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Mortality and use of psychotropic medication in stroke patients: a population-wide register-based study

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Author contributions: Poul Jennum (PJ) and Jakob Kjellberg (JK): creation, initiation and management of the project. PJ is the main author. JK and RI performed the statistical analyses and commented on the manuscript. LB and HI commented on the methods and critically revised the manuscript.

Key words: stroke, hypnotics, antidepressants, antipsychotics, benzodiazepines, all-cause mortality.

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ABSTRACT

Objectives: The study sought to describe whether psychotropic medication may have long-term side effects in stroke patients as compared to controls.

Setting: Use of all national register data from health care services were identified from the Danish National Patient Registry in Denmark. Information about psychotropic medication use was obtained from the Danish Register on Medicinal Product Statistics.

Objectives: We aimed to evaluate all-cause mortality in relation to the use of benzodiazepines, antidepressants and antipsychotics in stroke patients and matched controls.

Participants: Patients with a diagnosis of stroke and either no drug use or pre-index use of psychotropic medication (n = 49 968) and compared with control subjects (n = 86 100) matched on age, gender, marital status and community location.

Primary outcome measure: all-cause mortality

Results: All-cause mortality was higher in patients with previous stroke as compared to control subjects. Mortality hazard ratios were increased for subjects prescribed serotonergic antidepressant drugs (respectively, HR=1.699 (SD=0.030), P=0.001 in patients; HR=1.908 (0.022), P<0.001 in controls), tricyclic antidepressants (HR=1.365 (0.045), P<0.001; HR=1.733 (0.022), P<0.001), benzodiazepines (HR=1.643 (0.040), P<0.001); HR=1.776 (0.053), P<0.001), benzodiazepine-like drugs (HR=1.776 (0.021), p=<0.001; HR=1.547 (0.025, p<0.001), first-generation antipsychotics (HR=2.001 (0.076), p<0.001; HR=3.361 (0.159), P<0.001), and second-generation antipsychotics (HR=1.645 (0.070), p<0.001; HR=2.555 (0.086), p<0.001), as compared with no drug use. Interaction analysis suggested statistically significantly higher mortality hazard ratios for most classes of psychotropic drugs in controls compared with stroke patients.

Conclusion: All-cause mortality was higher in stroke patients and controls treated with benzodiazepines, antidepressants and antipsychotics than in their untreated counterparts. Our findings suggest that care should be taken in the use and prescription of such drugs, and that they should be used in conjunction with adequate clinical controls.

Strengths and limitations of this study

- Use of hypnotics, antidepressants and antipsychotics is more frequently used in stroke patients than in controls, and is associated with greater all-cause mortality in stroke patients and matched controls.
- Care should be taken in the use and prescription of such drugs, and that they should be used in conjunction with adequate clinical controls.
- The strengths of the National Patient Registry are that it is a national database that includes all identified patients and comorbid conditions and psychotropic medication, it is time-locked (all reports must be associated with patient contacts) and includes a substantial follow-up period.
- The limitation of the study is, although the study is controlled, it is not a randomized controlled trial, which means there is a potential bias towards more severe diseases among treated patients.

Introduction

Stroke is one of the most important neurological causes of morbidity, mortality and disability and affects a significant proportion of the population. Stroke has deleterious effects on patients' social function, employment, quality of life, and the disease entails a societal burden that is manifested as increased direct and indirect costs [1]. Early intervention and management of stroke in recent years have significantly improved prognosis, with reduced mortality and fewer neurological deficits. After the acute phase, up to 40% of patients suffer from post-stroke depression within the first year [2], and patients may suffer from comorbid insomnia and psychiatric symptoms, such as hallucinations and other psychotic symptoms[3].

In recent years, the increased frequency of off-label use of psychotropic drugs, their side effects, and the harm they may cause have been a growing concern [4-6]. Studies of large groups of patients with psychotic diseases and of patients with chronic insomnia have raised concerns about increased mortality rates in benzodiazepine-treated patients, especially when used in combination with other psychotropic drugs [7-9]. There is additional concern about the association between benzodiazepine use and cognitive decline in Alzheimer's disease [10-13]. Stroke patients suffer from major comorbidities, including cardiac arrhythmias and sleep-related hypoxemia, and thus there is a general consensus that the use of respiratory depressants should be avoided. Few studies have addressed the effect on mortality when using antidepressants in post-stroke patients. These studies have found reduced mortality rates in short-term studies in patients treated during the stable phase [14]. However, there have been no prospective studies of morbidity and mortality in stroke patients in relation to the use of psychotropic drugs.

The aim of this study was to evaluate the association between all-cause mortality and the use of benzodiazepines (BZDs), benzodiazepine-like (BZD-like) medications, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), and first-generation and second-generation antipsychotics (FGAs and SGAs) in stroke patients and matched controls.

Material and methods

Subjects

In Denmark, all hospital contacts are recorded in the National Patient Registry (NPR) with respect to the time of contact and information about primary and secondary diagnoses. The NPR includes administrative information and details on all diagnoses, diagnostic methods, hospitalizations, and ambulatory clinical contacts (initial and follow-up) in all public and private hospitals. These data are recorded using several international classification systems, including the International Classification of Diseases, 10th Edition (ICD-10). The NPR is a time-based nation-wide register that includes data from all inpatient and outpatient contacts. Thus, the

data extracted for this study are representative of all patients in Denmark who have been diagnosed with stroke, irrespective of other diagnoses. Data were available for the entire observation period so we were able to trace patients retrospectively and prospectively, relative to the time of their diagnosis.

Using the NPR, we identified all patients diagnosed with stroke between 1997 and 2009. To identify stroke diagnoses, we used the ICD-10 codes I61: cerebral hemorrhage, I63: brain infarction, I64: stroke not otherwise defined as being due to infarction or hemorrhage. The diagnosis code is recorded after patient evaluation in each hospital (based on a standardized evaluation of stroke). The expected distribution of stroke types is 15% hemorrhagic and 85% ischemic [15]. We did not include patients with a diagnosis of transitory ischemic episodes. Then, using data from Denmark's Civil Registration System Statistics, we randomly selected citizens of the same age, gender, county of residence and marital status as the patients, but who did not have a diagnosis of any stroke episodes. Parity of socio-economic status (SES) was ensured by selecting control subjects from the same part of the country in which the patient lived and by matching for partnership (including those married). A ratio of control subjects to patients of 2:1 was used to take into account the variation among the controls. Data from patients and matched controls that could not be identified in the Coherent Social Statistics database were excluded from the sample. The patients and matched control subjects were traced retrospectively and prospectively for up to 12 years in the NPR registry and prescription database. All observations were successfully matched at the year of diagnosis (index year). Patients and control subjects who could not be identified in the social security registry in the years before and after diagnosis (typically as a result of emigration) were excluded from the sample. More than 99% of the patients and controls had complete data.

Psychotropic medications studied

Information on type, number, dose and date of prescriptions were obtained from the Danish Register of Medicinal Product Statistics, which includes all medications prescribed outside hospitals. Seven medication classes were included in the analysis: BZDs, BZD-like, SSRIs, SNRIs, TCAs, FGAs and SGAs. Medication use was defined as filling of at least three prescriptions with a compliance rate of at least 60% in the 12 months before the index date. Compliance rate was defined as the daily defined dose (DDD) coverage of prescriptions and was set to 60% as an inclusion criterion. The no medication group was defined as those who had not collected any psychotropic drugs within 12 months prior to the index date or during the observation period.

A substantial number of patients used medication before the year of diagnosis. We created a dummy variable to control for this in the regression. Some patients discontinued medication; they were identified by determining whether the most recent prescription had been collected more than three years before the end-point (stop parameter). Such cases were scored as zero in the analysis.

