Published in final edited form as:

Am J Geriatr Psychiatry. 2016 March ; 24(3): 239–247. doi:10.1016/j.jagp.2015.12.003.

The Amyloid Hypothesis: Is There a Role for Anti-amyloid Treatment in Late-Life Depression?

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Abstract

Antidepressants have modest efficacy in late-life depression, perhaps because various neurobiological processes compromise frontolimbic networks required for antidepressant response. We propose that amyloid accumulation is an etiological factor for frontolimbic compromise that predisposes to depression and increases treatment resistance in a subgroup of older adults. In patients without history of depression, amyloid accumulation during the preclinical phase of Alzheimer's disease may result in the prodromal depression syndrome that precedes cognitive impairment. In patients with early-onset depression, pathophysiological changes during recurrent episodes may promote amyloid accumulation, further compromise neurocircuitry required for antidepressant response and increase treatment resistance during successive depressive episodes. The following findings support the amyloid hypothesis of late-life depression: a) Depression is a risk factor, a prodrome, and a common behavioral manifestation of Alzheimer's disease; b) Amyloid deposition occurs during a long pre-dementia period when depression is prevalent; c) Patients with lifetime history of depression have significant amyloid accumulation in brain regions related to mood regulation; d) Amyloid deposition leads to neurobiological processes, including vascular damage, neurodegeneration, neuroinflammation, disrupted functional connectivity, that impair networks implicated in depression. The amyloid hypothesis of late-life depression is timely, because availability of ligands allows *in vivo* assessment of amyloid in the human brain, a number of anti-amyloid agents are relatively safe, and there is evidence that some antidepressants may reduce amyloid production. A model of late-life depression introducing the role of amyloid may guide the design of studies aiming to identify novel antidepressant approaches as well as prevention strategies of Alzheimer's disease.

Keywords

Late-life depression; Alzheimer's disease; Anti-amyloid agents; Amyloid hypothesis

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Disclosures: Dr. Mahgoub has no competing interests.

Introduction

The lifetime prevalence of major depression in Alzheimer's disease (AD) patients ranges from 17% to 24%, while milder depressive syndromes afflict an additional 20% to 30% of AD patients (1). Depression is both a risk factor and a prodrome of AD (2). Approximately 10 to 15% of AD dementia cases are preceded by depression (3). The risk for developing dementia increases with the number of depressive episodes; each depressive episode increases the risk of later development of dementia by 14% (4).

Antidepressants are, at best, modestly effective in depressed patients with cognitive impairment or AD. Disruption of frontolimbic networks may be responsible for poor response to antidepressants (5). This view is consistent with findings suggesting that structural and functional abnormalities in the cognitive control network contribute to resistance to antidepressants even in non-demented depressed older patients (5–9). These abnormalities have been attributed to vascular compromise at least in a subgroup of depressed older patients (10–12). Several lines of evidence suggest that sustained elevations of beta-amyloid (A β) lead to brain abnormalities associated with depression (13, 14).

This position paper suggests that amyloid accumulation may predispose to late-life depression in some older patients with either early-onset, recurrent depression or late-onset depression, part of the prodromal phase of AD. This assertion is based on the following observations: 1) Patients with lifetime history of depression have significant amyloid accumulation in brain regions related to mood regulation, an event conceivably related to the increased risk of AD conferred by recurrent depression (15). 2) Amyloid deposition occurs during a preclinical phase of dementia when depressive syndromes and symptoms of AD patients are prevalent (1, 16). 3) Amyloid deposition leads to neurobiological processes (vascular damage, degeneration, inflammation, blood brain barrier changes, abnormal functional connectivity) that can impair networks implicated in depression (10–12); 4) AD patients with history of depression have more amyloid plaques in the hippocampus than AD patients without depression (17). The amyloid hypothesis of late-life depression is timely because brain amyloid can now be imaged, a number of anti-amyloid agents with acceptable safety and tolerability are available, and there is evidence that serotonergic antidepressants may reduce amyloid production (18).

A Putative Role of Amyloid in Late-Life Depression

A model of late-life depression postulates that compromised integrity of frontolimbic and frontostriatal networks confers vulnerability to late-life depression (19). Potential contributors to frontolimbic and frontostriatal abnormalities are vascular and degenerative processes, a pro-inflammatory state, and endocrine changes, all of which are enhanced by neurobiological responses to the chronic stress to which older adults are often exposed. In patients with early-onset depression, pathophysiological changes during recurrent episodes may promote amyloid (A β) deposition and initiate a vicious circle (Figure 1). Amyloid deposits, then, may lead to cerebrovascular compromise, neurodegeneration, and neuroinflammation, damage frontolimbic circuitry, worsen the outcomes of depression, and impair cognition. Conversely, during the preclinical phase of AD, A β accumulation may

lead to pathophysiological events that impair frontolimbic and frontostriatal circuitry and predispose to depressive symptoms or syndromes prior to the onset of cognitive impairment.

