Depression in Alzheimer’s Disease: The Roles of Cholinergic and Serotonergic Systems

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Abstract: Although depression and Alzheimer’s disease fundamentally result from distinct pathophysiological events, their coincidence is far from a rare occurrence. In addition to the difficulty in the diagnosis of depression in the patients with a cognitive impairment, caregivers and even physicians are mostly unaware that depression and Alzheimer’s disease can coexist. While depression has already a devastating impact on quality of life by itself, coinciding depression and Alzheimer’s disease may advance to a cataclysmic magnitude. This chapter underlines obstacles in the recognition of depression in the Alzheimer’s patients following a brief introduction to the concept of depression. Depression and Alzheimer’s disease appear to intersect in the cholinergic and serotonergic systems which may engender an exquisite strategy in the treatment of both disorders. Therefore, potential cholinergic and serotonergic targets are also emphasized.

Keywords: Alzheimer’s disease; cholinergic system; coincidence; depression; serotonergic system
INTRODUCTION

Depression is an affective disorder as old as mankind. Hippocrates has defined depressive psychological state as “melancholia,” which means “black bile” in Greek, by the words of “despair, apathy, unwillingness, insomnia, anxiety, incompetence, gloominess, sadness and fear” in around 400 BC (1). The brief description of depression is being possessed by unhappiness, moodiness and unwillingness (2). However, its description as a medical condition is continually evolving with the efforts of classification to make differential diagnosis clearer. Depression is an additional mental burden in Alzheimer’s patients who already struggle with cognitive impairments. Both depression and Alzheimer’s disease lower quality of life and harden daily activities of the patients who are mostly elders. Alzheimer’s disease often does not have a good prognosis whereas depression is a reversible, but recurrent disorder. Almost one-third of the Alzheimer’s patients suffer depression (3, 4). This chapter focuses on the interrelation between depression and Alzheimer’s disease, and discusses common properties of these neuropsychiatric disorders.

HOW DO WE RECOGNIZE DEPRESSION?

Diagnostic and Statistical Manual of Mental Disorders (DSM) by the American Psychiatric Association is the main guideline to diagnose depressive disorders whereas International Classification of Diseases (ICD) by the World Health Organization is the global system for reporting health conditions. According to the fifth edition of DSM, depressive disorders are categorized as major depressive disorder, dysthymic disorder, disruptive mood disorder, premenstrual dysphoric disorder, substance or drug related depressive disorder, depressive disorder due to a medical condition, and otherwise undifferentiated depressive disorder (5). With the system of ICD, the most commonly diagnosed depressive disorders are single depressive episode, recurrent depressive disorders, and persistent mood disorders (6). Depression is the most prevalent psychiatric disorder among general population (7). The patients with depression often have low self-esteem, suffer overwhelming unwillingness, and are afflicted by attention and concentration deficits which result in cognitive impairments (6, 8). Depression may exceed being an affective problem and lead to physical abnormalities. It can coincide with and aggravate existing physical pathologies (2, 6, 8). On the other side, chronic diseases can also generate depressive disorders (2, 9, 10). Together with its complications including the aggravation of physical health conditions, depression is a serious public health concern which also creates an important economic burden (10–12). Concerningly, depression has become the leading cause of disability (13). This insidious pandemic urges a better understanding of its pathophysiological mechanism and so, development of more advanced treatment options.
COGNITIVE DYSFUNCTION MAY LOOK ALIKE DEPRESSION

Although depression occurs frequently, it should not be mistaken as its diagnosis is unchallenging, particularly for the patients with cognitive impairment. Depressive symptoms are summarized above; however, the cognitive impairment can easily be confused with depression and *vice versa*. Lowered self-esteem, self-blame, forgetfulness and indecisiveness are shared behavioral symptoms of depression and cognitive impairment. Furthermore, hypomimia, apathy, psychomotor slowness, fatigue, and reluctance to communicate are the signs a physician may notice in a depressive patient which again resemble cognitive dysfunction (14, 15). Therefore, in the patients with cognitive impairment, diagnosis of depression often requires scrutinization of medical history and discrimination of the affective disorder with overlapping signs of cognitive inability. Depression can emerge at any age, but its prevalence is higher in adults, especially between 55 to 74 years old (16). Also, women are reported to experience depression about two times more than men (11, 16), indicating that sex is a risk factor for depression (17). Besides, there are numerous other factors that create a tendency toward depression such as divorce, separation, loneliness, and low socioeconomic status. (18).