Statistical analyses

Morbidity and mortality data were extracted as primary and secondary diagnoses from the NPR in accordance with the World Health Organization (WHO) ICD-10 criteria. For the purpose of this study, we used all-cause morbidity and all-cause mortality data. To avoid the influence of mortality due to factors other than medication use, we only included patients and controls who had survived for at least 1 year after the index date and who were treated with not more than one psychotropic medication to avoid the influence of the others. Statistical analysis involved the development of proportional Cox hazard models in which survival was conditional on the explanatory variables of age, gender and use of medication types. Three regressions were performed, for the case and control groups separately, and for both groups. In the latter, a dummy variable indicating case *vs.* control and interaction terms for medication*control were included. The interaction term should indicate whether the effect of that particular medication on survival was different for the case and control groups. After conditioning on one year of survival (removing both cases and controls from the population), we tested the model for proportionality to make sure that the assumption for the proportional Cox model was met. Since this was not the case for some covariates, an extended Cox model was developed, using a time*interaction term for the covariates that were not proportional. The interpretations of the covariates were not straightforward once the interaction with time had been included. The effect of the non-proportional covariates on survival could be calculated for each year after the index date. Statistical analyses were performed using SAS 9 (SAS, Inc., Cary, NC, USA).

Ethics

The study was approved by the Danish Data Protection Agency. Data were anonymized and so neither individual nor ethical approval was required.

Results

In total, the study population comprised 49 968 patients suffering from ischemic, hemorrhagic or unspecified stroke and 86 100 controls. The descriptive information for the study population is shown in Table 1. Stroke patients suffered from high pre-index (i.e., 12 months prior to the index date) mortality (Figure 1).

The distribution of the patients and control subjects along with their treatment is shown in Table 1. In general, stroke patients were more frequently treated with a psychotropic drug than were the controls (Table 1).

Survival after a stroke diagnosis

Survival data with respect to total medication use in stroke patients and their controls are shown in Figure 1 subdivided into treatment with any of the psychotropic drugs or not. Mortality hazard ratios for each class of medication are shown in Table 2 and the results of the Cox model with interactions in Table 3 adjusted for the effect of age, gender and Charlson comorbidity index. Survival was generally lower, with increased mortality hazard ratios, for all

drug classes in both stroke patients and controls. We found statistically significant interactions between group and psychotropic medication regarding TCAs, SSRIs, BZD-like and SGAs (Table 3), i.e. the associations of excess risk of death with use of these classes of psychotropic medications were more pronounced in control subjects compared with controls. The Hazard Ratios was highest among controls using any of the psychotropic drugs as compared to stroke patients (Table 3).

Discussion

This study, which included data from a nation-wide patient registry, yielded several important findings: a) psychotropic drugs are more frequently used by stroke patients than by matched control individuals; b) psychotropic drugs are generally associated with increased mortality, the highest mortality being observed in stroke patients and control subjects treated with antipsychotics, c) control subjects showed higher mortality hazard ratios (SSRI, TCA and BZD-like) as compared to stroke patients, and d) this association is present after adjusting for comorbidities and avoiding the initial phase with high mortality which may be due to the stroke and multiple comorbidities immediately after the stroke.

The higher mortality with the use of benzodiazepines, antidepressants and antipsychotics in patients with stroke was not be exclusively associated with the presence of stroke because the association was also found in control subjects. Previous studies have evaluated the mortality rates associated with BZDs in patients with other conditions, including patients with insomnia [7;8], patients in dialysis [16], and those with depression [17]. The need for further evaluation of the use of antidepressants and antipsychotics and their associations with morbidity, including metabolic syndrome and mortality in other groups of patients including psychiatric, neurodegenerative and cardiac diseases has been stressed by many authors [18-22]. A major concern about studies of this type is whether the group of people receiving treatment is a population with intrinsically higher comorbidity rates than the untreated population. We cannot discount this possibility in the population considered here. Depression is associated with an increased risk of developing cardiac and cerebrovascular events [23;24], and with new events in established cardiovascular patients [25]. Patients with stroke are more likely to be treated for depression [26-28] and to suffer from insomnia [29] and depressive symptoms [30;31]. Earlier studies addressed the potentially greater mortality in stroke patients using antipsychotics [31-33]. Although not proving that comorbid conditions play a role in the higher mortality of those treated with psychotropic drugs, it does suggest that the relation is associated with effect of the drugs. We included three major classes of psychotropic drugs in this study to evaluate the effects of their individual use. We also included the use of BZD-like drugs as it has previously been assumed that these drugs are safer than benzodiazepines. We found no such effect; there was no major difference in mortality between BZD and BZD-like drugs. This population is one of the largest ever studied, but, even though we found that the risk was still higher for SSRIs, BZD-like drugs and antipsychotics, our results suggest that even larger population-based studies,

with longer follow-up times, are required. This is reflected in Table 3, which illustrates a subgroup analysis of specific groups of drugs that attempts to evaluate the different types. Further sub-classification of morbidities that adequately controls for different types of psychiatric and medical diagnosis would require an even larger dataset.

There are several factors that could explain why some of the drugs studied might affect morbidity and even mortality rates. The drugs may affect arousals from sleep, metabolic, respiratory, autonomic and cardiac function [34-36]. BZDs may induce upper-airway collapse and potentially affect respiration. Use of clonazepam has been reported to induce sleep apnea [37]. This is potentially important as sleep apnea is very common in stroke patients [29]. The respiratory depression of hypnotics has not been fully identified in polysomnography studies [38]. These studies are performed under controlled circumstances in a small number of selected patients, while natural usage includes unselected patients in their natural environment, where dose and presence of other risk factors (e.g., co-medication, sleep deprivation, and alcohol consumption) are not controlled for. Overdoses and combinations have been reported in patients admitted to emergency rooms [39]. Furthermore, predictors of higher mortality include male gender, increasing age and lower educational level, combined with alcohol consumption and inappropriate lifestyles — factors that may be associated with the use of psychotropic drugs and that are not taken into consideration in clinical laboratory testing. Another Danish study confirmed our findings of higher total mortality but lower cardiovascular mortality among SSRI-treated stroke patients. It was concluded that this was due to the higher hemorrhagic mortality in treated patients [40]. Consequently, future studies should explore the relationship between psychotropic drugs, morbidity and mortality in greater detail.

In this study, we carried out a total evaluation, controlling for gender, age and demographic variables, which are all known to influence disease outcome, and for comorbidities. We also avoided the initial period when patients are much frailer and mortality rates are high due to the direct effect of the stroke, and the great comorbidity in these patients. As such, we believe that the risk associations found in the study are conservative, as is further supported by the finding that the risk association in stroke patients is lower than in controls.

Limitations of the study: the study has a number of limitations: a) it is based on clinic/hospital reports to the NPR; b) the diagnostic accuracy depends on the clinic's presentation and reporting of the diagnosis and any comorbidities; c) confounder variables (e.g., BMI and other cardiovascular risk factors) were not recorded; d) symptoms and clinical evaluation results were not considered (e.g., those measured by polysomnography, limited channel polygraphy and cardiac evaluations), so we could not relate our findings to disease severity. We did not exclude diseases, especially unidentified stroke, in the controls. The types of medication given on prescription are highly controlled in Denmark, but we do not know whether the drugs were taken or shared, or if they were taken from someone else's prescription (e.g., that of the patient's spouse). Nevertheless, we believe that using at least three prescriptions indicates more chronic use. We have no definitive explanation of the higher mortality rate among the controls compared with the stroke patients: one cause could be that

we only included patients who survived after one year. Evaluation of the total population showed smaller differences, so it is likely that those who survived the stroke incident have higher survival rates despite the treatment with psychotropic drugs.

The strengths of the NPR, however, are that it is a national database that includes all identified patients and comorbid conditions and psychotropic medication, it is time-locked (all reports must be associated with patient contacts) and includes a substantial follow-up period. In addition, although the study is controlled, it is not a randomized controlled trial, which means there is a potential bias towards more severe diseases among treated patients. We conclude that use of hypnotics, antidepressants and antipsychotics is more frequently used in stroke patients than in controls, and is associated with greater all-cause mortality in stroke patients and matched controls. Our findings suggest that care should be taken in the use and prescription of such drugs, and that they should be used in conjunction with adequate clinical controls.

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Reference List

(1) Cox AM, McKevitt C, Rudd AG, Wolfe CD. Socioeconomic status and stroke. *Lancet Neurol* 2006; 5(2):181-188.

(2) Andersen G, Vestergaard K, Riis J, Lauritzen L. Incidence of post-stroke depression during the first year in a large unselected stroke population determined using a valid standardized rating scale. *Acta Psychiatr Scand* 1994; 90(3):190-195.

(3) Mayer G, Jennum P, Riemann D, Dauvilliers Y. Insomnia in central neurologic diseases--occurrence and management. *Sleep Med Rev* 2011; 15(6):369-378.

