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Anti-Amyloid Drugs for Alzheimer's Disease: Considering the Role of Depression

Beatriz Pozuelo Moyano[a] Leonardo Zullo[a, b] Olivier Rouaud[b]
Pierre Vandel[a] Armin von Gunten[a] Gilles Allali[b]

[a]Service of Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Prilly, Switzerland; [b]Leenaards Memory Center, Department of Clinical Neurosciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

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Introduction

Depression is very common in Alzheimer's disease (AD), but it is poorly studied in clinical trials of anti-amyloid disease-modifying therapies [1]. There is growing evidence that depression – a treatable condition – is a risk factor for AD [2, 3]. Depressive syndromes can occur at different stages of the neurodegenerative process of AD [4]. A systematic review and meta-analysis assessing the prevalence of depression across the different stages of AD concluded that the global overall pooled prevalence of depressive symptoms in AD is 38%, with an average prevalence of depressive symptoms in mild AD of 37%, 40% in moderate AD, and 37% in severe AD [5]. At each stage, depressive symptoms accelerate the clinical progression from the AD preclinical state to mild cognitive impairment (MCI) and to major neurocognitive disorder, with an estimated 39.7% progression from MCI to major neurocognitive disorder in older patients with depression over a 27-month follow-up study [4, 6, 7].

The most prominent biological mechanisms linking depression to AD include hypothalamic-pituitary-adrenal axis dysregulation, inflammatory changes, hippocampal atrophy, deficits of nerve growth factors, cerebrovascular disease, and increased deposition of neurofibrillary tangles or amyloid-β plaques [4, 8–16]. During the last years, intensive efforts have been made to delay or prevent brain accumulation of amyloid-β using treatments that decrease the production of Aβ, antagonize Aβ aggregation, or increase Aβ clearance. The list of failed drugs includes Aβ aggregation inhibitors, Aβ antigens, anti-Aβ monoclonal and polyclonal antibodies, γ-secretase inhibitors and modulators, and β-secretase inhibitors [17].

Alexopoulos' model of late-life depression (LLD) postulates that compromised integrity of frontolimbic and frontostriatal networks confers vulnerability to LLD [18]. In 2016, this group suggested that amyloid accumulation may be an etiological factor for frontolimbic compromise predisposing to depression and increasing treatment resistance in a subset of older adults [19]. They concluded that the efficacy of anti-amyloid drugs in

karger@karger.com
www.karger.com/ndd

Correspondence to:
Beatriz Pozuelo Moyano, beatriz.pozuelo-moyano@chuv.ch

depression has not been adequately tested. Nearly 10 years later, and despite the increasing evidence linking depression and brain amyloid deposition, research has not evolved much in this realm. The main phase-3 clinical trials evaluating the effect of anti-amyloid treatment in AD have typically not included a change in depressive symptoms as an outcome and exclude AD patients with significant depressive symptoms. Only a few of them include a change in neuropsychiatric symptoms as a secondary outcome and some of them report depression or depressive symptoms as side effects [20–29] (shown in Table 1).

This article aimed to review the relationship between depression and AD and to discuss why some patients exhibiting depressive symptoms should be included for anti-amyloid treatment. Additionally, we aimed to highlight some aspects that should be taken into consideration for patients with depression included for anti-amyloid treatment.

Depression and AD

Major depressive disorder (MDD) is a heterogeneous disorder in terms of clinical manifestations including cognitive features, course, and response to pharmacological treatment. It has a number of potential underlying pathways that may be interrelated [30, 31]. The DSM-5 highlights specifiers that provide additional information about the nature of a current episode. These specifiers include, among others, anxious distress and melancholic, atypical, or psychotic features [32].

More than one-third of patients with LLD are resistant to antidepressant treatment [33, 34]. Treatment-resistant depression (TRD) is commonly defined as a lack of response to two or more adequate trials of antidepressants for at least 8 weeks in a single episode [35]. TRD in late life is associated with higher rates of suicide and suicide attempts, with high levels of burden on family carers, and higher healthcare costs [36–38]. AD may be an etiologic factor associated with TRD, suggesting that the underlying etiology of depression in patients with AD differs from the etiology of depression in the general population [39].

The depressive syndrome reflects the clinical expression of dysfunction in reward, salience, and cognitive control networks [40]. The severity of dysfunction in these networks may determine the intensity of symptoms related to mood, cognition, and/or motor behavior and may underlie the heterogeneous clinical presentations of the LLD [40].

In patients with AD, depressive symptoms often occur as part of the behavioral and psychological symptoms of dementia (BPSD) [41]. The term BPSD describes a heterogeneous group of symptoms and signs of disturbed perception, thought content, mood, or behavior that often occur in patients with all-cause dementia [41–43]. BPSD is associated with cognitive decline and progression to more severe stages of all-cause dementia [44]. BPSD also cause individual distress and impact on caregiver burden [41, 45]. In addition, they increase the risk of secondary complications such as falls and fractures, leading to emergency room visits and eventually institutionalization [46]. During the course of AD, the vast majority of patients will develop one or more BPSD [47, 48].