Brain Imaging and Autopsy Studies

Biomarkers of A β amyloid pathology may detect the AD process during the preclinical stage of the disease (20, 21). Biomarkers of A β amyloid as a rule are present before biomarkers of neuronal damage, i.e., atrophy on MRI, parietotemporal hypometabolism on PET, and elevation of CSF tau protein (16).

Positron emission tomography (PET) is the leading neuroimaging tool for early detection of AD amyloid pathology and for following its course. Positive scans are found in 30% of cognitively intact individuals over the age of 70 years and in 40–60% of individuals with mild cognitive impairment (20). Longitudinal studies of cognitively intact individuals with positive amyloid scans show a very slow rate of memory decline and suggest that the process of amyloid accumulation may extend for 15–20 years before dementia appears.

¹⁸F-florbetapir imaging revealed increased amyloid binding in the precuneus and the parietal cortices of cognitively unimpaired older adults with lifetime history of major depression relative to comparison subjects (15). Moreover, patients with mild cognitive impairment and lifetime history of major depression had significantly higher ¹⁸F-Florbetapir standardized uptake, an index of A β deposition, in the frontal cortex bilaterally, compared to patients with mild cognitive impairment without history of major depression (22).

Autopsy studies showed higher levels of amyloid plaques and tangles within the hippocampus of AD patients with history of depression compared to AD patients who had not been depressed (17). Within the group of patients with AD and a history of depression, patients with concurrent depression at the time of first diagnosis of AD had pronounced neuropathological changes in the hippocampus. However, others found that late-life depression is associated with subcortical and hippocampal neuronal loss but not with Alzheimer pathology (23).

Plasma and CSF Amyloid Studies

Findings on the association of plasma or serum amyloid β (A β) with late-life depression have been inconsistent (24). Two cross-sectional studies reported an elevation of plasma A β 42 in individuals with late-life major depression (25) or depressive symptoms and signs compared to non-depressed subjects (26). However, other cross-sectional studies found an inverse relationship between plasma A β 42 and depressive symptomatology (27) (28) (29). Depression with high plasma A β 40/A β 42 ratio was accompanied by impairment in memory, visuospatial task performance, and executive function (29). In contrast, depression without an elevation of plasma A β 40/A β 42 ratio was not associated with memory impairment but with other cognitive functions. In older adults, high plasma A β 42 at baseline predicted the development of first depressive episode at a 2.5 year follow-up and of AD at 5 year follow-up (30). A 9 year follow-up study showed that low A β 42/A β 40 was associated with an increased risk of developing depression over time only in among those with one or more apolipoprotein E4 (ApoE4) allele (31). The reasons for inconsistency in plasma and serum

A β findings are complex and may include methodological differences across studies and the effect of disease stage on A β levels possibly reflecting sequestration of A β 42 in senile plaques or semi-soluble oligomers (32).

A drawback of plasma A β studies is that plasma A β levels are not correlated with cerebrospinal fluid (CSF) or brain A β concentrations (33). Two studies reported lower CSF A β 42 levels in non-demented subjects with major depression than non-demented controls (34) (35). However, a third study showed that non-demented women with late-life major depression had higher levels of CSF A β 42 than comparison (N=70) subjects (36). CSF A β 42 levels of non-demented subjects with dysthymia were statistically indistinguishable from the A β 42 levels of AD subjects although CSF A β 42 was decreased in AD compared to non-depressed controls (37). Among non-demented subjects, subsyndromal depressive symptoms were inversely related to CSF A β 42, but only in the ApoE4 non-carriers (24). In a study of subjects with AD and subjective cognitive impairment, those with some depressive symptoms had similar CSF A β 42 levels with subjects with lower depression scores (38). Most of the above CSF studies included small numbers of depressed subjects and had methodological problems that do not permit definitive conclusions about the relationship of CSF A β 42 in late-life depression.