(4) Kripke DF, Klauber MR, Wingard DL, Fell RL, Assmus JD, Garfinkel L. Mortality hazard associated with prescription hypnotics. *Biol Psychiatry* 1998; 43(9):687-693.

(5) Rintoul AC, Dobbin MD, Nielsen S, Degenhardt L, Drummer OH. Recent increase in detection of alprazolam in Victorian heroin-related deaths. *Med J Aust* 2013; 198(4):206-209.

(6) Merlo J, Ostergren PO, Mansson NO, Hanson BS, Ranstam J, Blennow G et al. Mortality in elderly men with low psychosocial coping resources using anxiolytic-hypnotic drugs. *Scand J Public Health* 2000; 28(4):294-297.

(7) Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2012; 2(1):e000850.

(8) Mallon L, Broman JE, Hetta J. Is usage of hypnotics associated with mortality? *Sleep Med* 2009; 10(3):279-286.

(9) Jennum P, Baandrup L, Ibsen R, Kjellberg J. Increased all-cause mortality with use of psychotropic medication in dementia patients and controls: A population-based register study. *Eur Neuropsychopharmacol* 2015.

(10) Montastruc F, Gardette V, Cantet C, Piau A, Lapeyre-Mestre M, Vellas B et al. Potentially inappropriate medication use among patients with Alzheimer disease in the REAL.FR cohort: be aware of atropinic and benzodiazepine drugs! *Eur J Clin Pharmacol* 2013; 69(8):1589-1597.

(11) Lauterbach EC. Use of psychotropic medication in Alzheimer's disease is associated with more rapid cognitive and functional decline. *Evid Based Med* 2013; 18(5):e50.

(12) Rosenberg PB, Mielke MM, Han D, Leoutsakos JS, Lyketsos CG, Rabins PV et al. The association of psychotropic medication use with the cognitive, functional, and neuropsychiatric trajectory of Alzheimer's disease. *Int J Geriatr Psychiatry* 2012; 27(12):1248-1257.

(13) Vigen CL, Mack WJ, Keefe RS, Sano M, Sultzer DL, Stroup TS et al. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. *Am J Psychiatry* 2011; 168(8):831-839.

(14) Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. *Am J Psychiatry* 2003; 160(10):1823-1829.

(15) Wildenschild C, Mehnert F, Thomsen RW, Iversen HK, Vestergaard K, Ingeman A et al. Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. *Clin Epidemiol* 2014; 6:27-36.

(16) Winkelmayer WC, Mehta J, Wang PS. Benzodiazepine use and mortality of incident dialysis patients in the United States. *Kidney Int* 2007; 72(11):1388-1393.

(17) Allgulander C. Psychoactive drug use in a general population sample, Sweden: correlates with perceived health, psychiatric diagnoses, and mortality in an automated record-linkage study. *Am J Public Health* 1989; 79(8):1006-1010.

(18) Baandrup L, Jennum P, Lublin H, Glenthoj B. Treatment options for residual insomnia in schizophrenia. *Acta Psychiatr Scand* 2013; 127(1):81-82.

(19) Bhalerao S, Seyfried LS, Kim HM, Chiang C, Kavanagh J, Kales HC. Mortality risk with the use of atypical antipsychotics in later-life bipolar disorder. *J Geriatr Psychiatry Neurol* 2012; 25(1):29-36.

(20) Marras C, Gruneir A, Wang X, Fischer H, Gill SS, Herrmann N et al. Antipsychotics and mortality in Parkinsonism. *Am J Geriatr Psychiatry* 2012; 20(2):149-158.

(21) Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C et al. Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry* 2012; 169(1):71-79.

(22) Honkola J, Hookana E, Malinen S, Kaikkonen KS, Junttila MJ, Isohanni M et al. Psychotropic medications and the risk of sudden cardiac death during an acute coronary event. *Eur Heart J* 2012; 33(6):745-751.

(23) Jackson CA, Mishra GD. Depression and risk of stroke in midaged women: a prospective longitudinal study. *Stroke* 2013; 44(6):1555-1560.

(24) Majed B, Arveiler D, Bingham A, Ferrieres J, Ruidavets JB, Montaye M et al. Depressive symptoms, a time-dependent risk factor for coronary heart disease and stroke in middle-aged men: the PRIME Study. *Stroke* 2012; 43(7):1761-1767.

(25) Nielsen TJ, Vestergaard M, Christensen B, Christensen KS, Larsen KK. Mental health status and risk of new cardiovascular events or death in patients with myocardial infarction: a population-based cohort study. *BMJ Open* 2013; 3(8).

(26) Flaster M, Sharma A, Rao M. Poststroke depression: a review emphasizing the role of prophylactic treatment and synergy with treatment for motor recovery. *Top Stroke Rehabil* 2013; 20(2):139-150.

(27) Seifert CL, Poppert H, Sander D, Feurer R, Etgen T, Ander KH et al. Depressive symptoms and the risk of ischemic stroke in the elderly--influence of age and sex. *PLoS One* 2012; 7(11):e50803.

(28) El HN, Goldstein LB, Peterson ED, Zhao X, Pan W, Olson DM et al. Depression and antidepressant use after stroke and transient ischemic attack. *Stroke* 2012; 43(6):1609-1616.

(29) Mayer G, Jennum P, Riemann D, Dauvilliers Y. Insomnia in central neurologic diseases--occurrence and management. *Sleep Med Rev* 2011; 15(6):369-378.

(30) Wang S, Linkletter C, Dore D, Mor V, Buka S, Maclure M. Age, antipsychotics, and the risk of ischemic stroke in the Veterans Health Administration. *Stroke* 2012; 43(1):28-31.

(31) Pratt NL, Roughead EE, Ramsay E, Salter A, Ryan P. Risk of hospitalization for stroke associated with antipsychotic use in the elderly: a self-controlled case series. *Drugs Aging* 2010; 27(11):885-893.

(32) Glenn MB. Sudden cardiac death and stroke with the use of antipsychotic medications: implications for clinicians treating individuals with traumatic brain injury. *J Head Trauma Rehabil* 2010; 25(1):68-70.

(33) Sacchetti E, Trifiro G, Caputi A, Turrina C, Spina E, Cricelli C et al. Risk of stroke with typical and atypical anti-psychotics: a retrospective cohort study including unexposed subjects. *J Psychopharmacol* 2008; 22(1):39-46.

(34) Gueye PN, Lofaso F, Borron SW, Mellerio F, Vicaut E, Harf A et al. Mechanism of respiratory insufficiency in pure or mixed drug-induced coma involving benzodiazepines. *J Toxicol Clin Toxicol* 2002; 40(1):35-47.

(35) Wilton LV, Heeley EL, Pickering RM, Shakir SA. Comparative study of mortality rates and cardiac dysrhythmias in post-marketing surveillance studies of sertindole and two other atypical antipsychotic drugs, risperidone and olanzapine. *J Psychopharmacol* 2001; 15(2):120-126.

(36) Czekalla J, Kollack-Walker S, Beasley CM, Jr. Cardiac safety parameters of olanzapine: comparison with other atypical and typical antipsychotics. *J Clin Psychiatry* 2001; 62 Suppl 2:35-40.

(37) Schuld A, Kraus T, Haack M, Hinze-Selch D, Pollmacher T. Obstructive sleep apnea syndrome induced by clonazepam in a narcoleptic patient with REM-sleep-behavior disorder. *J Sleep Res* 1999; 8(4):321-322.

(38) Sivertsen B, Omvik S, Pallesen S, Nordhus IH, Bjorvatn B. Sleep and sleep disorders in chronic users of zopiclone and drug-free insomniacs. *J Clin Sleep Med* 2009; 5(4):349-354.

(39) Henderson A, Wright M, Pond SM. Experience with 732 acute overdose patients admitted to an intensive care unit over six years. *Med J Aust* 1993; 158(1):28-30.

(40) Mortensen JK, Larsson H, Johnsen SP, Andersen G. Post stroke use of selective serotonin reuptake inhibitors and clinical outcome among patients with ischemic stroke: a nationwide propensity score-matched follow-up study. *Stroke* 2013; 44(2):420-426.

Table 1 Number of the total population conditioned on 1 year of survival after the first onset of stroke, classified as stroke patients and their controls, and their distribution with respect to psychotropic drug use.

