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LETTER

Antidepressants and the risk of bleeding in the era of anti-amyloid drugs

Dear Editor,

The prevalence of depression ranges from 19% to 78% in dementia, and apathy and depression are the most frequent behavioral and psychological symptoms of dementia (BPSD) in Alzheimer's disease (AD).[1] Antidepressant annual prescription prevalence among AD patients is ≈ 28%.[2]They are approved in depressive and anxiety disorders and are an effective treatment for mood and anxiety disorders in patients with dementia and cognitive impairment. However, a Cochrane meta-analysis does not provide strong support for their efficacy for treating depression in dementia, especially beyond 12 weeks.[3]

Selective serotonin reuptake inhibitors (SSRIs) decrease serotonin content and cause hemostatic interference such as decreased platelet aggregability and activity with prolongation of bleeding time.[4] Drugs with the highest degree of serotonin reuptake inhibition, such as fluoxetine, sertraline, and paroxetine, are frequently associated with increased bleeding and modifications of hemostasis markers[4] that require special attention in the era of the anti-amyloid drugs.

In the multicenter, double-blind, phase 3 trial involving patients with early AD, among the 898 participants assigned to receive lecanemab the incidence of amyloid-related imaging abnormalities (ARIAs) with cerebral microhemorrhages, cerebral macrohemorrhages, or superficial siderosis (ARIA-H) was 17.3%.[5]

Patients with cerebral amyloid angiopathy (CAA) may have an increased risk of ARIAs.[6] The risk of bleeding is even greater if there is an underlying CAA (and an antiaggregant +/− lecanemab is added). According to Cummings et al.,[7] lecanemab can be administrated in patients with fewer than four microhemorrhages, which may still correspond to possible or probable CAA. Considering this, a parallel prescription with SSRIs deserves close monitoring, as antidepressant use is associated with an increased risk of developing microbleeds.[8]

In this observational retrospective study, we evaluate the prevalence of antidepressant drugs in eligible patients for lecanemab, according to the recently published US panel of experts[7] at the Leenaards Memory Center of the Lausanne University Hospital (Switzerland). This study was granted by a waiver from the institutional review board.

We identified a total of 47 eligible patients among the 410 AD patients evaluated in 2022 at the Leenaards Memory Center. Thirty-two percent of the eligible patients were on antidepressant treatment. Of these, the vast majority (80%) were on SSRIs (see Table 1). This prevalence is similar to those previously reported in AD patients in general.[2]

This high prevalence of AD patients eligible for lecanemab on antidepressant drugs, especially SSRIs, raises the question of an appropriate clinical management of these patients.

It is important to consider that: (1) the first 30 days after the introduction of an SSRI is a crucial period particularly at risk of intracerebral hemorrhage;[9] (2) tricyclic antidepressants, serotonin antagonist and reuptake inhibitors (such as trazodone) or some of the norepinephrine reuptake inhibitors (such as atomoxetine or bupropion) are associated with a lower risk of hemorrhage.[9,10] However, the use of tricyclic antidepressants is not always appropriate in AD patients due to their anticholinergic effect and their consecutive impact on cognition.[3]

Our recommendations are to pay special attention to patients on SSRIs, particularly if they already have microhemorrhages. The introduction of lecanemab treatment during the first 30 days after the introduction of SSRIs should be avoided. Patients on concomitant antiplatelet treatment may need additional monitoring because bleeding risk is increased by the concurrent use of these drugs.[4]

We remind practitioners that clinical guidelines advise using non-pharmacological interventions as a first therapeutic choice for treatment of BPSD.

To conclude, we estimate that in patients eligible for anti-amyloid drugs, the indication for antidepressant treatment and its dose should be periodically reevaluated as the antiplatelet effect in antidepressants is dose dependent.[4] It is important to also consider alternative choices, such as antidepressants with lower bleeding risk for mood disorders and antiepileptics (pregabalin and gabapentin) for an anxiety disorder or anxiety-type BPDS.

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TABLE 1 Clinical characteristics including age and sex distribution; MoCa (Montreal Cognitive Assessment) and HAD (Hospital Anxiety and Depression Scale) scores of the eligible patients for lecanemab with and without antidepressant drug treatment.

	Eligible patients (n = 47)	Eligible patients with antidepressant drug (n = 15)	Eligible patients without antidepressant drug treatment (n = 32)
Mean age at diagnosis (y)	73.43	69.87	75.09
Female (%)	40.43	40.00	40.63
MoCa mean (range)	22.89 (17–29)	23.33 (17–27)	22.69 (17–29)
HAD-DEP mean[a] (range)	3.15 (0–10) (34 patients)	4.09 (0–10) (11 patients)	2.69 (0–7) (23 patients)
HAD-ANX mean[a] (range)	7.24 (0–16) (34 patients)	8.90 (0–16) (11 patients)	6.43 (0–14) (23 patients)
		Type of antidepressant	
		SSRI 10	
		SSNI 2	
		SARI 1	
		SSRI and SARI 1	
		SSRI and TeCA 1	

Note: Distribution of different types of antidepressants among eligible patients for lecanemab with antidepressant drug treatment.
Abbreviations: SARI, serotonin antagonist and reuptake inhibitor; SSNI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TeCA, tetracyclic antidepressants.
[a]We have data on the HAD scale only in 34 patients (in 11 eligible patients with antidepressant drug and 23 eligible patients without antidepressant drug treatment).

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. Author disclosures are available in the supporting information.

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