More than 40% of patients with AD have depressive symptoms at some point in their illness [1, 5, 41, 42]. Younger age, a history of psychiatric disorder, a family history of psychiatric disorder, neuroticism, or an increased cardiovascular risk (within 6 months of dementia onset) predicts an increased depression risk in patients witth AD [49]. The functional decline, the presence of sleep disturbance or aggression are other predictive factors of depression in AD [49].

Depressive symptoms in patients with AD may vary according to the stage and onset of dementia [50]. Patients with early-onset AD are more at risk for increased levels of depression, which can be due to significant lifestyle changes, difficulties in social adjustment, and faster disease progression [50]. During the early stages of sporadic AD, patients may present more mood-related symptoms and daily mood fluctuations [50]. As AD progresses, cognitive impairments may disrupt the cortical control of emotional responses and patients present other psychiatric symptoms (less apparently related to depression as discussed further on) such as aberrant motor behavior, wandering, aggression, agitation, irritability, delusions or hallucinations that become more common [50, 51] (shown in Fig. 1).

In the scenario involving a patient presenting with both depression and AD, a common clinical questioning is whether depression is indicative of a relapse of a pre-existing MDD or whether it is etiopathologically more closely linked to AD pathophysiology. The assessment of individuals with AD and depressive symptoms may be challenging and should encompass at least three scenarios.

(1) In cases of AD diagnosis in individuals with a history of MDD or recurrent depressive disorder, cognitive symptoms may initially be explained by the depressive episode, which may result in delayed diagnosis of AD. This group of patients with a "young adult-like" LLD typically has an early depressive onset and is likely to respond to antidepressant treatment and achieve

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Table 1. Overview of depression, NPS, and other psychiatric disorders in key phase-3 anti-amyloid randomized clinical trials

Anti-amyloid treatment	Population	Exclusion criteria in the trial for depression or other psychiatric reasons	Outcome NPS (measure)	Outcome depression	Results NPS	Psychiatric side effects (depression or depressive symptoms)
Semagacestat [20]	Mild to moderate AD (MMSE score: 16–26)	Patients with depression (GDS >6)	NPI	No	NPI scores: significant worsening in the group receiving 140 mg of semagacestat as compared with the placebo group	No data
Verubecestat [25]	Prodromal AD (MMSE score: 24–30)	- Evidence of a clinically relevant or unstable psychiatric disorder, based on DSM-IV-TR criteria, including schizophrenia or other psychotic disorder, bipolar disorder, MD, or delirium. MD in remission is not exclusionary - Evidence of a current episode of MD based on investigator's judgment - Score on the 15-item GDS ≥5 requires an assessment by an appropriate healthcare professional to evaluate for the presence of MD	NPI	No	NPI scores: effects of verubecestat on NPS may be inferior to placebo (with a higher augmentation on the NPI score)	Anxiety[a]: - Verubecestat 12 mg: 6.8% - Verubecestat 40 mg: 9.1% - Placebo: 4.3% Depression[a]: - Verubecestat 12 mg: 6.6% - Verubecestat 40 mg: 10.3% - Placebo: 5.2% Suicidal ideation[a]: - Verubecestat 12 mg: 6.8% - Verubecestat 40 mg: 9.3% - Placebo: 6.4%
Verubecestat [23]	Mild to moderate AD (MMSE score: 15–26)	Same criteria to the previous study [25]	NPI	No	NPI scores: no significant differences between verubecestat and placebo in the NPI scores	Anxiety[b]: - Verubecestat 12 mg: 6% - Verubecestat 40 mg: 7.1% - Placebo: 3.7% Suicidal ideation[b]: - Verubecestat 12 mg: 6% - Verubecestat 40 mg: 5.8% - Placebo: 3.2%
Bapineuzumab (2 trials: one involving carriers of the apolipoprotein E (APOE) ε4 and the other involving non-carriers) [22]	Mild to moderate AD (MMSE score: 16–26)	Significant major psychiatric disorder according to the criteria of DSM-IV or symptom that could affect the subject's ability to complete the study	Neuropsychological test battery	No	Neuropsychological test battery scores: no significant between-group differences observed	*APOE[a]ε4 Carrier Study* Agitation: - Bapineuzumab 0.5 mg/kg: 8.5% - Placebo: 7.8% Depression: - Bapineuzumab: 8.9% - Placebo: 8.5% *APOE[a]ε4 non-Carrier Study* Agitation: - Bapineuzumab 0.5 mg/kg: 7.7%

Table 1 (continued)

