PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Mortality and use of psychotropic medication in stroke patients: a population-wide register-based study
AUTHORS	Jennum, Poul; Baandrup, Lone; Iversen, Helle; Ibsen, Rikke; Kjellberg, Jakob

VERSION 1 - REVIEW

REVIEWER	Sergio Starkstein School of Psychiatry and Neurosciences University of Western Australia Australia
REVIEW RETURNED	10-Dec-2015

GENERAL COMMENTS	Jennum et al examined all-cause mortality for psychotropic medication in stroke patients as compared to controls using the Danish National Patient Registry and the Danish Register on Medicinal Product Statistics. Mortality hazard ratios were increased for SSRIs, tricyclic antidepressants, benzodiazepines, “benzodiazepine-like” drugs, and first- and second-generation antipsychotics. Interestingly, mortality was higher in non-stroke as compared to stroke individuals. The authors concluded that care should be taken in prescribing psychoactive agents. This is an interesting study looking at the impact of psychoactive medication upon stroke survival. One of the strengths of the study is the use of a national registry that includes medical comorbidities as well as time-locked use of psychoactive medication. Moreover, only patients and controls taking one type of psychotropic drug were included in the study. The main question arising from the results is why do all psychoactive drugs cause increased mortality, and why is this mortality lower among stroke patients? One of the limitations with the study is that we are not provided with psychiatric diagnoses and their prevalence for individuals on or off medication. The relevance of this remark is that psychiatric disorders are significantly related to increased mortality. A recent meta-analysis (JAMA Psychiatry 2015;72:334-341) reported a relative risk of all-cause mortality for psychosis of 2.54, whereas the risk for depression was 1.71 and the risk for anxiety was 1.43. Therefore, the increase in mortality in this study may be related to the underlying psychiatric disorder rather than to its treatment. These findings are somewhat discrepant with the findings of a recent study by Tiihonen (not available to the authors at the time of submission) which suggests quite different results among individuals

	with schizophrenia: they found decreased overall mortality with neuroleptic and/or antidepressant use and higher mortality with benzodiazepine use. These findings suggest that drug-related mortality may depend on the psychiatric or neurological disorder in question. The authors should comment on two studies (Jorge et al, Am J Psychiatry 2003;160:1823-9 and Ried et al Ann Pharmacother 2011;45:888-97) showing that tricyclic antidepressants and SSRIs decreased post-stroke mortality. There is also some evidence suggesting that SSRIs may improve recovery after stroke (Mead et al JAMA 2013;11:1066-7). An intriguing finding of the study is that the control group had higher mortality hazard ratios for any psychotropic drug as compared to the stroke group. This counterintuitive finding should be properly discussed. It would be interesting to know whether any other medication unrelated to psychotropic drugs (e.g. antibiotics) are also associated with higher mortality in stroke (and in non-stroke individuals as well). Interventions for psychiatric disorders in neuropsychiatric conditions are difficult to carry out. Thus, we witness an increasing number of meta-analyses which include studies with important if not critical differences, population studies based on registers which include enormous samples but uncertainty as to the reliability of the main outcomes, retrospective studies with unclear value, and prospective studies which usually have low power. These are difficult times for clinicians wo have to make decisions on behalf of their patients. Should they treat post-stroke depression with antidepressants or should they worry about a higher mortality putatively related to the drug? Should benzodiazepines be excluded from psychiatric treatments, or could it be the case than when judiciously used these drugs may truly improve the quality of life of patients? And finally, medicine needs to face the ethical dilemma whether length of life is more relevant than a fulfilled life.

REVIEWER	Andreas Terent Medical Sciences Uppsala University Hospital Sweden
REVIEW RETURNED	31-Dec-2015

GENERAL COMMENTS	Abstract (page 2) 1. Objective: “to describe whether psychotropic medication may have long-term side effects in stroke patients compared to controls”. This was not found – on the contrary, all types of PM was associated with increased mortality both in patients and controls – in fact the association was stronger among controls for four drug classes; SSRI, tricyclic antidepressants, benzodiazepine-like drugs and second generation of antipsychotic drugs. This indicates “bias towards more severe disease among PM treated patients” (page 3 – strengths and limitations). Therefore: 2. The conclusion “Our findings suggest that care should be taken in the use of and prescription of such drugs” may be inadequate. Introduction (page 4) 1. “Stroke patients …there is general consensus that the use of respiratory depressants should be avoided”? No reference to such

	consensus is given. Material and methods (page 5) 1. All stroke patients in Denmark during the years 1997 to 2009 were identified. How many were there in total – before exclusions? 2. “The expected distribution of stroke subtypes is 15% hemorrhagic and 85% ischemic”. But which was the actual distribution of stroke subtypes in this cohort of one-year survivors? 3. How was use of PM after index stroke defined? Users (3 prescriptions and 60% of DDD during one year), non-users (all other patients including those with 2 prescriptions and 59% of DDD)? Results (page 6 and tables and figure) 1. 49 968 patients – out of how many in total during 12 years? 2. Mean age 66 years – lower than expected due to exclusion of those who died within 1 year? 3. Survival curves show identical survival in patients and controls after 1 year. Discussion (page 7 and 8) 1. Very lengthy discussion of PM in general in relation to the actual findings of this study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Sergio Starkstein
Institution and Country: School of Psychiatry and Neurosciences, University of Western Australia, Australia Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Jennum et al examined all-cause mortality for psychotropic medication in stroke patients as compared to controls using the Danish National Patient Registry and the Danish Register on Medicinal Product Statistics. Mortality hazard ratios were increased for SSRIs, tricyclic antidepressants, benzodiazepines, “benzodiazepine-like” drugs, and first- and second-generation antipsychotics. Interestingly, mortality was higher in non-stroke as compared to stroke individuals. The authors concluded that care should be taken in prescribing psychoactive agents.