Relationship to the “Vascular Depression Hypothesis”

Literature generated by the “vascular depression” hypothesis suggests that cerebrovascular compromise promotes late-life depression and worsens its outcomes (10–12). AD is associated with cerebrovascular changes including inhibition of angiogenesis, impaired vascular tone, hypoperfusion, and reduced hemodynamic responses (39). Vascular A β deposits and not parenchymal plaques, appear to be more sensitive predictors of dementia. Amyloid deposition in and around cerebral blood vessels plays a central role in a series of response mechanisms that lead to changes in the integrity of the blood-brain barrier, extravasations of plasma proteins, edema formation, and release of inflammatory mediators which, in turn, produce partial degradation of the basal lamina and increase the risk of microhemorrhages. The buildup of amyloid deposits in and around blood vessels chronically limits blood oxygen supply triggering a cascade of metabolic events generating nitrogen and oxygen free radicals with consequent oxidative stress and cell toxicity. In a transgenic mouse model of Alzheimer's disease (TgCRND8), cortical arterioles had high tortuosity, low caliber, and A β accumulation (40). These structural changes were accompanied by progressive functional compromise, reflected in higher dispersion of microvascular network transit times, elongation of the transit times, and impaired microvascular reactivity to hypercapnia. Moreover, inhibition of A β oligomerization and fibrillization with scyllo-inositol rescued both structural and functional impairment of the cortical microvasculature. These observations suggest that amyloid deposition may be one of the mechanisms leading to “vascular depression”.

Relationship to the “Inflammation Hypothesis of Late-Life Depression”

A β amyloid evokes an inflammatory response leading to synaptic dysfunction, neuronal death, and neurodegeneration (41). Pro-inflammatory cytokines compromise neurogenesis,

neural plasticity, neurotransmitter synthesis, and neuroendocrine function (42). In rats, intracerebrovascular administration of soluble A β ₁₋₄₂ led to depression-like behavior in the forced swim test (13). It also led to reduction in the content of serotonin and the expression of brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF).

Similar inflammatory processes have been implicated in late-life depression (43). Responses to stress include a pro-inflammatory state, changes in functional connectivity, neuroplasticity, neurogenesis, and increased production of oxygen species. Pro-inflammatory cytokines increase the expression of indoleamine 2,3-dioxygenase, the catalytic enzyme of tryptophan leading to reduction of serotonin synthesis (44, 45). Pro-inflammatory changes decrease neurotrophic support and alter glutamate function thus contributing to excitotoxicity (46). Alteration of glutamate metabolism by cytokines impairs hippocampal synaptic plasticity (47). Cytokines upregulate the HPA axis during periods of psychological and/or physical stress (48). Upregulation of the HPA axis occurs in a significant proportion of depressed patients (49). Some antidepressants may reduce the expression of inflammation markers (50). The anti-inflammatory agent infliximab reduced symptoms of depression in patients with high inflammatory markers (51). A recent study showed that escitalopram improved depressive symptoms more than nortriptyline in depressed patients with low C-reactive protein (CRP), while nortriptyline was more effective than escitalopram in depressed patients with elevated CRP (52).

Relationship to the Disconnection Hypothesis of Depression

Abnormalities in structural and functional connectivity in frontostriatal circuits have been reported in depression (53). Patients with late-life depression have microstructural white matter abnormalities and greater white matter hyperintensity burden within the emotional regulation and the cognitive control networks (5). Increased resting functional connectivity in the default mode network and decreased functional connectivity in the cognitive control network has been observed during episodes of late-life depression (6).

Amyloid deposition may disrupt neuronal connectivity in frontolimbic and frontostriatal circuits by compromising nerve cell integrity. Assembly of soluble proteins and peptides into fibrillar amyloid aggregates increases intracellular fibril load (54, 55). Fibril fragmentation disrupts intracellular membranes and reduces cell viability. Functional MRI studies have shown that functional connectivity is impaired within the default mode network (DMN) in early stage AD, in amnesic mild cognitive impairment (56). Resting state functional connectivity within the default mode network distinguished non-demented individuals with positive amyloid PET scans from non-demented individuals with negative amyloid PET PIB scans (57). These differences were in the same regions and in the same direction as differences found between Alzheimer's subjects and non-demented individuals with negative amyloid scans. These findings suggest A β deposition is associated with a disrupted functional connectivity within the DMN.

Emerging Anti-Amyloid Treatments

Brain accumulation of A β amyloid is part of the cascade leading to AD (58). Amyloid synthesis starts with proteolytic cleavage of the amyloid precursor protein (APP). There are

two APP proteolytic pathways, α -secretase cleavage and β -secretase cleavage. The latter is followed by γ -secretase cleavage and the generation of A β amyloid. Accordingly, four approaches to anti-amyloid treatment have been taken.