THE COINCIDENCE OF DEPRESSION AND ALZHEIMER’S DISEASE

Epidemiological and longitudinal studies indicate that there is a relation between Alzheimer’s and depression. However, it is debatable whether depression is a symptom arisen from the neurodegeneration or a reaction against cognitive inabilities. Some authors are defending that depression is a preceding pathology and a risk factor for Alzheimer’s disease whereas some others suggest that depression co-occurs in Alzheimer’s disease, and it becomes apparent as a component of Alzheimer’s (4, 19).

A yearly increase in elderly population is predicted in almost all countries (20). Because age is an individual risk factor for Alzheimer’s disease (3), an aging population means more patients with Alzheimer’s disease. About 5% of the people over 65 years have dementia and an additional 5% increases every 5 years. Thus, the prevalence of dementia is as high as 40% after 95 years of age (21). Today, it is estimated that there are 35 million demented people all around the world and this number is projected to be 115 million in 2050 (22).

Alzheimer’s disease is the most common form of dementia (23). One-ninth people over 65 years of age and one-third over 85 years struggle with Alzheimer’s disease (3). Alzheimer’s disease affects more than 5 million people only in the United States and it is reported to be the fourth cause of death (24). Furthermore, coinciding pathologies can significantly increase the incidence of the disease. For example, the risk for Alzheimer’s disease is 3 to 5 times more in Down’s syndrome (25).
Depression is an affective disorder that can afflict who takes a medical treatment and also, it is more prevalent in inpatients and elders under nursing care (3). Depression is a notable problem for overall elderly health. It has higher recurrence rates in elders than middle-aged people (26). Depression soars the death ratio independently of any medical interventions in patients under the nursing care (27). Suicide is the grassest consequence of depression and depressive elders have the highest suicide rates in all ages (28). Startlingly, suicidal ideation has been reported in 45% of the patients with concurring depression and Alzheimer's disease (29).

Depression is considered to be a “syndrome” rather than a “disease” which presently lacks a definitive biomarker and hence, is diagnosed by subjective questionnaire inventories. These inventories mainly aim to inspect neuropsychiatric symptoms such as negative emotional state, changes in personality and psychotic signs. The emotional and psychotic symptoms are relatively common in the Alzheimer's patients (30). Dysphoria, anxiety, aggressiveness, psychomotor agitation, loss of interest, and sleep disorders are the most frequent depressive symptoms. These symptoms encumber the care of Alzheimer's patients which is already difficult without them (Figure 1).

Clinical studies suggest that depression coincides with Alzheimer's disease in more than a half of the patients (29). Besides, depression in Alzheimer's disease often resembles severe depression, but with a variety of ambiguous symptoms.

Figure 1 Depression and Alzheimer's disease are often manifested with similar neuropsychological symptoms and signs.
For example, depression in Alzheimer’s disease can be represented with social isolation, self-abnegation or aggressiveness (3, 4). However, apathy and loss of interest remains to be the most common symptoms in coinciding depression and Alzheimer’s disease (4, 31).

Diagnosis of depression in Alzheimer’s disease is a strenuous task due to the lack of an objective and repeatable laboratory test to identify depression. Because of similarities with the patients with Alzheimer’s disease, depression inventories can be misleading. Accordingly, it is important to emphasize that the incidence of depression gradually increases from mild to moderate cognitive impairment whereas decreases sharply in severe dementia (32). This decrease in incidence is a clear indicator of the obstacle in the diagnosis of coexisting depression in Alzheimer’s disease.

**WHAT DOES LIE BEHIND COINCIDING ALZHEIMER’S DISEASE AND DEPRESSION?**

As mentioned above, the coincidence of Alzheimer’s and depression is not a rare occurrence, and it creates a serious challenge to the diagnosis and quality of life. Although the two pathologies converge on behavioral and cognitive disturbances, they apparently do not originate in a common pathophysiological basis. However, they have a number of overlapping features that may explain the high comorbidity of Alzheimer’s disease and depression.

The first report hinting the relation between Alzheimer’s and depression dates back to late 1920s. Herz and Füngeld (33) have described depression as a preceding disorder that is immediately followed by deteriorations in memory in Alzheimer’s patients. Numerous subsequent researches confirmed this link up to now, but post-mortem studies are peculiarly important since there is not a definitive ante-mortem diagnostic tool for Alzheimer’s disease (34). Because longitudinal studies are invaluable means to reveal if there is a relation between seemingly distinct conditions, we will briefly discuss the prominent longitudinal studies in which post-mortem diagnosis was established.