This is an interesting study looking at the impact of psychoactive medication upon stroke survival. One of the strengths of the study is the use of a national registry that includes medical comorbidities as well as time-locked use of psychoactive medication. Moreover, only patients and controls taking one type of psychotropic drug were included in the study.

The main question arising from the results is why do all psychoactive drugs cause increased mortality, and why is this mortality lower among stroke patients?

One of the limitations with the study is that we are not provided with psychiatric diagnoses and their prevalence for individuals on or off medication. The relevance of this remark is that psychiatric disorders are significantly related to increased mortality. A recent meta-analysis (JAMA Psychiatry 2015;72:334-341) reported a relative risk of all-cause mortality for psychosis of 2.54, whereas the risk for depression was 1.71 and the risk for anxiety was 1.43. Therefore, the increase in mortality in this study may be related to the underlying psychiatric disorder rather than to its treatment.

These findings are somewhat discrepant with the findings of a recent study by Tiihonen (not available to the authors at the time of submission) which suggests quite different results among individuals with schizophrenia: they found decreased overall mortality with neuroleptic and/or antidepressant use and

higher mortality with benzodiazepine use. These findings suggest that drug-related mortality may depend on the psychiatric or neurological disorder in question.

This is included in the discussion.

The authors should comment on two studies (Jorge et al, Am J Psychiatry 2003;160:1823-9 and Ried et al Ann Pharmacother 2011;45:888-97) showing that tricyclic antidepressants and SSRIs decreased post-stroke mortality. There is also some evidence suggesting that SSRIs may improve recovery after stroke (Mead et al JAMA 2013;11:1066-7).

Included in the citation.

An intriguing finding of the study is that the control group had higher mortality hazard ratios for any psychotropic drug as compared to the stroke group. This counterintuitive finding should be properly discussed. It would be interesting to know whether any other medication unrelated to psychotropic drugs (e.g. antibiotics) are also associated with higher mortality in stroke (and in non-stroke individuals as well).

This is an interesting question. However the use of antibiotics would apply for infection which is also associated with underlying disease. We speculated about this, but we are not sure whether we in fact would answer the question of the causality.

Interventions for psychiatric disorders in neuropsychiatric conditions are difficult to carry out. Thus, we witness an increasing number of meta-analyses which include studies with important if not critical differences, population studies based on registers which include enormous samples but uncertainty as to the reliability of the main outcomes, retrospective studies with unclear value, and prospective studies which usually have low power. These are difficult times for clinicians wo have to make decisions on behalf of their patients. Should they treat post-stroke depression with antidepressants or should they worry about a higher mortality putatively related to the drug? Should benzodiazepines be excluded from psychiatric treatments, or could it be the case than when judiciously used these drugs may truly improve the quality of life of patients? And finally, medicine needs to face the ethical dilemma whether length of life is more relevant than a fulfilled life.

We agree on these important questions, it is therefore important to discuss these issues in current and future management of the patients. I have been in doubt to which extend this is a general comments or we should include it. It is a little in conflict we reviewer II, who which a shorter discussion.

Reviewer: 2
Reviewer Name: Andreas Terent
Institution and Country: Medical Sciences, Uppsala University Hospital, Sweden Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below

Abstract (page 2)
1. Objective: “to describe whether psychotropic medication may have long-term side effects in stroke patients compared to controls”. This was not found – on the contrary, all types of PM was associated with increased mortality both in patients and controls – in fact the association was stronger among controls for four drug classes; SSRI, tricyclic antidepressants, benzodiazepine-like drugs and second generation of antipsychotic drugs. This indicates “bias towards more severe disease among PM

treated patients" (page 3 – strengths and limitations). Therefore:
2. The conclusion "Our findings suggest that care should be taken in the use of and prescription of such drugs" may be inadequate.
We have deleted the sentence, although we believe that indication and use of drugs should always rely on specific clinical indication with adequate control of treatment.
Introduction (page 4)
3. "Stroke patients …there is general consensus that the use of respiratory depressants should be avoided"? No reference to such consensus is given.
Correct this is not specified, the sentence is deleted, a reference to stroke and SDB is presented
Material and methods (page 5)
4.. All stroke patients in Denmark during the years 1997 to 2009 were identified. How many were there in total – before exclusions?
This is mentioned in the Subjects specified on diagnosis.
2. "The expected distribution of stroke subtypes is 15% hemorrhagic and 85% ischemic". But which was the actual distribution of stroke subtypes in this cohort of one-year survivors?
The numbers from the original inclusion is mentioned in the results
3. How was use of PM after index stroke defined? Users (3 prescriptions and 60% of DDD during one year), non-users (all other patients including those with 2 prescriptions and 59% of DDD)?
We inserted: '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'
Results (page 6 and tables and figure)
49 968 patients – out of how many in total during 12 years?
This is mentioned in the text
2. Mean age 66 years – lower than expected due to exclusion of those who died within 1 year?
One must assume, that the mean age will be lower when we condition on 1 year survival. The survival for all (including the persons who die within a year) is 69 years.
3. Survival curves show identical survival in patients and controls after 1 year.
The survival was very close after 1 year in the two groups so graphically it looked similar but is not the case.
Discussion (page 7 and 8)
1. Very lengthy discussion of PM in general in relation to the actual findings of this study.
We are of this, we deleted slightly.