	Stroke patients		Controls		
	N	%	N	%	P
Age (mean, SD)	66.6	14.4	65.3	14.5	
Gender (female)	21 995	44.0	36 595	42.5	
No medication	33 778	67.6	72 707	84.4	<0.001
SSRI/SNRI	8366	16.7	6789	7.9	<0.001
TCA	1082	2.2	756	0.9	<0.001
BZD	4675	9.4	3542	4.1	<0.001
Z-drugs	5165	10.3	4331	5.0	<0.001
FGA	381	0.8	349	0.4	<0.001
SGA	511	1.0	421	0.5	<0.001
Charlson comorbidity index (mean, SD)	0.8	0.8	0.1	0.4	<0.001
All	49 968		86 100		

Abbreviations:
SSRI: Selective serotonin reuptake inhibitors
SNRI: Serotonin–norepinephrine reuptake inhibitors
TCA: Tricyclic antidepressants
BZD: Benzodiazepines
FGA: First-generation antipsychotics
SGA: Second-generation antipsychotics

Table 2 Hazard ratios of mortality in stroke and control subjects.

	Stroke patients			Controls		
	Hazard ratio	SD	P	Hazard ratio	SD	P
Age	**1.087***	<0.001	<0.001	**1.114**	<0.001	<0.001
Gender (female)	**0.786**	0.016	<0.001	**0.679**	0.017	<0.001
Charlson comorbidity index	**1.076***	0.014	<0.001	**1.403***	0.014	<0.001
SSRI (incl. SNRI)	**1.699***	0.030	<0.001	**1.908**	0.022	<0.001
TCA	**1.365**	0.045	<0.001	**1.733**	0.060	<0.001
BZD	**1.643***	0.040	<0.001	**1.776***	0.053	<0.001
BZD-like	**1.386**	0.021	<0.001	**1.547**	0.025	<0.001
FGA	**2.001**	0.076	<0.001	**3.361***	0.159	<0.001
SGA	**1.645**	0.070	<0.001	**2.555**	0.086	<0.001
Observations	49 968			100 86		
% censored	64.5%			81.3%		

Note: time*interaction coefficient not reported

*Time-varying covariates were calculated in year 2, when all time-dependent covariates were significant in the time test
Estimate = a + a_t * year

Abbreviations:
SSRI: Selective serotonin reuptake inhibitors
SNRIs: Serotonin–norepinephrine reuptake inhibitors
TCA: Tricyclic antidepressants
BZDs: Benzodiazepines
FGAs: First-generation antipsychotics
SGAs: Second-generation antipsychotics

Table 3 Mortality hazard ratios for psychotropic drugs in the total study sample.

	Basic Cox model*			Cox model with interactions*		
	Hazard ratio	SD	P	Hazard ratio	SD	P
Age	**1.102**	0.001	<0.001	**1.102**	0.001	<0.001
Gender (female)	**0.734**	0.012	<0.001	**0.734**	0.012	<0.001
Control group	**0.600**	0.013	<0.001	**0.547**	0.015	<0.001
Charlson comorbidity index	**1.175**	0.010	<0.001	**1.169**	0.010	<0.001
SSRI (incl. SNRI)	**1.737**	0.014	<0.001	**1.270**	0.029	<0.001
TCA	**1.500**	0.036	<0.001	**1.404**	0.045	<0.001
BZD	**1.720**	0.032	<0.001	**1.532**	0.023	<0.001
BZD-like	**1.536**	0.027	<0.001	**1.340**	0.021	<0.001
FGA	**2.374**	0.057	<0.001	**2.260**	0.076	<0.001
SGA	**1.934**	0.054	<0.001	**1.745**	0.070	<0.001
Interactions						
Control*SSRI				**1.165**	0.045	<0.001
Control*TCA				**1.209**	0.075	0.011
Control*BZD				1.164	0.057	0.143
Control*BZD-like				**1.236**	0.032	<0.001
Control*FGA				1.125	0.115	0.305
Control*SGA				**1.327**	0.111	0.011
Observations	136 068			136 068		
% censored	75.1%			75.1%		

* time interaction coefficient not reported

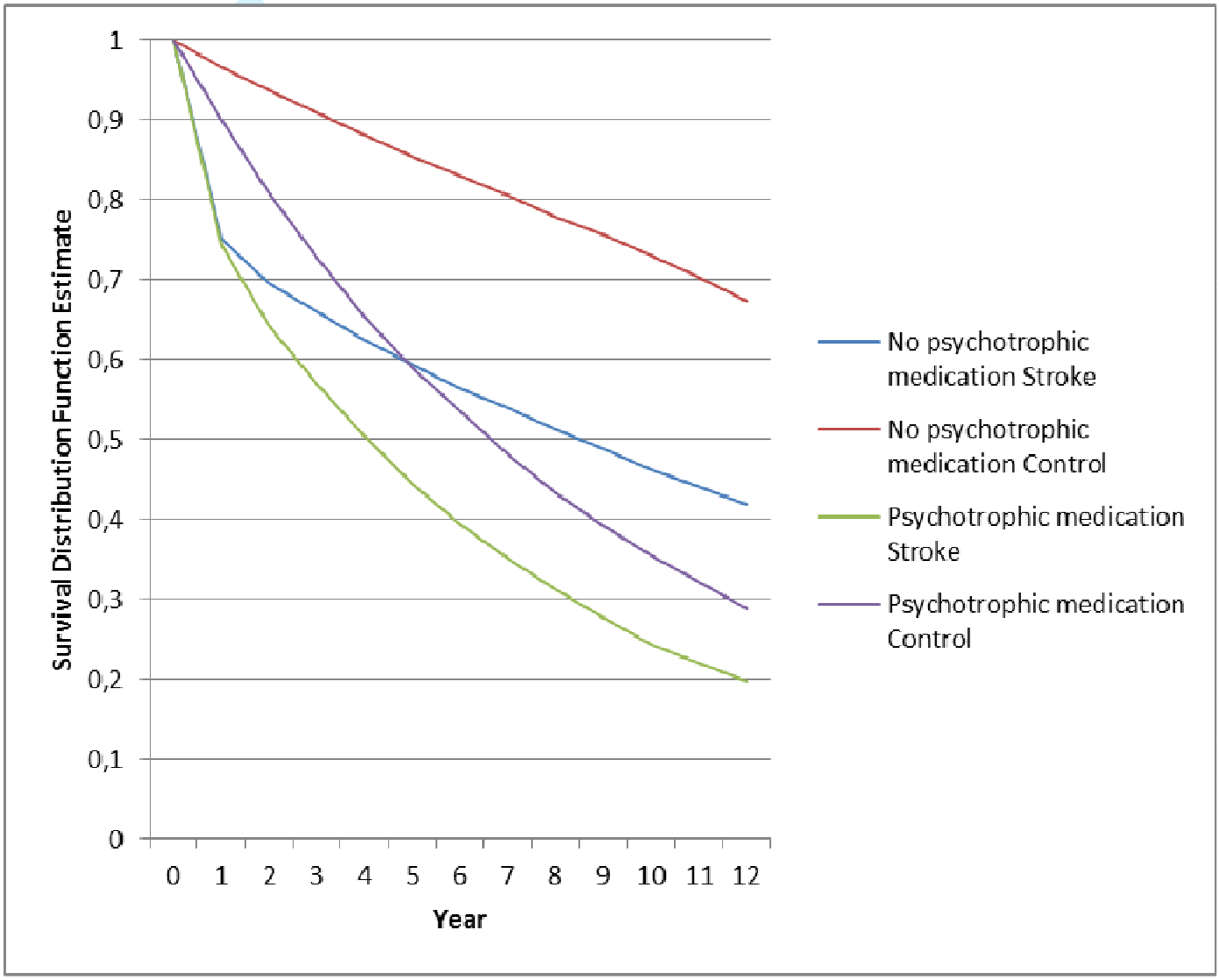
Note: Time-varying covariates were calculated in year 2, when all time-dependent covariates were significant in the time test

Estimate = a + a_t * year

Figure legends

Figure 1

Survival by groups: total stroke patients versus total controls, and stroke patients versus controls subdivided into those treated or not treated with any psychotropic drugs, by years of follow-up.



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Mortality and use of psychotropic medication in stroke patients: a population-wide register-based study

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Key words: stroke, hypnotics, antidepressants, antipsychotics, benzodiazepines, all-cause mortality.