Anti-amyloid treatment	Population	Exclusion criteria in the trial for depression or other psychiatric reasons	Outcome NPS (measure)	Outcome depression	Results NPS	Psychiatric side effects (depression or depressive symptoms)
						- Bapineuzumab 1 mg/kg: 4.6% - Bapineuzumab 2 mg/kg: 11.3% - Placebo: 7.1% Anxiety: - Bapineuzumab 0.5 mg/kg: 5.6% - Bapineuzumab 1 mg/kg:11.9% - Bapineuzumab 2 mg/kg: 7.8% - Placebo: 8.2%
Solanezumab EXPEDITION2 trial [21]	Mild to moderate AD (MMSE score: 16–26)	Patients with depression (GDS >6)	NPI	No	NPI scores: no significant treatment-related changes differences	Agitation: - Solanezumab: 4.6% - Placebo: 4.6% Anxiety: - Solanezumab: 6.4% - Placebo: 6.7% Depression: - Solanezumab: 4.5% - Placebo: 4.9% Insomnia: - Solanezumab: 3.7% - Placebo: 3.5%
Solanezumab EXPEDITION3 trial [24]	Mild AD (MMSE score: 20–26)	Patients with depression (GDS >6)	No	No	No	Agitation: - Solanezumab: 3.7% - Placebo: 3.1% Anxiety: - Solanezumab: 5.2% - Placebo: 5.6% Depression: - Solanezumab: 5.9% - Placebo: 5.4% Insomnia: - Solanezumab: 2.8% - Placebo: 3.2%
Aducanumab (2 trials: EMERGE and ENGAGE) [26]	Prodromal AD (MMSE score: 24–30)	Clinically significant unstable psychiatric illness (e.g., uncontrolled MD or uncontrolled schizophrenia) within 6 months prior to screening	NPI-10	No	*EMERGE study*: mean change from baseline at week 78 on the NPI-10, with high-dose aducanumab: −1.3 vs. placebo (−87%; $p = 0.022$) *ENGAGE study*: no significant treatment-related changes differences in the NPI scores	No data

Table 1 (continued)

Anti-amyloid treatment	Population	Exclusion criteria in the trial for depression or other psychiatric reasons	Outcome NPS (measure)	Outcome depression	Results NPS	Psychiatric side effects (depression or depressive symptoms)
Lecanemab [29]	Early AD (MMSE 22–30)	GDS score >8 at screening	No data	No	No data	Anxiety: - Lecanemab: 5% - Placebo: 4.2%
Donanemab [28]	Early AD (MMSE 20–28)	- Participants with any current primary psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the participant's ability to complete the study - Participants with history of schizophrenia or other chronic psychosis	No data	No	No data	Anxiety: - Donanemab: 6.0% - Placebo: 5.7% Depression: - Donanemab: 5.6% - Placebo: 3.6%
Gantenerumab (2 trials: GRADUATE I and GRADUATE II) [27]	Early AD (MMSE 22–30)	- History of schizophrenia, schizoaffective disorder, MD, or bipolar disorder - History of MD is acceptable if participant has had no episode within the past year or is considered in remission or depression is controlled by treatment	No	No	No	No

AD, Alzheimer disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MD, Major Depression; NPI, Neuropsychiatric Inventory; NPS, neuropsychiatric symptoms. [a]Side events that occurred within 14 days after the last dose over 104 weeks. [b]Side events that occurred within 14 days after the last dose over the course of 78 weeks.

depression remission [39]. Although patients with early-onset depression have a higher risk of AD than the population without depression, the incidence of AD is lower than in those with late-onset depression [52].

(2) Patients without a psychiatric history of depression may have a depressive episode as an early clinical manifestation of AD. Substantial evidence supports that LLD and treatment-resistant LLD may be, in some cases, an early prodromal feature of AD and a "direct" result of AD pathophysiology [30, 53, 54]. In a continuum perspective where subjective cognitive decline (SCD) is considered to be the earliest clinical manifestation of AD, cross-sectional studies have demonstrated its association with depression [55]. The impact of AD-driven cerebral pathology on mood may be one of the earliest changes together with SCD [56]. In connection with this, the concept of mild behavioral impairment (MBI) may be of interest as it refers to early or prodromal behavioral changes, among them depression, as indicators of an underlying neurocognitive disorder [57].

This group of patients with early affective manifestations in AD is the primary focus of this article as the etiology of their depressive symptoms may differ from those associated with primary psychiatric disorders [58] (shown in Fig. 1). Furthermore, these patients may be less likely to respond to antidepressant treatments, highlighting the urgent need for effective depression treatment in this population [39, 58]. Patients with AD and late-onset TRD are those in whom the efficacy of anti-amyloid treatments on depressive symptoms should be assessed first.

(3) Symptoms of depression such as apathy, irritability, or anxiety in patients with an AD diagnosis. The presence of apathy, irritability, agitation, and anhedonia in AD patients raises the question of whether these symptoms are indicative of subsyndromal depression or if they represent other isolated BPSD. Apart from depression, most common BPSD in AD are apathy with a prevalence of 49%, aggression (40%), anxiety (39%), sleep disorder (39%), and irritability (36%) [1]. Interestingly, patients with depression and all-cause dementia are at high risk (96.4%) of presenting with BPSD such as anxiety, agitation, or irritability, suggesting that they may be related to depression [59]. Patients with depression-related symptoms such as apathy, irritability, agitation, and anhedonia may sometimes be too far advanced dementia stage to receive or benefit from anti-amyloid treatment. Unfortunately, in clinical practice, the above differentiation is by no means always straightforward. Indeed, in patients with a history of MDD, AD may also present with depressive symptoms and an initial AD case may coincide with a late-onset primary depressive episode.

