Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are considered first-line pharmacotherapy for depression due to fewer side effects compared to other classes of antidepressants. Antidepressants are widely used in patients with dementia to improve neuropsychiatric symptoms, such as anxiety, depression, and sleep disorders. Still, the clinical efficacy of antidepressants on dementia progression is uncertain. In this nationwide study, Swedish scientists investigated the long-term impact of antidepressants on dementia patients' cognitive deterioration, bone fractures, and mortality. Additionally, they examined how various classes of antidepressants, drugs, and doses affect dementia progression.

Previous studies on the use of antidepressants and cognitive decline in people with dementia have produced mixed results. In the majority of the cases reported, antidepressants had the same effect on cognition as placebo, but some reported a significant decline in the Mini-Mental State Examination (MMSE) scores in antidepressant users. However, previous studies have mainly been conducted in patients with Alzheimer's disease (AD), so, the results concerning other dementias, such as vascular dementia (VaD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and Parkinson's disease dementia (PDD), are scarce. The authors noted that cognitive dysfunction in dementia appears to reduce the effectiveness of some SSRIs.

About the study

This cohort study is based on the nationwide Swedish Registry for Cognitive/Dementia Disorders (SveDem), which provides data on patients with dementia diagnosis, the Swedish Prescribed Drug Register with complete data on prescribed medications, and the Cause of Death Registry that contains data on overall and specific mortality. SveDem contains information on demographics, diagnostic processes, and cognitive and mortality outcomes. Although SveDem represents a large nationally representative cohort of individuals with dementia, the national coverage of new dementia cases is not absolute. SveDem covers 100% of memory clinics, 75% of primary care units, and almost one-third of all expected new dementia cases in Sweden.

The study included patients with dementia registered in SveDem from 2007 to 2018. Patients with missing information on MMSE scores at baseline, with a record of antidepressant administration prior to the 6 months before the date of dementia diagnosis, or patients with no follow-up were excluded. Patients who received prescriptions for different antidepressants within a class or antidepressants from various classes in the same 6-month period were also excluded.

Dementia disorders were clinically diagnosed according to the International Classification of Diseases, Tenth Revision (ICD-10) codes, with the McKeith criteria used for dementia with Lewy bodies (DLB), the Lund-Manchester criteria for frontotemporal dementia (FTD), and the Movement Disorder Society Task Force criteria for Parkinson's disease dementia (PDD), respectively. Dementia was coded as Alzheimer's dementia (AD), mixed dementia, vascular dementia (VaD), DLB, FTD, PDD, and other dementias, including unspecified and other not-classified dementia.

Antidepressant drugs were classified into five classes according to their mode of action: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and others. Antidepressant classes and drugs were compared, and dose-response was analyzed.

Cox proportional hazards models were used to calculate the hazard ratios for severe dementia (MMSE score <10), fracture, and death. The main outcome was cognitive decline, defined as MMSE score change over the years. The secondary outcomes were severe dementia, fracture, and death. Severe dementia was specifically defined as an MMSE score <10 during follow-up.

Results

In total, 18,740 patients were included in this cohort study; 54.5% were women, the mean age was 78.2 years, and the mean MMSE score at baseline was 22.1. The total number of years of follow-up was 80,737, with a mean of 4.3 years per patient.

During follow-up, a total of 11,912 prescriptions for antidepressants were written; 23% of patients received at least one prescription for an antidepressant. SSRIs were the most commonly prescribed, accounting for 64.8%, followed by TCAs (2.2%), SNRIs (2.0%), and the group of other antidepressants (31.0%). The six most commonly prescribed antidepressant drugs that comprised 99% of all prescriptions were citalopram (SSRI), mirtazapine (others), sertraline (SSRI), escitalopram (SSRI), amitriptyline (TCA), and venlafaxine (SNRI).

Antidepressants and cognitive decline

Compared with non-use, the use of antidepressants, in particular the use of sertraline, citalopram, escitalopram, and mirtazapine, was associated with faster cognitive deterioration during follow-up. The association was stronger in patients with severe dementia (initial MMSE scores 0–9). Escitalopram was associated with a faster rate of cognitive deterioration than sertraline, while citalopram showed a slower cognitive decline.

Patients with severe dementia and the lowest initial MMSE scores (0–9) exhibited the greatest subsequent cognitive decline.

The results were similar for AD and mixed dementia, VaD, and other dementias, except LBD and FTD. Younger (<78 years) patients with FTD had a slower cognitive decline. In addition, cognitive deterioration was greater in male patients who had lower MMSE scores at baseline and were not taking anxiolytics or hypnotics than in female patients who had higher MMSE scores at baseline and were taking anxiolytics and hypnotics.

Higher doses of SSRIs were not only associated with greater cognitive decline during follow-up but also with an increased risk of bone fractures and all-cause mortality compared to non-use.

Conclusion

This nationwide cohort study showed that the current use of antidepressants, in particular SSRIs (i.e., citalopram, sertraline, and escitalopram) and mirtazapine, was associated with faster cognitive decline in patients with dementia compared with non-use. These effects appeared to be more pronounced in patients with more severe dementia. Higher dispensed doses of SSRIs were associated with greater cognitive decline, as well as increased risks of severe dementia, all-cause mortality, and fracture.

The authors stressed that this study is unable to determine whether the results are attributable to the underlying psychiatric indication or the antidepressants. They emphasized how important it is to carefully and consistently monitor the use of various antidepressants in dementia patients.

This article was published in BMC Medicine.

Journal Reference

Mo, M., Abzhandadze, T., Hoang, M.T. *et al*. Antidepressant use and cognitive decline in patients with dementia: a national cohort study. BMC Med 2025, 23, 82 (Open Access). https://doi.org/10.1186/s12916-025-03851-3