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ABSTRACT

Objectives: The study sought to describe whether psychotropic medication may have long-term side effects in stroke patients as compared to controls.

Setting: Use of all national register data from health care services were identified from the Danish National Patient Registry in Denmark. Information about psychotropic medication use was obtained from the Danish Register on Medicinal Product Statistics.

Objectives: We aimed to evaluate all-cause mortality in relation to the use of benzodiazepines, antidepressants and antipsychotics in stroke patients and matched controls.

Participants: Patients with a diagnosis of stroke and either no drug use or pre-index use of psychotropic medication (n = 49 968) and compared with control subjects (n = 86 100) matched on age, gender, marital status and community location.

Primary outcome measure: all-cause mortality

Results: All-cause mortality was higher in patients with previous stroke as compared to control subjects. Mortality hazard ratios were increased for subjects prescribed serotonergic antidepressant drugs (respectively, HR=1.699 (SD=0.030), P=0.001 in patients; HR=1.908 (0.022), P<0.001 in controls), tricyclic antidepressants (HR=1.365 (0.045), P<0.001; HR=1.733 (0.022), P<0.001), benzodiazepines (HR=1.643 (0.040), P<0.001); HR=1.776 (0.053), P<0.001), benzodiazepine-like drugs (HR=1.776 (0.021), p=<0.001; HR=1.547 (0.025, p<0.001), first-generation antipsychotics (HR=2.001 (0.076), p<0.001; HR=3.361 (0.159), P<0.001), and second-generation antipsychotics (HR=1.645 (0.070), p<0.001; HR=2.555 (0.086), p<0.001), as compared with no drug use. Interaction analysis suggested statistically significantly higher mortality hazard ratios for most classes of psychotropic drugs in controls compared with stroke patients.

Conclusion: All-cause mortality was higher in stroke patients and controls treated with benzodiazepines, antidepressants and antipsychotics than in their untreated counterparts. Our findings suggest that care should be taken in the use and prescription of such drugs, and that they should be used in conjunction with adequate clinical controls.

Strengths and limitations of this study

- Hypnotics, antidepressants and antipsychotics are more frequently used in stroke patients than in controls, and is associated with greater all-cause mortality in stroke patients and matched controls.
- Care should be taken in the use and prescription of such drugs, and that they should be used in conjunction with adequate clinical control.
- The strengths of the National Patient Registry includes the following: it is a national database that includes all identified patients and comorbid conditions and psychotropic medication, it is time-locked (all reports must be associated with patient contacts) and includes a substantial follow-up period.
- The limitation of the study is that although the study is controlled, it is not a randomized controlled trial, which means there is a potential bias towards more severe diseases among treated patients.

Introduction

Stroke is one of the most important neurological causes of morbidity, mortality and disability and affects a significant proportion of the population. Stroke has deleterious effects on patients' social function, employment, quality of life, and the disease entails a societal burden that is manifested as increased direct and indirect costs [1]. Early intervention and management of stroke in recent years have significantly improved prognosis, with reduced mortality and fewer neurological deficits. After the acute phase, up to 40% of patients suffer from post-stroke depression within the first year [2], and patients may suffer from comorbid insomnia and psychiatric symptoms, such as hallucinations and other psychotic symptoms[3].

In recent years, the increased frequency of off-label use of psychotropic drugs, their side effects, and the harm they may cause have been a growing concern [4-6]. Studies of large groups of patients with psychotic diseases and of patients with chronic insomnia have raised concerns about increased mortality rates in benzodiazepine-treated patients, especially when used in combination with other psychotropic drugs [7-9]. There is additional concern about the association between benzodiazepine use and cognitive decline in Alzheimer's disease [10-13]. Stroke patients suffer from major comorbidities, including cardiac arrhythmias and sleep-related hypoxemia[14]. Few studies have addressed the effect on mortality when using antidepressants in post-stroke patients. These studies have found reduced mortality rates in short-term studies in patients treated during the stable phase [15], and there is also some evidence that the use of selective serotonin reuptake inhibitors (SSRIs) may improve recovery after stroke[16]. However, there have been no prospective studies of morbidity and mortality in stroke patients in relation to the use of psychotropic drugs.

The aim of this study was to evaluate the association between all-cause mortality and the use of benzodiazepines (BZDs), benzodiazepine-like (BZD-like) medications, tricyclic antidepressants (TCAs), SSRIs, serotonin noradrenaline reuptake inhibitors (SNRIs), and first-generation and second-generation antipsychotics (FGAs and SGAs) in stroke patients and matched controls.

Material and methods

Subjects

In Denmark, all hospital contacts are recorded in the National Patient Registry (NPR) with respect to the time of contact and information about primary and secondary diagnoses. The NPR includes administrative information and details on all diagnoses, diagnostic methods, hospitalizations, and ambulatory clinical contacts (initial and follow-up) in all public and private hospitals. These data are recorded using several international classification systems, including the International Classification of Diseases, 10th Edition (ICD-10). The NPR is a time-based nation-wide register that includes data from all inpatient and outpatient contacts. Thus, the

data extracted for this study are representative of all patients in Denmark who have been diagnosed with stroke, irrespective of other diagnoses. Data were available for the entire observation period, and thus we were able to trace patients retrospectively and prospectively, relative to the time of their diagnosis.

Using the NPR, we identified all patients diagnosed with stroke between 1997 and 2009. To identify stroke diagnoses, we used the ICD-10 codes I61: cerebral hemorrhage, I63: brain infarction, I64: stroke not otherwise defined as being due to infarction or hemorrhage. We observed 76.591 cases in the total period. Under evaluation for compliance 69,970 cases and 49,968 survived one year. The diagnosis code is recorded after patient evaluation in each hospital (based on a standardized evaluation of stroke). The expected distribution of stroke types is 15% hemorrhagic and 85% ischemic [17]. We did not include patients with a diagnosis of transitory ischemic episodes. Then, using data from Denmark's Civil Registration System Statistics, we randomly selected citizens of the same age, gender, county of residence and marital status as the patients, but who did not have a diagnosis of any stroke episodes. Parity of socio-economic status (SES) was ensured by selecting control subjects from the same part of the country in which the patient lived and by matching for partnership (including those married). A ratio of control subjects to patients of 2:1 was used to take into account the variation among the controls. Data from patients and matched controls that could not be identified in the Coherent Social Statistics database were excluded from the sample. The patients and matched control subjects were traced retrospectively and prospectively for up to 12 years in the NPR registry and prescription database. All observations were successfully matched at the year of diagnosis (index year). Patients and control subjects who could not be identified in the social security registry in the years before and after diagnosis (typically as a result of emigration) were excluded from the sample. More than 99% of the patients and controls had complete data.

Psychotropic medications studied

Information on type, number, dose and date of prescriptions were obtained from the Danish Register of Medicinal Product Statistics, which includes all medications prescribed outside hospitals. Seven medication classes were included in the analysis: BZDs, BZD-like, SSRIs, SNRIs, TCAs, FGAs and SGAs. Medication use was defined as filling of at least three prescriptions with a compliance rate of at least 60% in the 12 months before the index date. Compliance rate was defined as the daily defined dose (DDD) coverage of prescriptions and was set to 60% as an inclusion criterion. The no medication group was defined as those who had not collected any psychotropic drugs within 12 months prior to the index date or during the observation period. The compliance was determined in the pre-period for the compliant group. Non-compliant was defined as not meeting the compliance goal but collecting medication in the pre-period and they were excluded from the population. Non-user did not collect any medication in either the pre or post-period, so they are true non-users'

A substantial number of patients used medication before the year of diagnosis. We created a dummy variable to control for this in the regression. Some patients discontinued medication; they were identified by determining whether the most recent prescription had been collected more than three years before the end-point (stop parameter). Such cases were scored as zero in the analysis.

