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# Low adherence to antidepressants is associated with increased mortality following stroke: A large nationally representative cohort study

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**Abstract**
Post stroke depression is common and pervasive. In the general population, there has been some controversy that antidepressant (AD) medication is associated with premature mortality. Data is still lacking regarding the association between adherence to antidepressants (AD) and all-cause mortality. In this retrospective analysis of a population-based cohort of patients, 32,361 post-stroke patients who purchased at least one AD were followed for all-cause mortality over 4-years. Adherence to AD was measured as a ratio between dispensed and prescribed durations and was modeled as: non-adherence (<20%, $n$=8619), poor (20-50%, $n$=5108), moderate (50-80%, $n$=5656), and good (>80%, $n$=12,978) adherence. Multivariable survival analyses, adjusted for demographic and clinical variables including physical comorbidities known to influence mortality, were conducted. Unadjusted mortality rates were 16.5%, 20.2%, 22.2% and 23.7% in those classified as non-adherent, poor, moderate and good adherence respectively ($\chi^2$=174.6, $p$<0.0001). In the adjusted model, the non-adherent and poor

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adherence groups had significantly increased mortality Hazard Ratios (HR) of 1.25 (95% CI: 1.17-1.33) and 1.17 (95% CI: 1.09-1.26) respectively compared to the good adherence group. This nationally representative data suggests that poor adherence to AD is associated with increased all-cause mortality among people who had a stroke. Given our findings and the high prevalence of anxiety and depression along with AD effectiveness, efforts to promote AD adherence in this population may be warranted in clinical practice.


## 1. Introduction

Depression is common among people who suffered from a stroke, with a prevalence of approximately 29% and cumulative incidence of 39-52% in the 5 years post event (Ayerbe et al., 2013). Depression is also highly co-morbid and associated with a range of deleterious outcomes post stroke including lower quality of life, increased disability, more marked cognitive impairment, worse recovery, caregiver burden and increased mortality (Ayerbe et al., 2013; Bartoli et al., 2013; Hackett et al., 2005; Hackett and Anderson, 2005; Kouwenhoven et al., 2011; Robinson and Jorge, 2016; Turner-Stokes and Hassan, 2002). Whilst the aetiological factors associated with post stroke depression and anxiety are complex and multifactorial and include genetic predisposition, demographic and psychosocial factors, the recognition and appropriate treatment of depression and anxiety following a stroke is of utmost importance (Cumming et al., 2016; Robinson and Jorge, 2016; van Mierlo et al., 2014).

A frontline intervention for the treatment of depression and anxiety is the use of antidepressant medication (AD) (Fournier et al., 2010). Among people with stroke, there is evidence from meta-analyses of randomized control trials that Selective serotonin reuptake inhibitors (SSRIs) can improve depressive symptoms (Standardized mean difference (SMD) −1.91 (95% CI −2.34 to −1.48)), reduce disability (SMD 0.91 (95% CI 0.60 to 1.22)), neurological impairment (SMD −1.00 (95% CI −1.26 to −0.75)) and anxiety (SMD-0.77 (95% CI −1.52 to −0.02)) (Mead et al., 2013; Xu et al., 2016). In addition, there is evidence that milnacipran may also prevent the onset of depression post stroke (Tsai et al., 2011) and discontinuing antidepressant medication (fluoxetine ($N$=32), nortriptyline ($N$=22)) once started may increase the post stroke depressive symptoms (Mikami et al., 2011). Perhaps the most intriguing literature to date is regarding antidepressant medication use and mortality post stroke. A seminal randomized controlled trial found that survival was increased following the prescription of antidepressant medication (nortriptyline, fluoxetine, versus placebo) (Jorge et al., 2003). More recently, some studies have found that various antidepressant use is associated with increased mortality post stroke (Ayerbe et al., 2014; Mortensen et al., 2013) whilst others have suggested that a number of antidepressant medications may reduce the odds of mortality (Mortensen et al., 2015).

Whilst a number of studies have considered the relationship between antidepressant medication and mortality among people after stroke, a number of limitations and gaps within the literature exist. First, there is a paucity of nationally representative studies considering the relationship between antidepressant medication and mortality post stroke. Second, no study to our knowledge has considered the influence of adherence to antidepressant medication and mortality in stroke. Medication adherence is known to be variable among people with stroke (Jamison et al., 2016; Jenkins et al., 2016) and associated with other worse outcomes (Bailey et al., 2010), but the relationship with mortality is unclear. Third, there is a lack of clarity whether a gender effect exists in the relationship between antidepressant medication use and mortality post stroke. Previous research has suggested high levels of depression in males post stroke (Mitchell et al., 2017) and noted elevated mortality in males with depression (Correll et al., 2017). Finally, the adjustment for important risk factors such as comorbidities (e.g. physician-diagnosed physical comorbidities) has been inconsistent and may influence the results observed to date. There is literature demonstrating that a higher number of morbidities is associated with elevated mortality (Nunes et al., 2016).

Given the aforementioned gaps and limitations, our primary objective was to evaluate the association between adherence to antidepressants and all-cause mortality among a representative cohort of individuals with stroke from a database covering in excess of 4 million individuals, taking into account important confounders. We hypothesized that lower levels of adherence to antidepressants, would be associated with an incremental increased odds of mortality among people with stroke. We also hypothesized that mortality would be greater among males and those with a higher number of comorbidities.

## 2. Experimental procedures

### 2.1. Population and study period

For the current study, data was utilized from the integrated medical records of Clalit Health Services (CHS), the largest health provider in Israel, covering over 4 million subjects, equivalent to 53% of the national population. Full details of the CHS database have been described in full elsewhere (Krivoy et al., 2016). Briefly, the CHS database includes comprehensive demographic information, diagnoses from ambulatory services, family physicians, hospital admissions and specialists, drug prescriptions, laboratory tests and imaging results.

Within the current study, we retrospectively analyzed the entire CHS patient population during the study period (1.1.2008 until 31.12.2011) across all ages ($N$=4,056,700). We included all patients with at least one AD prescription during the study period and a clinical diagnosis of Cerebrovascular Accident (CVA) ICD code I.63

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