Amyloid Deposition, Depression, and Anti-Amyloid Treatment

Among the neuropathological hallmarks of AD, amyloid deposition is associated with depression. Thus, the mechanisms by which anti-amyloid treatments exert their effects may relate to depression as well as other clinical manifestations of AD.

Numerous studies have examined the association between amyloid and tau levels in plasma, cerebrospinal fluid (CSF), or through imaging techniques, and their relationship to depression at various stages of AD. However, these studies vary in quality and sample size and have different results.

In 2015, a systematic review including 15 cross-sectional studies showed a possible association between amyloid and MDD in older adults, but the studies were limited by their cross-sectional design, reliance on blood-based measures of Aβ, and potential sample bias [60]. Since this review, other studies have assessed the relationship between amyloid and depression with mixed results. In a longitudinal study, plasma levels of amyloid-β1-40 (Aβ40) and amyloid-β1-42 (Aβ42) were measured over three consecutive years in 48 cognitively intact elderly subjects with LLD and 45 age-matched cognitively healthy patients. Plasma Aβ42/Aβ40 ratio was lower in depressed subjects compared to controls ($p < 0.001$). Furthermore, plasma Aβ42/Aβ40 was associated with depression severity at 3 years [61]. Another recent cross-sectional study showed that both lower CSF amyloid beta (Aβ)42 and higher total tau/Aβ42 as well as hyperphosphorylated tau 181/Aβ42 in the CSF of patients with MCI or in the cognitively unimpaired were associated with clinical depression [62]. A neuroimaging study suggested an association between depressive symptoms and higher amyloid load in patients with subjective cognitive decline [16]. Another retrospective study conducted during the COVID-19 pandemic showed that cognitively unimpaired older adults with CSF amyloid positivity were more likely to have greater depressive symptoms under the same stressors [63].

However, other studies have yielded negative results regarding the association between amyloid and depression. For instance, CSF concentrations of Aβ1-42, T-tau, and P-tau typical for AD were not associated with cognitive impairment in LLD of AD [64]. Anti-Amyloid Treatment in the Asymptomatic Alzheimer Disease (A4) Study concluded that, in cognitively unimpaired adults with low levels of depression and anxiety, cortical amyloid-β deposition was associated with anxiety but not depressive symptoms [65].

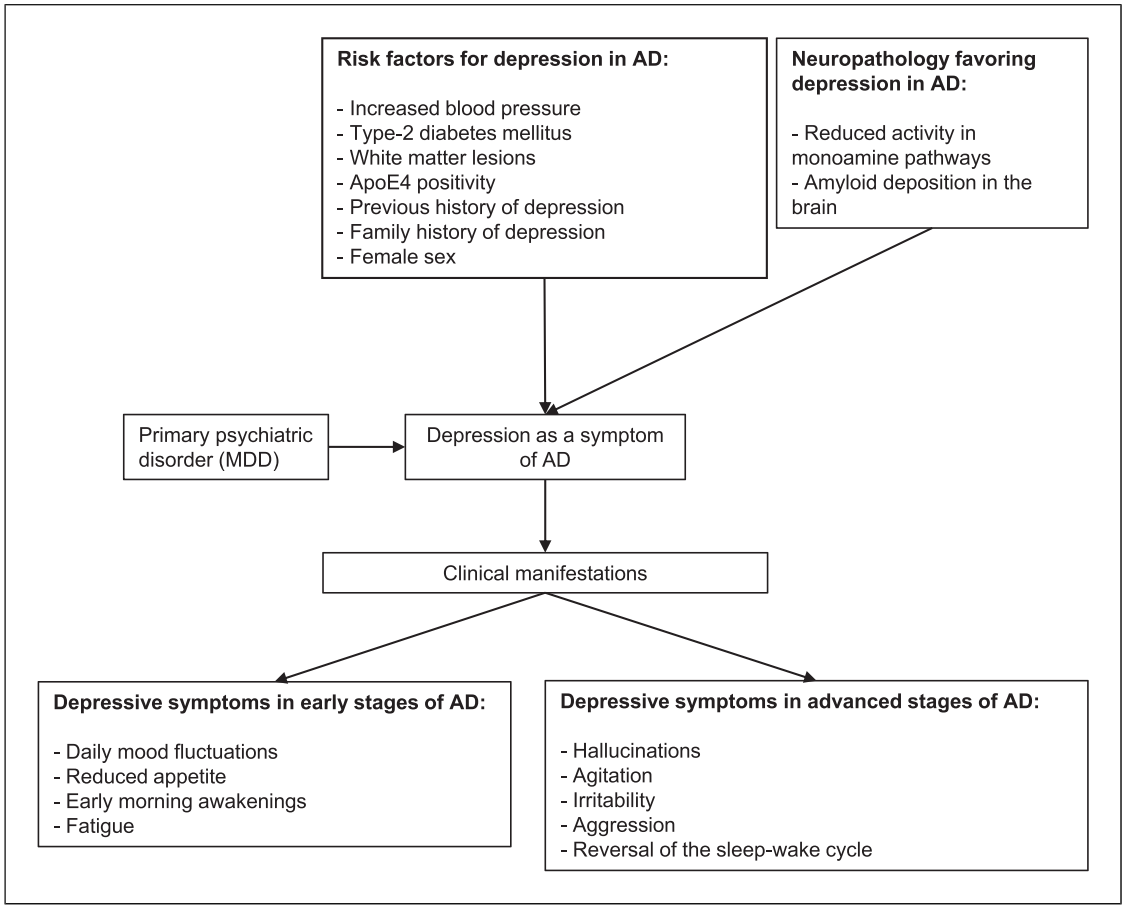

Fig. 1. Depressive symptoms and AD. AD, Alzheimer's disease; MDD, major depressive disorder.

