Association of depression and SSRIs with mortality after stroke

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In both early and late stages of stroke course, depression remains a common comorbid condition lacking well-defined clinical, social, or demographic predictors.[1] According to a recent meta-analysis, the prevalence of depression among people who had a stroke was 29% (from 25% to 32%), remaining stable up to 10 years after stroke.[2] Despite a large body of literature published in this field, uncertainties on outcome and health consequences linger. Although a systematic review and meta-analysis involving 59,598 individuals from 13 studies reported an association between depression after stroke and mortality,[3] the high level of heterogeneity across the included studies in terms of study design, follow-up duration, source of recruitment, and time or methods of depression assessment limits interpretability of these findings. On the other hand, another meta-analysis found prestroke depression was associated with a pooled higher risk (hazard ratio 1.55; 95% confidence interval 1.25–1.93) of fatal stroke.[4] However, routine use of antidepressants after stroke remains controversial, due to the heterogeneity and methodologic limitations of pharmacologic trials published in this field.[5]

In this issue of *Neurology*®, Ayerbe et al.[6] investigate the association between depression 3 months after stroke and all-cause mortality up to 5 years, examining the role of potential explanatory factors, such as treatment with selective serotonin reuptake inhibitors (SSRIs). The authors analyzed data from the South London Stroke Register (1998–2013), assessing for depression 1,354 individuals 3 months after their first ever stroke. The Hospital Anxiety and Depression Scale was used to identify cases of depression.

The study provides 2 main findings. First, individuals with depression—representing about one-third of the whole sample—showed a significantly higher 5-year mortality. The association appeared stronger among patients under 65 years of age, showing a threefold higher risk of mortality as compared to the nondepressed counterpart. The results persisted after controlling for several potential confounders.

Second, analyses on SSRI effects show mixed results. Only a small proportion of the overall sample (about 11%) was treated with an antidepressant medication. Those treated with SSRIs before their stroke did not show any increase in mortality risk. On the other hand, people started on an SSRI after stroke showed a significant increase in mortality within 5 years of stroke. These findings are in line with recently published data on ischemic stroke patients from Danish medical registries[7] highlighting that, although SSRI users had lower risk of myocardial infarction and recurrent ischemic stroke as a combined outcome, they also showed a higher likelihood of overall major bleeding and an increased risk of death. In contrast, a retrospective study in a cohort of veterans with a diagnosis of stroke showed a trend between poststroke SSRI treatment and longer survival, even though a diagnosis of depression was associated with earlier mortality.[8]

Despite some limitations, such as missing data and lack of information on prestroke depressive symptoms that can potentially increase the risk of both depression[1] and mortality[4] after stroke, the findings of the study by Ayerbe et al.[6] emphasize the importance of regular screening for depressive disorders after stroke—possibly with the most accurate available diagnostic instruments[9]—but also long-term monitoring for potential adverse events, especially among younger patients or those treated with SSRIs.

Future epidemiologic research should clarify the nature of the association between depression and mortality after stroke. Depression may affect prognosis after stroke because patients with depression may be less compliant with treatment.[3] On the other hand, patients who have more disabling forms of stroke may be more likely to develop depression.[1,2] Furthermore, biological mechanisms and immune dysregulation processes may be involved.[3,4] Special attention should be paid to antidepressant treatment, and further research is needed to analyze benefits and adverse outcomes of SSRI treatment in this special population. Although SSRIs have a beneficial effect on remission of depression[10] as well as an improvement in dependence, disability, and neurologic impairment,[5] clinicians should carefully evaluate pros and cons of SSRIs as a therapeutic option among patients with depression after stroke, taking into account their potential negative effect on survival.

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