Agents to reduce A β production

The proteolytic enzymes β - and γ -secretase have been targeted with pharmacological agents aiming to decrease A β amyloid production in AD. The development of effective β -secretase inhibitors has been challenging because of the complex structure of the enzyme and the poor blood-brain barrier penetration of β -secretase inhibitors. Two β -secretase inhibitors, CTS-21166 and LY2811376, underwent phase I trials and showed dose-dependent reduction of amyloid (59). Another β -secretase inhibitor, MK-8931 was adequately tolerated and resulted in a dose dependent reduction of CSF A β levels in mild-to-moderate AD patients (60).

The γ -secretase inhibitor stemocleure lowered A β amyloid level in the brain of a mouse model (59). However, inhibition of γ -secretase has been associated with inhibition of vital substrates such as the Notch protein. Reducing Notch activity may interfere with cell proliferation and differentiation causing hematological and gastrointestinal toxicity. The γ -secretase inhibitor semagacestat was developed to avoid the side effects of stemocleure. However, phase III trials were terminated because the treatment group showed faster cognitive decline than the placebo group. Avagacestat and begacestat demonstrated selectivity for A β amyloid over Notch cleavage and warrant further investigation in AD (61). CHF5074 is a novel γ -secretase modulator that significantly reduced plaque burden in cortex and hippocampus and attenuates spatial memory impairment in transgenic mice (62).

An alternative to inhibitors of secretases are agents modulating the production of A β . The non-steroidal anti-inflammatory drug R-flurbiprofen modulates the Alzheimer-related A β production by targeting APP. R-flurbiprofen is relatively safe and tolerated but failed to improve cognitive outcomes in phase III trials of AD patients perhaps because of inadequate brain penetration (63).

Agents to prevent A β aggregation

Agents interfering with A β aggregation may eliminate the neurotoxic and synaptotoxic activities of A β (58). Tramiprosate binds to A β and reduces polymerization *in vitro* and A β brain depositions in animal models. While adequately tolerated, phase III trials failed to show cognitive improvement (59).

Valproic acid and lithium inhibit glycogen synthase kinase-3 (GSK-3), reduce tau phosphorylation, and in theory may reduce A β neurotoxicity. However, they failed to show cognitive improvement in clinical trials of AD (59). A 26-week phase II trial of the GSK3 inhibitor tideglusib in mild AD found it acceptably safe but produced no clinical benefit. There was, however, a non-linear dose response, especially in mildly affected patients, suggesting that further dose finding studies in early disease stages and for longer duration are warranted to examine GSK-3 inhibition in AD patients (64).

Agents to accelerate A β clearance

Anti-A β amyloid immunotherapy is based on the hypothesis that immune-mediated A β clearance could be achieved by phagocytosis of A β by microglia, A β solubilization by antibody binding, and A β extraction from the brain by plasma antibodies (65).

Active immunization through inoculation with A β peptide was associated with reduction of amyloid deposits in the brains of patients examined post-mortem. AN-1792 was the first-generation vaccine targeting A β . Development of T-cell-mediated meningoencephalitis in 6% of patients led to termination of phase II trials (66). Second-generation vaccines have been developed that do not cause brain inflammations and are being tested in clinical trials (65). Passive immunization with intravenous immunoglobulin (IVIg) failed to improve the cognitive primary outcomes in the North American Phase 3 clinical trial in mild to moderate AD. However, cognitive improvement was noted among APOE- ϵ 4 carriers, moderately impaired AD patients in pre-planned analyses (67).

The humanized monoclonal antibody bapineuzumab reduced amyloid depositions in the brain but did not improve the primary cognitive outcomes in phase II trials and led to adverse events including reversible vasogenic cerebral edema in MRI scans (68). Solanezumab, another humanized monoclonal antibody, was adequately tolerated, but failed to improve cognition and disability in two phase III trials (69). Gantenerumab, a human anti-A β antibody elicits cell-mediated removal of human A β . In transgenic mice, gantenerumab reduced small A β plaques by employing microglia and prevented new plaque formation. Gantenerumab induced cellular phagocytosis of human amyloid- β deposits in AD brain (70). Its efficacy in improving cognition is under investigation.

Serotonin Antidepressants

There is a reciprocal relationship between A β and serotonin. Administration of fibrillar A β into the left retrosplenial cortex resulted in a loss of serotonergic neurons in the dorsal and median raphe nuclei (71). Conversely, *in vitro* and animal studies suggest that serotonin reuptake inhibitors (SSRIs) reduce brain A β levels. Stimulation of serotonin receptor subtypes 5-HT_{2A} or 5-HT_{2C} in transfected 3T3 cells by dextrofenfluramine or serotonin increased secretion of an APP metabolite (72). In mice, activation of 5-HT_{2C} receptors by dextrofenfluramine stimulated CSF APP secretion and reduced A β production *in vivo* (73). Administration of several SSRIs reduced brain interstitial fluid A β levels by 25% in mice (74). Infusion of serotonin into the hippocampus also reduced A β levels perhaps mediated by the extracellular regulated kinase (ERK) signaling cascade. Chronic treatment of mice with citalopram led to a 50% reduction in brain plaque load. A single dose of citalopram decreased A β in the brain's interstitial fluid in a dose dependent manner in aged, transgenic (APP/PS1), plaque bearing, AD mice (18). Chronic administration of citalopram arrested the growth of preexisting plaques and the development of new plaques by 78%.