Statistical analyses

Morbidity and mortality data were extracted as primary and secondary diagnoses from the NPR in accordance with the World Health Organization (WHO) ICD-10 criteria. For the purpose of this study, we used all-cause morbidity and all-cause mortality data. To avoid the influence of mortality due to factors other than medication use, we only included patients and controls who had survived for at least 1 year after the index date and who were treated with not more than one psychotropic medication to avoid the influence of the others. Statistical analysis involved the development of proportional Cox hazard models in which survival was conditional on the explanatory variables of age, gender and use of medication types. Three regressions were performed, for the case and control groups separately, and for both groups. In the latter, a dummy variable indicating case *vs.* control and interaction terms for medication*control were included. The interaction term should indicate whether the effect of that particular medication on survival was different for the case and control groups. After conditioning on one year of survival (removing both cases and controls from the population), we tested the model for proportionality to make sure that the assumption for the proportional Cox model was met. Since this was not the case for some covariates, an extended Cox model was developed, using a time*interaction term for the covariates that were not proportional. The interpretations of the covariates were not straightforward once the interaction with time had been included. The effect of the non-proportional covariates on survival could be calculated for each year after the index date. Statistical analyses were performed using SAS 9 (SAS, Inc., Cary, NC, USA).

Ethics

The study was approved by the Danish Data Protection Agency. Data were anonymized and so neither individual nor ethical approval was required.

Results

In total, the study population comprised 49 968 patients suffering from ischemic, hemorrhagic or unspecified stroke and 86 100 controls. The descriptive information for the study population is shown in Table 1. Stroke patients suffered from high pre-index (i.e., 12 months prior to the index date) mortality.

The distribution of the patients and control subjects along with their treatment is shown in Table 1. In general, stroke patients were more frequently treated with a psychotropic drug than were the controls (Table 1).

Survival after a stroke diagnosis

Survival data with respect to total pre-index medication use in stroke patients and their controls are shown in Figure 1 subdivided into treatment with any of the psychotropic drugs or not. Mortality hazard ratios for each class of medication are shown in Table 2 and the results of the Cox model with interactions in Table 3 adjusted for the effect of age, gender and Charlson comorbidity index. Survival was generally lower, with increased mortality hazard ratios, for all drug classes in both stroke patients and controls. We found statistically significant interactions between group and psychotropic medication regarding TCAs, SSRIs, BZD-like and SGAs (Table 3), i.e. the associations of excess risk of death with use of these classes of psychotropic medications were more pronounced in control subjects compared with stroke patients. The Hazard Ratios was highest among controls using any of the psychotropic drugs as compared to stroke patients (Table 3).

Discussion

This study, which included data from a nation-wide patient registry, yielded several important findings: a) psychotropic drugs are more frequently used by stroke patients than by matched control individuals; b) psychotropic drugs are generally associated with increased mortality, the highest mortality being observed in stroke patients and control subjects treated with antipsychotics, c) control subjects showed higher mortality hazard ratios (SSRI, TCA and BZD-like) as compared to stroke patients, and d) this association is present after adjusting for comorbidities and avoiding the initial phase with high mortality which may be due to the stroke and multiple comorbidities immediately after the stroke.

The higher mortality with the use of benzodiazepines, antidepressants and antipsychotics in patients with stroke was not exclusively associated with the presence of stroke because the association was also found in control subjects. Previous studies have evaluated the mortality rates associated with BZDs in patients with other conditions, including patients with insomnia [7;8], patients in dialysis [18], and those with depression [19]. The need for further evaluation of the use of antidepressants and antipsychotics and their associations with morbidity, including metabolic syndrome and mortality in other groups of patients including psychiatric, neurodegenerative and cardiac diseases has been stressed by many authors [20-24]. A major concern about studies of this type is whether the group of people receiving treatment is a population with intrinsically higher comorbidity rates than the untreated population. We cannot discount this possibility in the population considered here. Depression is associated with an increased risk of developing cardiac and cerebrovascular events [25;26], and with new events in established cardiovascular patients [27]. Patients with stroke are more likely to be treated for depression [28-30] and to suffer from insomnia [31] and depressive symptoms [32;33]. Earlier studies addressed the potentially greater mortality in stroke patients using antipsychotics [33-35]. All-cause mortality is increased in psychiatric diseases, the highest rates are found among

psychosis, followed by depression and anxiety[36]. The increase in mortality in this study may be related to the underlying psychiatric disorder rather than to its treatment. In a recent study, lower mortality was found among schizophrenia patients with moderate antipsychotic and antidepressant medication but higher mortality when treated with benzodiazepines[37]. These findings suggest that drug-related mortality may depend on the psychiatric or neurological disorder in question. Although not proving that comorbid conditions play a role in the higher mortality of those treated with psychotropic drugs, it does suggest that the relation is associated with effect of the drugs. We included three major classes of psychotropic drugs in this study to evaluate the effects of their individual use. We also included the use of BZD-like drugs as it has previously been assumed that these drugs are safer than benzodiazepines. We found no such effect; there was no major difference in mortality between BZD and BZD-like drugs. This population is one of the largest ever studied, but, even though we found that the risk was still higher for SSRIs, BZD-like drugs and antipsychotics, our results suggest that even larger population-based studies, with longer follow-up times, are required. This is reflected in Table 3, which illustrates a subgroup analysis of specific groups of drugs that attempts to evaluate the different types. Further sub-classification of morbidities that adequately controls for different types of psychiatric and medical diagnosis would require an even larger dataset.

There are several factors that could explain why some of the drugs studied might affect morbidity and even mortality rates. The drugs may affect arousals from sleep, metabolic, respiratory, autonomic and cardiac function [38-40]. BZDs may induce upper-airway collapse and potentially affect respiration. Use of clonazepam has been reported to induce sleep apnea [41]. This is potentially important as sleep apnea is very common in stroke patients [31]. The respiratory depression of hypnotics has not been fully identified in polysomnography studies [42]. These studies are performed under controlled circumstances in a small number of selected patients, while natural usage includes unselected patients in their natural environment, where dose and presence of other risk factors (e.g., co-medication, sleep deprivation, and alcohol consumption) are not controlled for. Overdoses and combinations have been reported in patients admitted to emergency rooms [43]. Furthermore, predictors of higher mortality include male gender, increasing age and lower educational level, combined with alcohol consumption and inappropriate lifestyles — factors that may be associated with the use of psychotropic drugs and that are not taken into consideration in clinical laboratory testing. Another Danish study confirmed our findings of higher total mortality but lower cardiovascular mortality among SSRI-treated stroke patients. It was concluded that this was due to the higher hemorrhagic mortality in treated patients [44]. Consequently, future studies should explore the relationship between psychotropic drugs, morbidity and mortality in greater detail.

In this study, we carried out a total evaluation, controlling for gender, age and demographic variables, which are all known to influence disease outcome, and for comorbidities. We also avoided the initial period when patients are much frailer and mortality rates are high due to the direct effect of the stroke, and the great comorbidity in these patients.

As such, we believe that the risk associations found in the study are conservative, as is further supported by the finding that the risk association in stroke patients is lower than in controls.

The study has a number of limitations: a) it is based on clinic/hospital reports to the NPR; b) the diagnostic accuracy depends on the clinic's presentation and reporting of the diagnosis and any comorbidities; c) confounder variables (e.g., BMI and other cardiovascular risk factors) were not recorded; d) symptoms and clinical evaluation results were not considered (e.g., those measured by polysomnography, limited channel polygraphy and cardiac evaluations), so we could not relate our findings to disease severity. We did not exclude diseases, especially unidentified stroke, in the controls. The types of medication given on prescription are highly controlled in Denmark, but we do not know whether the drugs were taken or shared, or if they were taken from someone else's prescription (e.g., that of the patient's spouse). Nevertheless, we believe that using at least three prescriptions indicates more chronic use. We have no definitive explanation of the higher mortality rate among the controls compared with the stroke patients: one cause could be that we only included patients who survived after one year. Evaluation of the total population showed smaller differences, so it is likely that those who survived the stroke incident have higher survival rates despite the treatment with psychotropic drugs.

The strengths of the NPR, however, are that it is a national database that includes all identified patients and comorbid conditions and psychotropic medication, it is time-locked (all reports must be associated with patient contacts) and includes a substantial follow-up period. In addition, although the study is controlled, it is not a randomized controlled trial, which means there is a potential bias towards more severe diseases among treated patients.

We conclude that use of hypnotics, antidepressants and antipsychotics is more frequently used pre-index in stroke patients than in controls, and is associated with greater all-cause mortality in stroke patients and matched controls.

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Competing interest: none of the authors report competing.

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Reference List

(1) Cox AM, McKevitt C, Rudd AG, Wolfe CD. Socioeconomic status and stroke. *Lancet Neurol* 2006; 5(2):181-188.