Vascular Depression and Anti-Amyloid Treatment

Some of the risk factors that may contribute to the development of depression in patients with AD are increased blood pressure, type 2 diabetes mellitus, white matter lesions, ApoE4 positivity, both a previous history and a family history of depression, and female sex [66]. Several of these factors are associated with cerebrovascular risk factors and relate to the "vascular depression hypothesis" [67]. This hypothesis posits that ischemic lesions, particularly in the frontostriatal brain regions, can lead to cognitive deficits, especially executive dysfunction and psychomotor retardation [67]. Vascular depression is a type of major late-onset depression, often found in elderly patients with vascular risk factors and related vascular encephalopathy. It is characterized by silent strokes and white matter hyperintensities [67–70]. Compared to patients with early-onset depression without associated vascular lesions, those with vascular depression exhibit more psychomotor retardation, lack of insight, cognitive impairment, especially in executive functions, and greater disability [68, 70].

One of the etiopathological theories underlying vascular depression involves proinflammatory processes, which may contribute to the pathogenesis of AD [69, 71]. Alexopoulos and Morimoto suggested that this immune dysregulation may specifically influence both affective and cognitive symptoms in LLD [72]. Even in the absence of medical illness, individuals with depression display elevated levels of proinflammatory cytokines and decreased levels of anti-inflammatory cytokines [73]. In the context of LLD, aging disrupts immune function, increasing peripheral immune activity and creating a proinflammatory state in the central nervous system. Elevated levels of peripheral cytokines, particularly IL-6, IL-1β, IL-8, and TNFα, have been consistently linked to depressive symptoms in older adults [74]. This proinflammatory state is associated with cognitive deficits including poorer executive function, memory performance, global cognition, and accelerated cognitive decline [75]. Additionally, higher

levels of IL-6 are associated with AD and higher levels of IL-6 and C-reactive protein correlate with increased white matter hyperintensity burden [76, 77]. Proinflammatory processes are also implicated in neurodegenerative diseases and central inflammation and may play an important role in the pathogenesis of AD [78].

Hypertension, diabetes, and atherosclerosis lead to vascular wall hypertrophy inducing a reduced arterial lumen diameter, a reduced arterial distensibility, and endothelial cell dysfunction [79, 80]. However, perfusion deficits do not necessarily cause ischemia. Reduced cerebral blood flow impairs protein synthesis which is crucial for cognition. Thus, mild reductions in cerebral blood flow may impair cognitive and affective processes, whereas more severe reductions in cerebral blood flow may cause ischemic injury [69]. Cerebral hypoperfusion is associated with AD, MCI, and cerebral amyloid angiopathy (CAA), a common type of cerebral small vessel disease. CAA, especially in the orbitofrontal cortex, is associated with higher levels of apathy, one of the typical symptoms of MDD [81–84]. The possible association between vascular depression and AD is of particular interest in terms of the use of anti-amyloid treatments. It suggests that, when considering anti-amyloid treatment for patients with depressive symptoms and AD, an early treatment intervention may be crucial. Indeed, these patients may face an increased risk of bleeding over time, potentially leading to exclusion from treatment regardless of their cognitive status (shown in Fig. 2).

Apathy is a symptom of particular importance for the potential eligibility of patients with depression for anti-amyloid treatment as it has been associated with increased cardiovascular risk. A cross-sectional study of more than 3,500 individuals without dementia concluded that apathy, in the absence of depression, was related to a history of stroke (odds ratio, 1.79; 95% CI, 1.38–2.31) and cardiovascular disease other than stroke (1.28; 1.09–1.52). Exploratory analysis among 1,889 participants free of stroke and other cardiovascular disease revealed an association between an apathy score and the following cardiovascular risk factors: systolic blood pressure ($p = 0.03$), body mass index ($p = 0.002$), type 2 diabetes mellitus ($p = 0.07$), and C-reactive protein ($p < 0.001$) [85]. A prospective study including older patients without dementia concluded that apathy, but not depression, is a strong, independent risk factor for incident cardiovascular disease [86]. Even though both trials were conducted in subjects without dementia, given that apathy is one of the main features of vascular depression, it could be hypothesized that patients with apathy would require special monitoring if they were to be treated with an anti-amyloid treatment because of the possible increased risk of bleeding [68].