In 2004, Milwain and Nagy (35) examined 89 histopathologically confirmed Alzheimer’s patients with depression and found that the patients in the intermediate stage of the disease scored lower in CAMCOG, a neuropsychological battery to assess cognition (36), than the patients without depression. The worsened cognition in depressive Alzheimer’s patients was implying a deterioration in the neuropathology, although this was not evidenced in that report. Rapp et al. (37) have investigated the post-mortem brains of 95 patients with clinically diagnosed Alzheimer’s disease, of which 44 had a life-time history of major depressive disorder and 51 without depression. They noted that the Alzheimer’s patients who suffered a life-time depression had about two times more amyloid plaques and neurofibrillary tangles in their hippocampi. In another longitudinal study that presents patient data from almost 40 years, Brunnström et al. (38) emphasized that the onset of dementia is lower in the depression sufferer Alzheimer’s patients compared to those without depression.
Alzheimer’s disease and depression appear to have a reciprocal relationship. Depression is an individual risk factor for Alzheimer’s disease (39) even when the latency between the two pathologies is as late as more than 25 years (40). Preceding depression is a specifically notable predictor of Alzheimer’s disease for the patients who do not carry apolipoprotein E (ApoE) ε4 allele which is an Alzheimer’s-associated polymorphism (41). Thereby, non-ApoE4 allele carriers with depression have higher risk for Alzheimer’s disease when compared with whom without depression. Furthermore, depression can have an outrageously high frequency in Alzheimer’s disease. Usman et al. (42) have reported that depression was observed in three-fourths of the Alzheimer’s patients without considering sex as a variable, and the prevalence was as high as 90% in females. This is particularly important because depression does not only aggravate amyloid pathology, but also worsens the clinical progress in Alzheimer’s disease (43).

The mentioned interrelation points out some shared molecular features in Alzheimer’s and depression even though they apparently originate from diverse pathological processes. Disturbances in the neurotransmitter systems and hypothalamic-pituitary-adrenal axis are prevailing peculiarities shared in the two pathologies. Indeed, the functions of the brain cannot be accredited to any individual neurotransmitter or neuromodulator because all systems should be operational in a stupendous harmony to achieve an efficient function. However, aberrations in the cholinergic, monoaminergic and serotonergic transmission are evident in both Alzheimer’s disease and depression which compose a pathophysiological intersection.

Cholinergic system in the central nervous system consists of two sub-systems as nicotinic and muscarinic. Although cholinergic projections are clustered in distinct regions, both nicotinic and muscarinic receptors are widely distributed throughout the brain and hence, cholinergic transmission involves in numerous brain functions that are carried out by diverse brain areas (44). The nicotinic system works out through the neuronal nicotinic acetylcholine receptors which are simply cation channels (45) whereas the muscarinic system employs any of the five muscarinic acetylcholine receptors (M1-5) which all are G-protein coupled receptors (46). It is long known that cholinergic dysfunction is a problem in Alzheimer’s disease (47). The cholinergic hypothesis of Alzheimer’s disease proposes that the deterioration in the cholinergic signaling is responsible for learning and memory deficits, a condition which also can be experimentally mimicked by the administration of anti-cholinergic drugs (48). This hypothesis is supported by symptom relieving effects of acetylcholine esterase inhibitors whereas disapproved by the presence of cholinesterase inhibitor-resistant patients (48). Nevertheless, the cholinergic system is evidently disturbed in a remarkable portion of the patients and it shows a correlation with cognitive inabilities (49). This is probably because the cholinergic neurons are particularly affected by the amyloid accumulation (50). With regard to the cholinergic system, the relation between Alzheimer’s and depression seems to be paradoxical, considering that reduced cholinergic signaling is linked to cognitive decline. The involvement of the cholinergic system in depression is known for almost 50 years (51) and preliminary studies have underlined the hyperactivity in the cholinergic signaling in depression (52). Consecutive researches have noted that enhanced cholinergic transmission leads to depression (53, 54) and
antagonizing nicotinic signaling can exert an anti-depressant-like effect (55). Contrarily, the activation of a sub-type of nicotinic receptors, alpha7 receptor, has been shown to alleviate depression in mice through restoring the hippocampal function (56). Therefore, instead of a widespread contribution of the cholinergic system to depression, its influence on hippocampus should be taken into account. As illustrated in Figure 2, decreased cholinergic innervation diminishes the hippocampal neurogenesis and function, and improving the cholinergic transmission by means of cholinesterase inhibitors reverses this consequence (53). In regard to alterations in the cholinergic system, the hippocampus is the crossroad where cognitive deficits meet with depressive behaviors. This probably explains the finding of that cholinesterase inhibitors improve neuropsychiatric symptoms in some Alzheimer’s patients (57, 58). On the other side, it should be kept in mind that cholinergic hyperactivity created by cholinesterase inhibitors can result in depression (59) and hence, fine dose adjustment and a strict follow-up are particularly important issues in the Alzheimer’s patients with a history of depression.