(2) Andersen G, Vestergaard K, Riis J, Lauritzen L. Incidence of post-stroke depression during the first year in a large unselected stroke population determined using a valid standardized rating scale. *Acta Psychiatr Scand* 1994; 90(3):190-195.

(3) Mayer G, Jennum P, Riemann D, Dauvilliers Y. Insomnia in central neurologic diseases--occurrence and management. *Sleep Med Rev* 2011; 15(6):369-378.

(4) Kripke DF, Klauber MR, Wingard DL, Fell RL, Assmus JD, Garfinkel L. Mortality hazard associated with prescription hypnotics. *Biol Psychiatry* 1998; 43(9):687-693.

(5) Rintoul AC, Dobbin MD, Nielsen S, Degenhardt L, Drummer OH. Recent increase in detection of alprazolam in Victorian heroin-related deaths. *Med J Aust* 2013; 198(4):206-209.

(6) Merlo J, Ostergren PO, Mansson NO, Hanson BS, Ranstam J, Blennow G et al. Mortality in elderly men with low psychosocial coping resources using anxiolytic-hypnotic drugs. *Scand J Public Health* 2000; 28(4):294-297.

(7) Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2012; 2(1):e000850.

(8) Mallon L, Broman JE, Hetta J. Is usage of hypnotics associated with mortality? *Sleep Med* 2009; 10(3):279-286.

(9) Jennum P, Baandrup L, Ibsen R, Kjellberg J. Increased all-cause mortality with use of psychotropic medication in dementia patients and controls: A population-based register study. *Eur Neuropsychopharmacol* 2015.

(10) Montastruc F, Gardette V, Cantet C, Piau A, Lapeyre-Mestre M, Vellas B et al. Potentially inappropriate medication use among patients with Alzheimer disease in the REAL.FR cohort: be aware of atropinic and benzodiazepine drugs! *Eur J Clin Pharmacol* 2013; 69(8):1589-1597.

(11) Lauterbach EC. Use of psychotropic medication in Alzheimer's disease is associated with more rapid cognitive and functional decline. *Evid Based Med* 2013; 18(5):e50.

(12) Rosenberg PB, Mielke MM, Han D, Leoutsakos JS, Lyketsos CG, Rabins PV et al. The association of psychotropic medication use with the cognitive, functional, and

neuropsychiatric trajectory of Alzheimer's disease. *Int J Geriatr Psychiatry* 2012; 27(12):1248-1257.

(13) Vigen CL, Mack WJ, Keefe RS, Sano M, Sultzer DL, Stroup TS et al. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. *Am J Psychiatry* 2011; 168(8):831-839.

(14) Hermann DM, Bassetti CL. Sleep-related breathing and sleep-wake disturbances in ischemic stroke. *Neurology* 2009; 73(16):1313-1322.

(15) Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. *Am J Psychiatry* 2003; 160(10):1823-1829.

(16) Mead GE, Hsieh CF, Hackett M. Selective serotonin reuptake inhibitors for stroke recovery. *JAMA* 2013; 310(10):1066-1067.

(17) Wildenschild C, Mehnert F, Thomsen RW, Iversen HK, Vestergaard K, Ingeman A et al. Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. *Clin Epidemiol* 2014; 6:27-36.

(18) Winkelmayer WC, Mehta J, Wang PS. Benzodiazepine use and mortality of incident dialysis patients in the United States. *Kidney Int* 2007; 72(11):1388-1393.

(19) Allgulander C. Psychoactive drug use in a general population sample, Sweden: correlates with perceived health, psychiatric diagnoses, and mortality in an automated record-linkage study. *Am J Public Health* 1989; 79(8):1006-1010.

(20) Baandrup L, Jennum P, Lublin H, Glenthoj B. Treatment options for residual insomnia in schizophrenia. *Acta Psychiatr Scand* 2013; 127(1):81-82.

(21) Bhalerao S, Seyfried LS, Kim HM, Chiang C, Kavanagh J, Kales HC. Mortality risk with the use of atypical antipsychotics in later-life bipolar disorder. *J Geriatr Psychiatry Neurol* 2012; 25(1):29-36.

(22) Marras C, Gruneir A, Wang X, Fischer H, Gill SS, Herrmann N et al. Antipsychotics and mortality in Parkinsonism. *Am J Geriatr Psychiatry* 2012; 20(2):149-158.

(23) Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C et al. Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry* 2012; 169(1):71-79.

(24) Honkola J, Hookana E, Malinen S, Kaikkonen KS, Junttila MJ, Isohanni M et al. Psychotropic medications and the risk of sudden cardiac death during an acute coronary event. *Eur Heart J* 2012; 33(6):745-751.

(25) Jackson CA, Mishra GD. Depression and risk of stroke in midaged women: a prospective longitudinal study. *Stroke* 2013; 44(6):1555-1560.

(26) Majed B, Arveiler D, Bingham A, Ferrieres J, Ruidavets JB, Montaye M et al. Depressive symptoms, a time-dependent risk factor for coronary heart disease and stroke in middle-aged men: the PRIME Study. *Stroke* 2012; 43(7):1761-1767.

(27) Nielsen TJ, Vestergaard M, Christensen B, Christensen KS, Larsen KK. Mental health status and risk of new cardiovascular events or death in patients with myocardial infarction: a population-based cohort study. *BMJ Open* 2013; 3(8).

(28) Flaster M, Sharma A, Rao M. Poststroke depression: a review emphasizing the role of prophylactic treatment and synergy with treatment for motor recovery. *Top Stroke Rehabil* 2013; 20(2):139-150.

(29) Seifert CL, Poppert H, Sander D, Feurer R, Etgen T, Ander KH et al. Depressive symptoms and the risk of ischemic stroke in the elderly--influence of age and sex. *PLoS One* 2012; 7(11):e50803.

(30) El HN, Goldstein LB, Peterson ED, Zhao X, Pan W, Olson DM et al. Depression and antidepressant use after stroke and transient ischemic attack. *Stroke* 2012; 43(6):1609-1616.

(31) Mayer G, Jennum P, Riemann D, Dauvilliers Y. Insomnia in central neurologic diseases--occurrence and management. *Sleep Med Rev* 2011; 15(6):369-378.

(32) Wang S, Linkletter C, Dore D, Mor V, Buka S, Maclure M. Age, antipsychotics, and the risk of ischemic stroke in the Veterans Health Administration. *Stroke* 2012; 43(1):28-31.

(33) Pratt NL, Roughead EE, Ramsay E, Salter A, Ryan P. Risk of hospitalization for stroke associated with antipsychotic use in the elderly: a self-controlled case series. *Drugs Aging* 2010; 27(11):885-893.

(34) Glenn MB. Sudden cardiac death and stroke with the use of antipsychotic medications: implications for clinicians treating individuals with traumatic brain injury. *J Head Trauma Rehabil* 2010; 25(1):68-70.

(35) Sacchetti E, Trifiro G, Caputi A, Turrina C, Spina E, Cricelli C et al. Risk of stroke with typical and atypical anti-psychotics: a retrospective cohort study including unexposed subjects. *J Psychopharmacol* 2008; 22(1):39-46.

(36) Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry* 2015; 72(4):334-341.

(37) Tiihonen J, Mittendorfer-Rutz E, Torniainen M, Alexanderson K, Tanskanen A. Mortality and Cumulative Exposure to Antipsychotics, Antidepressants, and Benzodiazepines in Patients With Schizophrenia: An Observational Follow-Up Study. *Am J Psychiatry* 2015;appiajp201515050618.

(38) Gueye PN, Lofaso F, Borron SW, Mellerio F, Vicaut E, Harf A et al. Mechanism of respiratory insufficiency in pure or mixed drug-induced coma involving benzodiazepines. *J Toxicol Clin Toxicol* 2002; 40(1):35-47.

(39) Wilton LV, Heeley EL, Pickering RM, Shakir SA. Comparative study of mortality rates and cardiac dysrhythmias in post-marketing surveillance studies of sertindole and two other atypical antipsychotic drugs, risperidone and olanzapine. *J Psychopharmacol* 2001; 15(2):120-126.

(40) Czekalla J, Kollack-Walker S, Beasley CM, Jr. Cardiac safety parameters of olanzapine: comparison with other atypical and typical antipsychotics. *J Clin Psychiatry* 2001; 62 Suppl 2:35-40.