In community volunteers, those who had received treatment with antidepressants over a period of 5 years (mean: 34.5 months) had significantly lower amyloid load in brain PET scans than those who had never received antidepressants (74). The length of antidepressant treatment prior to scanning correlated with lower plaque load. In healthy subjects, acute

administration of citalopram 60 mg slowed the production of A β in the CSF by 37% compared to placebo (18). The reduction of CSF A β by SSRIs is consistent with findings suggesting that serotonin reduces A β production.

Anti-Amyloid Treatments in Late-Life Depression

The clinical and pathophysiological relationships of depression and AD raises important questions. Is amyloid accumulation a critical part of the mechanisms causing frontolimbic changes predisposing to depression and worsening its outcomes? And if so, is the reduction of amyloid production one of the mechanisms by which antidepressants improve depression and prevent recurrences? These questions can be answered with appropriately designed studies using brain amyloid imaging. Appropriately targeted studies may identify the role of antidepressants in improving the outcomes of depression with significant amyloid accumulation and in delaying the onset of AD.

If amyloid accumulation is part of the mechanisms causing some late-onset depression syndromes, anti-amyloid treatments may be a logical treatment in depressed patients with amyloid deposits but clinical trials are lacking (75). So far, anti-amyloid agents with acceptable safety and tolerability are available. Although their efficacy in improving cognition has been unimpressive, it is unclear if they have an antidepressant effect. Most clinical trials exclude depressed patients with mild cognitive impairment or AD and do not assess depressive symptoms as a secondary treatment outcome. Tools are available for studying treatment response of depressive syndromes and symptoms in AD patients (76, 77). Inclusion of patients with depressive symptoms or syndromes in AD or mild cognitive impairment trials of anti-amyloid agents may give information about these agents' efficacy in reducing depressive symptoms. If the results of such trials are encouraging, subsequent studies may examine whether anti-amyloid agents can improve depression of cognitively unimpaired patients with amyloid deposits, prevent relapses and recurrences, and even prevent or delay development of dementia in these patients.

Conclusion

This position paper contends that a confluence of findings suggests an interaction between the neurobiological events during depressive episodes and A β deposition. In patients without history of depression, amyloid accumulation during the preclinical phase of Alzheimer's disease may lead into the prodromal depression syndrome that precedes cognitive impairment. In patients with early-onset depression, pathophysiological changes during recurrent episodes may promote amyloid accumulation, further compromise neurocircuitry required for antidepressant response, and increase treatment resistance during successive depressive episodes. The availability of ligands for *in vivo* assessment of brain amyloid in humans can be used in studies focusing on the role of A β in depression. Reasonably safe and tolerated anti-amyloid agents have been developed, but their efficacy in depression has been inadequately tested. Further, the available serotonin acting antidepressants may lower A β production and development of new plaques. A model of late-life depression introducing the role of A β can guide the design of studies aiming to identify novel approaches for the

prevention of treatment resistance and reoccurrences of early-onset depression and for the delay of onset or the prevention of AD.

Acknowledgments

Dr. Alexopoulos received grant support from Forest; served as a consultant to Scientific Advisory Boards of Forest, Hoffman-LaRoche, Janssen, Lilly, Lundbeck, Otsuka, and Pfizer; and has been a member of speakers' bureaus sponsored by Avanir, Merck, Forest, Astra Zeneca, Novartis, Sunovion, and Takeda-Lundbeck.

Grant support: NIMH grants P30 MH085943 and the Sanchez Foundation (GSA).

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Figure 1. Amyloid Model of Late-Life Depression

Model 1) Depression increases the risk of dementia: Pathophysiological changes occurring during depressive episodes in early life lead to frontolimbic and frontostriatal dysfunction directly and/or through amyloid accumulation. Frontolimbic and frontostriatal dysfunction predisposes to depressive syndromes in late life and worsens their outcomes.

Model 2) Depression is a prodrome of dementia: Amyloid deposition during the asymptomatic phase of Alzheimer's disease or of other amyloid-related dementias.