The other neurotransmitter system that bridges between Alzheimer’s disease and depression is the serotonergic system that is named after its neurotransmitter, serotonin (5-hydroxytryptamine; 5-HT). Serotonin has 7 families of receptors (5-HT_{1-7}) which are all G-protein coupled except for the ionotropic 5-HT_{3}.

![Figure 2](image.png) The cholinergic depletion reduced hippocampal neurogenesis that contributes to cognitive impairments.
receptor (60). The most commonly prescribed anti-depressants, selective serotonin reuptake inhibitors (SSRIs), aim the restoration of serotonin in the central nervous system. The alleviation of depression with SSRIs constitutes the foundation for the serotonin hypothesis of depression in which depressed mood and its complications are accredited to reduced serotonergic neurotransmission and neuromodulation (61). Besides the serotonin transporter (SERT), three sub-types of serotonin receptors, 5-HT\textsubscript{1A}, 5-HT\textsubscript{1B} and HT\textsubscript{2A}, which are mainly localized in the limbic system, appear to bear higher importance in depression (61). Recently, 5-HT\textsubscript{4} and 5-HT\textsubscript{6} receptors have been suggested to have a role in depression. The stimulation of 5-HT\textsubscript{4} receptors has been shown to lead to an anti-depressant-like effect that is similar to fluoxetine (62, 63). Moreover, 5-HT\textsubscript{4} stimulation has been found to restore cognitive abilities that are altered in depression (63). An opposite link has been revealed for 5-HT\textsubscript{6} receptors which are abundant in the hippocampus (64). The inhibition of these receptors has been suggested to exert an anti-depressant-like effect (65). Indeed, the strongest relation between Alzheimer’s disease and depression may lie behind the serotonergic system. The patients with Alzheimer’s disease display depleted serotonin and 5-hydroxyindoleacetic acid, the main metabolite of serotonin, in their frontal and temporal cortices (49). Amyloidogenic activity increases in the post-menopausal period and this may be originated in decreased serotonergic signaling due to decreased estrogen (66) which is in accordance with the epidemiological data of higher prevalence of Alzheimer’s disease in women (67). The Alzheimer’s patients have a decreased 5-HT\textsubscript{1A} receptor expression particularly in their hippocampi and raphe nuclei, and the hippocampal receptor decrement is correlated with worsened clinical symptoms (68, 69). Similarly, 5-HT\textsubscript{2} receptors decrease up to 69% in Alzheimer’s disease as documented by decreased setoperone binding, a 5-HT\textsubscript{2} ligand that has particular affinity to 5-HT\textsubscript{2A} receptors (70), and by decreased altanserin binding, a 5-HT\textsubscript{2A} ligand (71). More recently discovered 5-HT\textsubscript{4} and 5-HT\textsubscript{6} receptors, which are novel anti-depressant treatment targets, also involve in the pathophysiology of Alzheimer’s disease. Similar to that for depression, 5-HT\textsubscript{4} agonism alleviates Alzheimer’s amyloidogenic pathology whereas 5-HT\textsubscript{6} antagonism augments memory and learning in the Alzheimer’s patients (72). Moreover, a decrease in SERT accompanies the decrease in the receptors of interest which results in an extensive disruption in the serotonergic signaling in Alzheimer’s disease (73). Overall, the serotonergic system, as summarized in Figure 3, plays a crucial role in both Alzheimer’s disease and depression and constitutes a highly promising treatment target which may ease depressive mood while soothing cognitive deficits in the Alzheimer’s patients with depression.

In addition to current treatment targets of cholinergic and serotonergic systems in Alzheimer’s disease and depression, they share some other pathophysiological features such as disturbances in the hypothalamic-pituitary-adrenal axis, inflammation and oxidative stress (74). However, it is not clear whether these disorders are reasons or consequences. Nonetheless, it is evident that the treatments targeting either cholinergic or serotonergic systems can reduce coinciding immunohumoral and oxidative disruptions to some degree in both diseases (75, 76).
CONCLUSION

Alzheimer’s disease and depression are debilitating disorders which need further scrutinization to understand their pathophysiological properties and to develop novel treatment options. Alzheimer’s disease is an incurable neurodegenerative disorder, at least for now, and undiagnosed/untreated depression in Alzheimer’s patients creates a serious problem since it worsens neurodegeneration while causing further cognitive deficits and lowering quality of life. Considering abovementioned shared molecular features of both disorders, awareness among clinicians of the possibility of depression in Alzheimer’s patients would let them prescribe not only against cognitive symptoms, but also affective disturbances which can benefit to both Alzheimer’s disease and depression.

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Depression in Alzheimer’s Disease

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