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The Concomitant Use of Selective Serotonin Reuptake Inhibitors and Anti-Amyloid Treatment in Alzheimer's Disease: Balancing Benefits and Risks

Polona Rus Prelog[a, b] Matija Zupan[b, c] Milica Gregorič Kramberger[b, d, e] Senta Frol[b, c]

[a]Centre for Clinical Psychiatry, University Psychiatric Clinic Ljubljana, Ljubljana, Slovenia; [b]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; [c]Department of Vascular Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia; [d]Department of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia; [e]Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, Huddinge, Sweden

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Depression and related neuropsychiatric symptoms are highly prevalent in Alzheimer's disease (AD), with large cohort studies showing nearly half of AD patients receive antidepressant treatment within 5 years of diagnosis [1, 2]. Despite the introduction of several new antidepressants, selective serotonin reuptake inhibitors (SSRIs) remain the most frequently prescribed class due to their tolerability and broad indication profile [3]. SSRIs are used to manage major depressive episodes, but also persistent low mood, apathy, anxiety, and agitation as part of the behavioral and psychological symptoms in AD [2]. The introduction of anti-amyloid monoclonal antibodies (MABs), more recently lecanemab and donanemab, has created a new paradigm in AD therapy, but has also raised concerns about the interplay between psychiatric and disease-modifying treatments – particularly regarding cerebrovascular safety in the context of cerebral amyloid angiopathy (CAA) [4, 5].

SSRIs, especially those with the highest degree of serotonin reuptake inhibition, such as fluoxetine, sertraline, and paroxetine, while valued for their neuropsychiatric benefit, are well documented to cause decreased platelet aggregability and activity, thus raising bleeding susceptibility [6]. This pharmacodynamic property is most clinically significant in elderly adults and is exacerbated when combined with additional risk factors – among them, the presence of CAA and the use of anti-amyloid therapies. Studies published since 2022 confirm that CAA, as identified by radiological markers such as cerebral microbleeds and cortical superficial siderosis, especially co-occurring with the ε4 variant of the *APOE* gene [7], stands as a major independent risk factor for hemorrhagic amyloid-related imaging abnormalities when anti-amyloid MABs are administered [8, 9].

Milica Gregorič Kramberger and Senta Frol share last authorship.

karger@karger.com
www.karger.com/dee

Correspondence to:
Polona Rus Prelog, polona.rus@psih-klinika.si

The co-administration of SSRIs with MABs in patients with CAA appears to further elevate the risk for both symptomatic and asymptomatic cerebral bleeding events, while cases of macrohemorrhage with MABs are rare but possible [4, 10]. Therefore, registry and cohort data emphasize the necessity of baseline and ongoing MRI, individualized risk stratification, and enhanced clinical vigilance throughout combined treatment, especially when additional antithrombotic agents are present (e.g., anticoagulants or double antiplatelets), or when intravenous thrombolysis is contemplated in the event of an acute ischemic stroke [11].

Despite these risk considerations, there is a parallel and scientifically compelling line of evidence supporting potential positive modulatory effects of SSRIs in AD. Recent investigations with advanced biomarker and imaging techniques have found that SSRIs may exert a modifying influence on critical disease pathways in AD. In fact, SSRI have an effect on the amyloid production and levels, as well as the tau related pathways [12, 13]. For example, Terstege et al. [14] reported that long-term SSRI use in AD is linked to lower plasma phosphorylated tau 181 (p-tau181) – a key biomarker of neurodegeneration – and restoration of dorsal raphe nucleus metabolism. These effects were specific to those already burdened by AD pathology and not present in healthy controls, suggesting SSRIs may have disease-modifying influence on tau pathways.

In addition, observational and imaging-based research has reinforced a possible correlation between long-term SSRI therapy and reduced amyloid burden, as well as delayed conversion from mild cognitive impairment to dementia [15–17]. Proposed neurobiological mechanisms include the promotion of non-amyloidogenic processing of amyloid precursor protein and the potential dampening of neurotoxic amyloid-β forms [18] – though, it must be emphasized, these benefits are more reliably observed with earlier and sustained SSRI use and appear diminished in advanced disease stages. The impact on cognitive performance, meanwhile, is nuanced: while SSRIs consistently improve depression, anxiety, and agitation [19] – and thus quality of life – recent registry studies have noted that cognitive trajectories under SSRI therapy can be mixed, with some domains improving and others potentially showing accelerated decline, particularly in severe dementia or with high-dose or multiple antidepressant regimens [2, 14, 20].

Given the absence of a formal clinical consensus on SSRI use during anti-amyloid therapy in AD, current recommendations center on individualized risk-benefit analysis. Anti-amyloid MABs therapy intrinsically requires rigorous candidate selection and regular MRI surveillance both prior to and throughout treatment, given the elevated risk of amyloid-related imaging abnormalities and other cerebrovascular complications. Where bleeding risk is elevated – such as with MRI evidence of CAA or use of other antithrombotic medications – clinicians are encouraged to consider alternative antidepressants like mirtazapine or bupropion and to prioritize non-pharmacological interventions when feasible. However, for patients presenting with moderate to severe neuropsychiatric symptoms and depression where SSRIs offer substantial relief, close clinical and imaging follow-up and multidisciplinary management remain paramount.

Important practical recommendations that we suggest:

- Individualized Antidepressant Selection: Given bleeding risk, favoring non-SSRI antidepressants with lower impact on platelet function (mirtazapine, bupropion) for AD patients at higher vascular risk or with radiological evidence of CAA [5].
- Proactive Imaging and Monitoring: Baseline and interval MRI is strongly recommended for patients considered for anti-amyloid therapy, especially if they are to be maintained on SSRIs
- Collaborative Care: Ongoing multidisciplinary management is essential – with neurology, psychiatry, neuroradiology, hematology specialists, etc., with shared decision-making and continual reevaluation of medication regimens and neuroimaging data
- Informed Consent and Education: Discussing benefits and risks (such as potential bleeding) with patients and caregivers, emphasizing the current uncertainties and individualized nature of decision-making.

In conclusion, SSRIs remain the most prescribed antidepressant class in AD, reflecting strong symptomatic benefit and practical experience. New evidence underscores their potential for modest disease-modifying effects on tau and amyloid pathology, particularly with prolonged early use, but also highlights inconsistent cognitive impact and reinforces a real, if modest, risk of bleeding – accentuated in patients with CAA and/or undergoing anti-amyloid therapy. There is no clear formal consensus on optimal management yet, so vigilance, individualized assessment, and interdisciplinary collaboration remain paramount at the complex intersection between psychiatric and disease-modifying therapies. As anti-amyloid agents become more widely used, and real-world data on combined treatments accumulate, further research is critically needed to provide clearer guidance. Prospective studies and registry

analyses should specifically evaluate clinically meaningful outcomes – including bleeding events, cognitive trajectories, and neuropsychiatric stability – in individuals receiving both SSRIs and anti-amyloid agents. Only with robust longitudinal data can we hope to achieve a more definitive understanding of how best to manage this common and clinically significant therapeutic intersection in AD care.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.R.P. contributed to the conceptualization, literature review, and writing and editing of the manuscript. M.Z. contributed to the literature review and writing and editing of the manuscript. M.G.K. and S.F. contributed to the conceptualization and writing and editing of the manuscript. All authors have read and approved the final submitted manuscript and agree to be accountable for the work.

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