48]. Interestingly, almost 100% of these veterans with PTSD had a diagnosis of major depression or dysthymia over their lifetime, whereas 80% had a current comorbid diagnosis.

Animal models of the stress response have provided much of the evidence for the cortisol-hippocampal link and suggest that high-stress conditions or exogenous glucocorticoids can cause hippocampal neuronal damage [49] and memory impairment [50] and that hippocampal damage can accumulate over a life course of exposure to increased stress and glucocorticoid excess [51]. A similar cycle may exist in humans in whom there is a high correlation between exposure to stressful events and depressive episodes [52–54] and the HPA axis is hyperactive in depression [55,56]. This is particularly concerning in military veterans who are at increased risk of exposure to trauma, and, thus, heightened exposure to high-stress conditions, leading to sequelae of depression as well as PTSD [57].

Studies have found that loss of hippocampal volume increases the risk of cognitive decline [58,59] and even dementia [60] in adults with depression, but findings are conflicting [61,62]. In one study, a history of depression was not associated with hippocampal volumes at baseline, and these volumes did not mediate the increased risk for AD associated with prior depression [61]. This finding implies that the effect of depression is not through hippocampal atrophy. In contrast, reductions in hippocampal volume have been found more consistently among individuals with recurrent depression and longer duration of illness [47,63,64], or in those with comorbid depression-PTSD, as seen in military veterans [48], suggesting support for the cortisol-hippocampal pathway. Among Gulf War veterans, chronic PTSD compared with remitted PTSD was associated with smaller hippocampal volume even after researchers adjusted for current depression [65]. This finding suggests, along with the findings on recurrent depression and longer duration of depression associated with reduced hippocampal volume, that effective treatment of mental health disorders may reverse the reduction in hippocampal volume once symptoms remit and the patient recovers. It is also possible that a small hippocampus is a risk factor for a type of depressive disorder or PTSD that is resilient to treatment.

However, even if it is confirmed that the relationship between depression and hippocampal atrophy exists, it is unclear whether this association is mediated by increased levels of cortisol [45,47]. In some studies, hippocampal atrophy was associated with inflammatory changes and deficits of nerve growth factors in patients with depression and other psychiatric disorders [66–68], which suggests that mechanisms other than or in addition to elevated cortisol levels may be important; however, further research is necessary to elucidate pathways.

2.3. *Deposition of Aβ plaques*

Like hippocampal atrophy, amyloid plaques in the brain are a diagnostic feature of AD. Both Aβ and tau protein

accumulate in AD and are the main constituents of neuritic plaques and neurofibrillary tangles, respectively [69]. Interestingly, studies have shown that AD patients with depression have a greater accumulation of plaques and tangles in the hippocampus compared with AD patients without depression [70,71]. Furthermore, current evidence supports the role of Aβ as primary in promoting the cascade of events that leads to neuronal death and AD [72,73]. Thus, it is likely that depression is also linked to AD through the formation of amyloid plaques [74].

The formation of amyloid plaques is particularly concerning for military veterans, who are at high risk of TBI and comorbid depression [75]. Recent research has shown that TBI may accelerate the formation of AD-related pathologies. In mouse models, controlled cortical impact TBI increased intra-axonal Aβ accumulations and phospho-tau immunoreactivity 1 and up to 7 days after impact [76]. Compared with uninjured, age-matched control patients, survivors of a single TBI had more neurofibrillary tangles and Aβ plaques in greater density postmortem even after almost 50 years [18]. These findings suggest that the underlying mechanisms resulting in neurodegenerative disease are probably instigated or enhanced as part of the sequelae after survival post-TBI.

Thus, depression may be part of this process, because it is known that even single-incident, mild, "closed-head" TBI leads to symptoms of depression [75]. Also, PTSD is a common comorbidity of military-related TBI, along with depression, particularly in severe cases [77,78]. Furthermore, evidence is emerging that individuals who have sustained multiple TBIs either through military service or sports injuries are at risk of a syndrome of chronic traumatic encephalopathy (CTE) [79,80]. CTE is characterized by depression, impulsivity, executive dysfunction, and dementia. The hypothetical sequence of events in both TBI and CTE suggests that depression shares a similar disease process that causes dementia with distinct patterns of Aβ and tau pathology [75]. A recent study of 760 US Army soldiers supports the importance of depression as an integral part of the process to cognitive decline post-TBI. Milder TBI was significantly associated with functional impairment but not neuropsychologic consequences, whereas both depression and PTSD were associated with several neuropsychologic performance deficits, and more enduring cognitive compromise, as well as functional impairment [77].

Figure 2 presents two proposed pathways involving Aβ. One implicates glucocorticoid intermediaries and the other involves depression directly. Although the nature of the relationship between depression and Aβ has not been fully elucidated, it is possible that increased Aβ production is initiated by the stress response associated with depression alone, or depression comorbid with PTSD [48], and glucocorticoids [12,41]. In animal models of AD, the administration of stress-level glucocorticoids promotes Aβ formation by increasing steady-state levels of amyloid precursor protein and the Aβ precursor protein cleaving enzyme [81]. In contrast, depression may influence Aβ accumulation through direct interaction with the amyloidogenic processing early in AD, a process that may be linked to the serotonergic system [41,82,83], or possibly head injury [75,76].

Finally, studies indicate that there is a relationship between plasma Aβ levels in patients with depression and cognitive impairment. In a cross-sectional study, a type of amyloid-associated depression (depression with a high ratio of plasma Aβ peptide 40 [$A\beta_{40}$] to $A\beta_{42}$) was associated with impairment on several cognitive domains, including memory, visuospatial abilities, and executive function [84]. Thus, amyloid-associated depression may represent a preclinical or prodromal depression of AD.