Pharmacological Treatment of Depression in AD Patients

Although antidepressants are commonly used to treat depressive symptoms in AD, currently available evidence does not provide strong support for the effectiveness of antidepressants in treating depression in AD, especially their use beyond 12 weeks [58]. A systematic review and network meta-analysis, incorporating 25 trials, concluded that sertraline and mirtazapine were more effective than placebo in the treatment of depression in AD [87]. However, one meta-analysis concluded there was no clinical benefit from introducing this treatment to AD patients with depression [88].

Clinical practice guidelines underscore the importance of avoiding antidepressants with anticholinergic side effects in individuals with all-cause dementia [89]. The most often used selective serotonin reuptake inhibitors (SSRIs) are associated with hyponatraemia (especially in older patients [30]) as well as gastrointestinal side effects (eg, loss of appetite, nausea or abdominal pain), headaches, anxiety, and dizziness [30, 90]. SSRI are additionally associated with intracranial bleeding, prompting additional monitoring in patients eligible for anti-amyloid treatment [90].

Indeed, patients with CAA may have an increased risk of amyloid-related imaging abnormalities [91]. Recommendations for appropriate use suggest that lecanemab may be given to patients with fewer than four microbleeds, although this is compatible with the existence of a possible or probable CAA [92]. SSRI reduce serotonin content and cause hemostatic interference through decreased platelet aggregability and activity with prolongation of bleeding time [93]. In this context, a concomitant prescription with SSRI deserves close monitoring as SSRI use is associated with an increased risk of microbleeds [94]. The selection of a specific antidepressant should carefully consider potential adverse effects that vary among different molecules.

Anti-Amyloid Treatment and Depression

Lecanemab and donanemab are two of the most recent monoclonal antibodies designed to clear beta-amyloid from the brain [28, 29]. Clinical trials have shown a significant reduction in the rate of cognitive decline associated with AD [28, 29]. Indeed, in the lecanemab phase-3 trial, authors found a reduction in the CDR-SB score and the ADAS-cog14 progression in the lecanemab group as well as a reduction in the brain amyloid burden

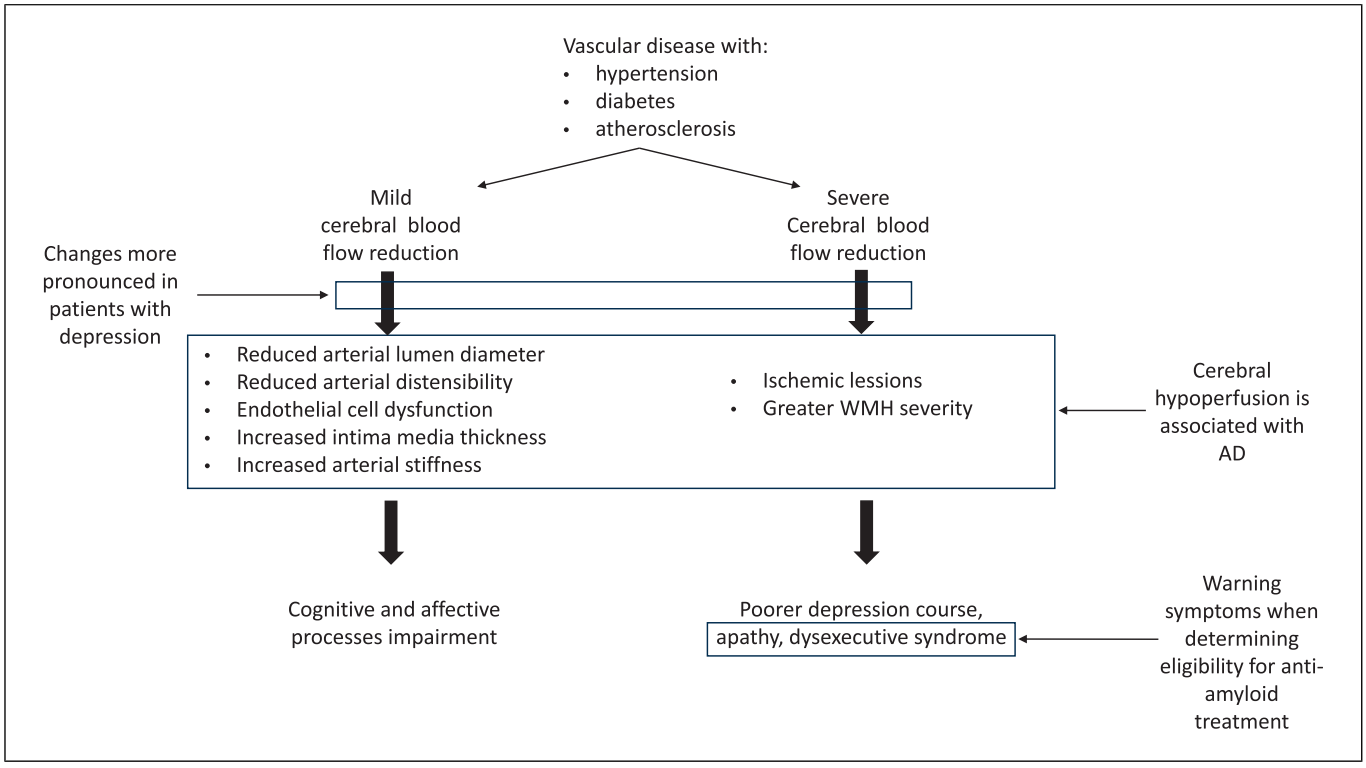

Fig. 2. Associations between vascular disease, depression, and AD. Apathy and a dysexecutive dysfunction may be depression-related symptoms that should be carefully considered when determining eligibility for anti-amyloid treatment. AD, Alzheimer's disease; WMH, white matter hyperintensities.