(41) Schuld A, Kraus T, Haack M, Hinze-Selch D, Pollmacher T. Obstructive sleep apnea syndrome induced by clonazepam in a narcoleptic patient with REM-sleep-behavior disorder. *J Sleep Res* 1999; 8(4):321-322.

(42) Sivertsen B, Omvik S, Pallesen S, Nordhus IH, Bjorvatn B. Sleep and sleep disorders in chronic users of zopiclone and drug-free insomniacs. *J Clin Sleep Med* 2009; 5(4):349-354.

(43) Henderson A, Wright M, Pond SM. Experience with 732 acute overdose patients admitted to an intensive care unit over six years. *Med J Aust* 1993; 158(1):28-30.

(44) Mortensen JK, Larsson H, Johnsen SP, Andersen G. Post stroke use of selective serotonin reuptake inhibitors and clinical outcome among patients with ischemic stroke: a nationwide propensity score-matched follow-up study. *Stroke* 2013; 44(2):420-426.

Table 1 Number of the total population conditioned on 1 year of survival after the first onset of stroke, classified as stroke patients and their controls, and their distribution with respect to psychotropic drug use.

	Stroke patients		Controls		
	N	%	N	%	P
Age (mean, SD)	66.6	14.4	65.3	14.5	
Gender (female)	21 995	44.0	36 595	42.5	
No medication	33 778	67.6	72 707	84.4	<0.001
SSRI/SNRI	8366	16.7	6789	7.9	<0.001
TCA	1082	2.2	756	0.9	<0.001
BZD	4675	9.4	3542	4.1	<0.001
Z-drugs	5165	10.3	4331	5.0	<0.001
FGA	381	0.8	349	0.4	<0.001
SGA	511	1.0	421	0.5	<0.001
Charlson comorbidity index (mean, SD)	0.8	0.8	0.1	0.4	<0.001
All	49 968		86 100		

Abbreviations:
SSRI: Selective serotonin reuptake inhibitors
SNRI: Serotonin–norepinephrine reuptake inhibitors
TCA: Tricyclic antidepressants
BZD: Benzodiazepines
FGA: First-generation antipsychotics
SGA: Second-generation antipsychotics

Table 2 Hazard ratios of mortality in stroke and control subjects.

	Stroke patients			Controls		
	Hazard ratio	SD	P	Hazard ratio	SD	P
Age	**1.087***	<0.001	<0.001	**1.114**	<0.001	<0.001
Gender (female)	**0.786**	0.016	<0.001	**0.679**	0.017	<0.001
Charlson comorbidity index	**1.076***	0.014	<0.001	**1.403***	0.014	<0.001
SSRI (incl. SNRI)	**1.699***	0.030	<0.001	**1.908**	0.022	<0.001
TCA	**1.365**	0.045	<0.001	**1.733**	0.060	<0.001
BZD	**1.643***	0.040	<0.001	**1.776***	0.053	<0.001
BZD-like	**1.386**	0.021	<0.001	**1.547**	0.025	<0.001
FGA	**2.001**	0.076	<0.001	**3.361***	0.159	<0.001
SGA	**1.645**	0.070	<0.001	**2.555**	0.086	<0.001
Observations	49 968			100 86		
% censored	64.5%			81.3%		

Note: time*interaction coefficient not reported

*Time-varying covariates were calculated in year 2, when all time-dependent covariates were significant in the time test

Estimate = a + a_t * year

Abbreviations:

SSRI: Selective serotonin reuptake inhibitors

SNRIs: Serotonin–norepinephrine reuptake inhibitors

TCA: Tricyclic antidepressants

BZDs: Benzodiazepines

FGAs: First-generation antipsychotics

SGAs: Second-generation antipsychotics

Table 3 Mortality hazard ratios for psychotropic drugs in the total study sample.

	Basic Cox model*			Cox model with interactions*		
	Hazard ratio	SD	P	Hazard ratio	SD	P
Age	**1.102**	0.001	<0.001	**1.102**	0.001	<0.001
Gender (female)	**0.734**	0.012	<0.001	**0.734**	0.012	<0.001
Control group	**0.600**	0.013	<0.001	**0.547**	0.015	<0.001
Charlson comorbidity index	**1.175**	0.010	<0.001	**1.169**	0.010	<0.001
SSRI (incl. SNRI)	**1.737**	0.014	<0.001	**1.270**	0.029	<0.001
TCA	**1.500**	0.036	<0.001	**1.404**	0.045	<0.001
BZD	**1.720**	0.032	<0.001	**1.532**	0.023	<0.001
BZD-like	**1.536**	0.027	<0.001	**1.340**	0.021	<0.001
FGA	**2.374**	0.057	<0.001	**2.260**	0.076	<0.001
SGA	**1.934**	0.054	<0.001	**1.745**	0.070	<0.001
Interactions						
Control*SSRI				**1.165**	0.045	<0.001
Control*TCA				**1.209**	0.075	0.011
Control*BZD				1.164	0.057	0.143
Control*BZD-like				**1.236**	0.032	<0.001
Control*FGA				1.125	0.115	0.305
Control*SGA				**1.327**	0.111	0.011
Observations	136 068			136 068		
% censored	75.1%			75.1%		

* time interaction coefficient not reported

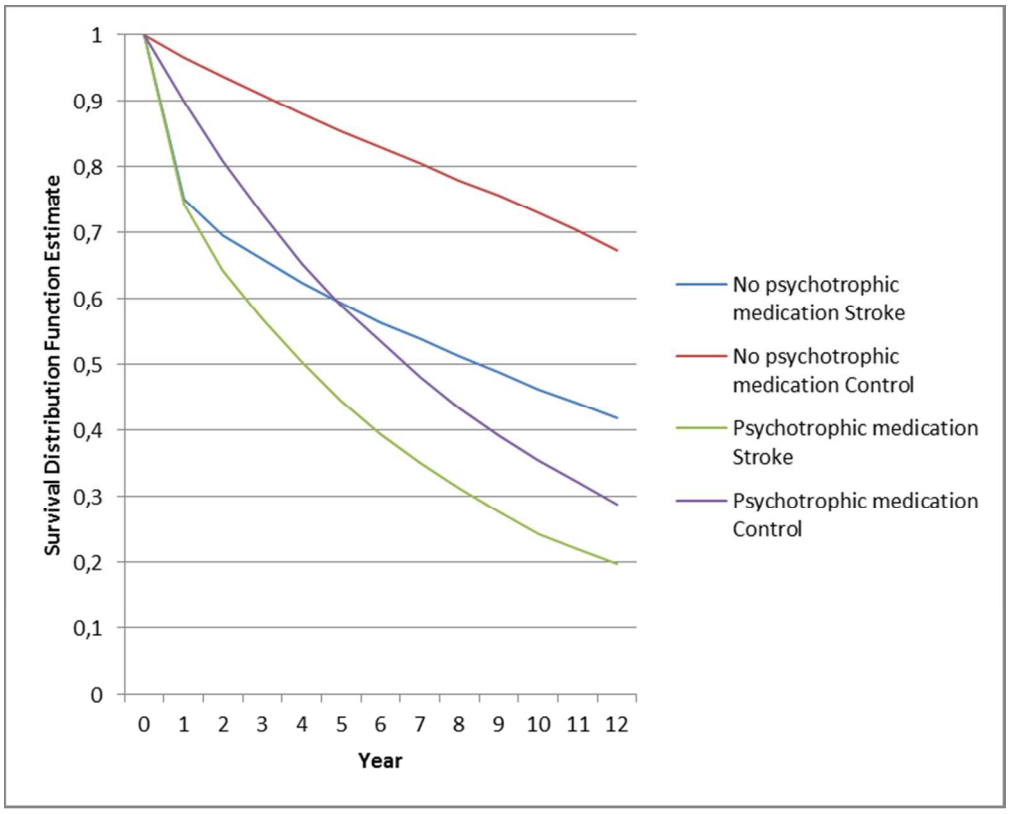
Note: Time-varying covariates were calculated in year 2, when all time-dependent covariates were significant in the time test

Estimate = a + a_t * year

Figure legends

Figure 1

Survival by groups: total stroke patients versus total controls, and stroke patients versus controls subdivided into those treated or not treated with any psychotropic drugs, by years of follow-up.



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