2.4. Inflammatory changes

Research suggests that chronic inflammation has a central role in the pathophysiology of both depression and dementia [76,85,86]. Figure 2 presents two proposed pathways that involve inflammatory changes within the central nervous system. First, the increase in levels of cytokines such as interleukin-6 and tumor necrosis factor found in depression may lead to a decrease in anti-inflammatory and immunosuppressant regulation, an increase in proinflammatory changes within the central nervous system, and ultimately cognitive deficits and dementia [87,88]. Second, proinflammatory cytokines interfere with serotonin metabolism and affect synaptic plasticity and neurogenesis in the hippocampus [12,66].

There are numerous and complex neurodegenerative pathways that could link depression to the inflammatory process of proinflammatory cytokines. Moreover, PTSD, a frequent comorbid condition in veterans with depression, also has been linked to inflammation [89]. However, depression may be a direct link in this pathway, because after adjustment for depression PTSD had a less statistically significant effect on inflammation. In studies in vitro and in vivo, Aβ activates the microglia to release proinflammatory cytokines [90], and microglia activation has been found in patients with mild cognitive impairment [91]. Thus, chronic inflammation may explain why a history of depression can promote development of dementia; however, more studies are necessary to elucidate and confirm this link, because the role of microglial cells and inflammation has been challenged [92].

2.5. Alterations of nerve growth factors

Alterations in neurotrophic factors, including brain-derived neurotrophic factor (BDNF), could also serve as a link between depression and dementia (Figure 2) [12]. Neurotrophins such as BDNF are a class of growth factors that are necessary for maintenance of neuronal health and modulation of synaptic plasticity [93]. Impaired BDNF signaling has been observed in animal models of depression [94], in patients with depression [68,95], and in patients with AD [96,97]. Studies also have reported decreased mRNA

levels of BDNF in the hippocampus of patients with depression and among those with AD [41,68]; however, findings have been inconsistent [98,99]. Given these findings and the key role BDNF plays in regulating hippocampal plasticity, BDNF along with other neurotrophic factors like transforming growth factor-β1, insulin-like growth factor-1, and vascular endothelial-derived growth factor [100] are hypothesized to play a critical role in maintaining the integrity of the hippocampus and cognitive function.

3. Treatment and management implications

This review provides evidence suggesting that screening for cognitive impairment should be a component of the management and care of veterans with depression or those reporting depressive symptoms. In addition, because stakeholders and health care providers determine the most effective health care strategies for veterans who are diagnosed with depression, attention to the screening, monitoring, and management of other psychiatric symptoms, including, in particular, those related to PTSD and TBI, will be paramount. It may be that effective psychiatric and psychosocial intervention will have broad effects by not only treating symptoms of emotional distress but also by contributing a secondary benefit, addressing military-related neuropsychologic decrements.

Although there is evidence to suggest that treatment of depression in elderly patients (i.e., pharmacologic, behavioral, or other modalities) improves cognition, leading to improved memory and other cognitive performance [101–104] and may reduce pathophysiological alterations related to dementia [63,105–107], other studies have found that despite successful treatment for depression, cognitive impairment continues to persist or even develop [108–110]. Recent work investigating the multifunctional protein p11 provides a molecular and cellular framework for the development of novel antidepressant therapies [111]. Expression of p11 overlaps with brain regions that also are implicated in the pathophysiology of depression, as well as dementia, including the hippocampus. Although such interventions are still in the early phases of development, the possibility that p11 can regulate depression-like behaviors and responses to antidepressants are promising to future interventions that may additionally slow the progression of cognitive decline and dementia. Furthermore, recent preliminary research shows that a change in p11 is indicative of therapeutic benefit of an antidepressant much earlier than clinical phenotypic change [112].

An alternative strategy to interrupting the course of cognitive decline with depression-interventions is an integrated treatment approach. A pilot study in this area has shown promising results, where the addition of a cholinesterase inhibitor after antidepressant medication treatment in elderly depressed, cognitively impaired patients led to a significant improvement in memory [113]. Another approach would be to combine antidepressants with behavioral interventions that may protect against cognitive decline (e.g., exercise, cardiovascular risk modification, psychotherapy, or rehabilitative treatment for trauma injury/exposure). A combined treatment approach of antidepressants, cholinesterase inhibitors, vitamins, and diet, and lifestyle and exercise modifications has been found to protract cognitive decline over 24 months and improve memory and frontal lobe functions [114]. Such integrated strategies hold great promise to reducing the progression of dementia, and possibly preventing it, especially among veterans with depression or depressive symptoms and high rates of comorbidity. Thus, future studies in veterans should examine the implication for depression modification in clinical trials, focusing on whether simultaneous or subsequent interventions have additive or multiplicative effects on cognition.

This review highlights the need for study of potential mechanisms linking depression to dementia to target intervention, prevention, and health care needs among veterans. The most likely links are the following hypothesized mechanisms: (1) vascular disease; (2) changes in glucocorticoid steroids and hippocampal atrophy; (3) deposition of Aβ plaques; (4) inflammatory changes; and (5) deficits of nerve growth factors or neurotrophins. The impact of comorbid PTSD or TBI in military veterans is unknown but likely exacerbates the mechanistic link between depression-related processes and dementia-specific neuropathology.

In summary, the veteran population is rapidly aging [6], which coincides with the escalating dementia epidemic [115]. As a result, studying the effects of a modifiable risk factor like depression and its potential for dementia prevention is imperative, particularly in veterans. The underlying pathway linking depression to dementia is multifactorial and probably not mutually exclusive, suggesting a combined regimen as the most promising treatment approach in military veterans.

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