[29]. In the CSF substudy and in plasma, analysis showed numerical improvements for all assessments comparing lecanemab with placebo, with the exception of CSF neurofilament light chain [29]. The phase-3 clinical trial of donanemab showed a slowed progression of CDR-SB and ADCS-iADL scores and a reduced amyloid plaque volume and plasma tau levels in the donanemab group [28].

However, the emphasis in anti-amyloid treatment research primarily centers on cognitive and functional decline, hardly ever taking into account outcomes related to depression or other BPSD despite their clinical importance. Indeed, neither lecanemab nor donanemab phase-3 trials include a behavioral or psychological assessment as an outcome measure. In the lecanemab clinical trial, participants with a Geriatric Depression Scale score above 8 at screening were excluded [28, 29, 92] (shown in Table 1). Similarly, in the lecanemab and donanemab clinical trials, patients with significant psychiatric symptoms were also excluded, making impossible the assessment of the effects of anti-amyloid therapeutics on depressive symptoms [28, 92].

Depression and Potential Benefits of Anti-Amyloid Treatment

Whether anti-amyloid treatments have a beneficial effect on depressive symptoms in AD patients should be evaluated more carefully considering that (i) the patients with significant depressive or other psychiatric symptoms are excluded from trials, although these symptoms may represent secondary symptoms of AD itself, (ii) the etiopathogeny of depression in people with AD may differ from depression in people without dementia, (iii) there is limited efficacy of conventional antidepressant treatments in dementia, and (iv) there is a need for depression management in AD cases given its exacerbating effect on disease progression, associated mortality, and decreased quality of life. Our stance is that patients with AD and mild to moderate depression should not be systematically precluded from anti-amyloid treatment. However, it is crucial that psychiatric symptoms are properly monitored by a specialist beforehand (shown in Fig. 3).

This assessment should encompass various scenarios involving depression and AD as outlined above. The following scenarios are closely linked to research

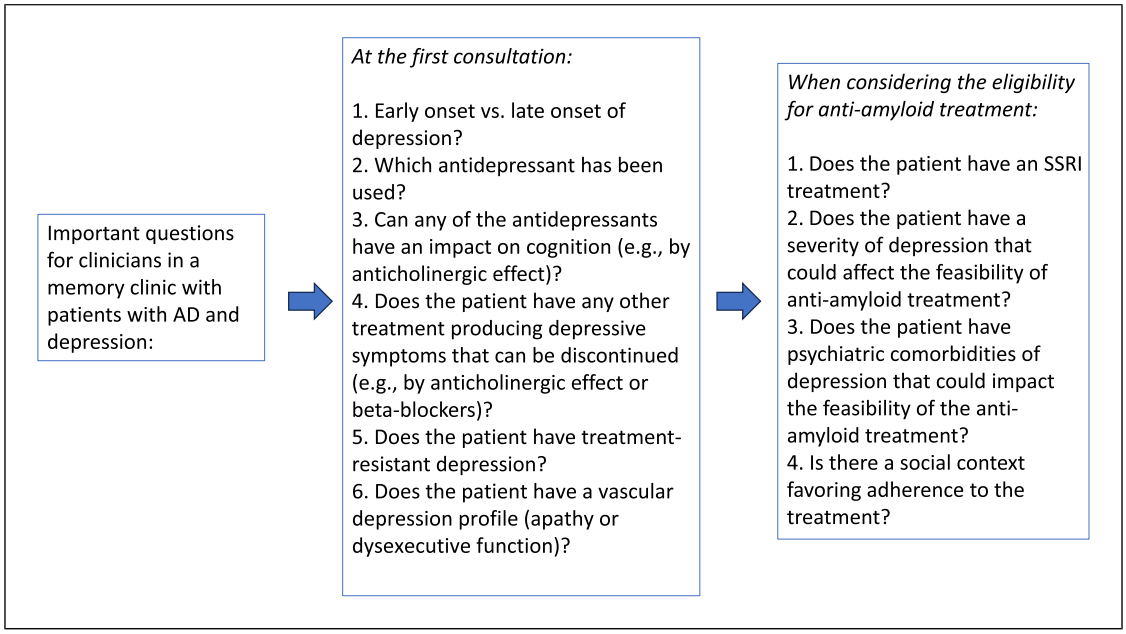

Fig. 3. Important questions for clinicians in a memory clinic to consider for patients with AD and depression. Questions to consider when determining the eligibility of a patient with depression and AD for anti-amyloid treatment. AD, Alzheimer's disease; SSRI, selective serotonin reuptake inhibitors.

questions that should be investigated in order to clarify the indication and safety of amyloid-targeting agents in AD patients with depression.

(1) In patients with both an AD diagnosis and a history of MDD, recurrent depressive disorder, a single depressive episode, or patients with other psychiatric comorbidities with depressive manifestations during the course of the illness (bipolar disorder or schizoaffective disorder), adequate treatment should be conducted. In the event that patients with depressive symptoms are ultimately considered to be eligible, treatment should be determined only after adequate psychiatric treatment.

Further research is needed to answer the following questions, among others: Is there a difference in the cognitive outcomes of anti-amyloid treatment when concurrent treatment for depression (with SSRIs or lithium) is present compared to when it is not? Is there a difference in the efficacy of anti-amyloid treatment in reducing depression symptoms when concurrent treatment for depression (with SSRIs or lithium) is present compared to when it is not? Is there an increased bleeding risk in patients treated simultaneously with SSRIs and anti-amyloids?

(2) In situations where patients present a depressive episode as an early manifestation without a psychiatric history of depression, further investigation is needed to answer the following questions: Does anti-amyloid treatment demonstrate effectiveness in addressing both depressive and cognitive outcomes? Are the effects on cognition and depressive symptoms linked?

Influence of Depression-Related Factors on Anti-Amyloid Treatment Efficacy

Several factors other than the above discussed pathophysiological aspects related to depression with or without AD and anti-amyloid treatments are to be considered. Among them, we wish to emphasize frequent comorbidities, both somatic and psychiatric, and the patients' adherence to treatment.

Psychiatric Comorbidities of Depression

Considering the most prevalent comorbidities of depression in the treatment plan is of great importance when treating them in patients with AD, as they can impact treatment efficacy or increase the occurrence of adverse effects of anti-amyloid treatments through diverse mechanisms. The incidence of disorders occurring together with depression increases with the severity of depression reaching a 30–40% higher prevalence for most

psychiatric disorders in severe compared to mild depression cases [95]. The difference is even larger for schizophrenia (three and two times higher in severe and moderate compared to mild depression, respectively) [95]. Anxiety as well as stress-related and somatoform disorders are the most common comorbidities with depression (65% in severe depression, 61% in moderate depression and 52% in mild depression). The next common psychiatric comorbidity is substance use disorders with a prevalence of 12%, 16% and 20% in mild, moderate, and severe cases, respectively [95].

Most importantly, anxiety disorders, psychotic disorders, and substance abuse disorders are associated with poor adherence and response to pharmacological treatment [96]. In the general adult population, moderate depression is associated with a 23% and 33% higher risk of hypertensive and metabolic diseases, respectively [95]. The strength of these associations gradually increases with the severity of depression [95]. The imperative for early and specialized multidisciplinary assessment and intervention in the treatment of depression is crucial to mitigate the risk of developing associated comorbidities [95].

Depression, AD, and Adherence to Treatment

Patients with depression or other psychiatric disorders are less likely to adhere to therapy. The estimated odds of a depressed patient being non-adherent to the treatment of diseases are 1.76 times the odds of a non-depressed patient [97]. Although this figure is unknown for individuals with AD, it is likely, if anything, to be even higher. This association is influenced by depression severity with higher depression leading to lower adherence [96]. Adequate antidepressant treatment can help patients adhere to prescribed treatments and improve outcomes. For example, in patients with multiple sclerosis, treating depression improves adherence to Interferon beta-1b therapy [98]. Similar information would be crucial for the treatment of patients with dementia and psychiatric comorbidities.

Finally, in older people without dementia, less social contact is associated with smaller volumes in the temporal lobe, occipital lobe, cingulum, hippocampus, and amygdala, and this association appears to be mediated by depressive symptoms [99]. In some cases, settings required to implement anti-amyloid treatments may promote social contact and, thus, adherence to treatment, although it must be kept in mind that a systematic review of the literature shows that medication adherence in older patients with all-cause dementia is low, ranging from 17% to 42% [100].

Depression, Comprehension Difficulties, and Suicide Risk

The reasons to exclude patients with depression are that MDD interferes with understanding of the requirements, potential benefits and potential harms of treatment, and that in patients with MDD, disclosure of a positive biomarker may trigger suicidal ideation [92]. These circumstances may be common when treating a patient with AD and depression. However, appropriate follow-up by an old-age psychiatrist could help reduce these risks, and the active participation and involvement of proxy carers is also crucial in this regard.

Conclusion

Clinical trials of anti-amyloid disease-modifying therapies exclude patients with depression, although these patients are tremendously frequent in real-life settings. These trials do not include changes in depression symptoms as a target outcome, although depression reduces effective treatment of cognitive, functional, and quality-of-life-related parameters in people with AD. Thus, people with depression should probably not be systematically excluded from anti-amyloid treatments. However, the inclusion of individuals with depression and AD will require a specific pre-treatment psychiatric assessment and a targeted follow-up.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Beatriz Pozuelo Moyano: writing – original draft, conceptualization, and investigation. Leonardo Zullo: writing – original draft and conceptualization. Olivier Rouaud: resources, writing – review and editing, and validation. Pierre Vandel: resources and validation. Armin von Gunten and Gilles Allali: supervision, conceptualization, writing – review and editing, and validation.

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