Selective serotonin reuptake inhibitors (SSRIs) for stroke (Protocol)

Mead GE, Hankey GJ, Kutlubaev MA, Lee R, Bailey M, Hackett ML

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[Intervention Protocol]

Selective serotonin reuptake inhibitors (SSRIs) for stroke

Gillian E Mead[1], Graeme J Hankey[2], Mansur A Kutlubaev[3], Rebecca Lee[4], Matthew Bailey[5], Maree L Hackett[6]

[1]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK. [2]Department of Neurology, Royal Perth Hospital, Perth, Australia. [3]Division of Clinical Neurosciences, Western General Hospital, Edinburgh, UK. [4]Department of Medicine of the Elderly, Western General Hospital, Edinburgh, UK. [5]Department of Medicine of the Elderly, Liberton Hospital, Edinburgh, UK. [6]Department of Neurological and Mental Health, The George Institute for International Health, Sydney, Australia

Contact address: Gillian E Mead, Centre for Clinical Brain Sciences, University of Edinburgh, Room S1642, Royal Infirmary, Little France Crescent, Edinburgh, EH16 4SA, UK. gillian.e.mead@ed.ac.uk. gmead@staffmail.ed.ac.uk.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

Our objective is to determine whether SSRIs improve recovery after stroke.

BACKGROUND

Description of the condition

Stroke is defined as a sudden onset focal neurological disturbance, assumed to be vascular in origin, and lasting more than 24 hours (Hatano 1976). Each year, it affects about 16 million people for the first time and causes about 5.7 million deaths (Strong 2007). Moreover, survivors of stroke account for about 51 million disability-adjusted life years (DALYs). This is because recovery of functional independence after stroke only occurs in about half of all survivors of stroke, and mainly during the first six months after a stroke (Hankey 2007a; Hankey 2007b). Although major advances in the early reperfusion of ischaemic stroke have been realised in recent years, for example by intravenous thrombolysis and prevention of early recurrent stroke, effective, safe and widely accessible and affordable treatments that facilitate early and sustained recovery after stroke are urgently needed to further reduce the burdens of disability and dependency after stroke.

Description of the intervention

Selective serotonin reuptake inhibitors (SSRIs) are a class of drug that have been available for many years. Their main use in clinical practice is for mood disorders, particularly depression. They are sometimes used in stroke to manage emotionalism (Hackett 2010) (that is emotional behaviour that the patient reports as being outside normal control and which occurs in situations that previously would not have provoked such behaviour). Recently, SSRIs have been described in small studies as possibly having a favourable effect on motor recovery after stroke (Yi 2010; Chollet 2011). The recently published 'Fluoxetine on Motor Rehabilitation after Ischemic Stroke' (FLAME) trial reported that 15 (26%) of 56 acute stroke patients allocated to receive fluoxetine and 5 (9%) of 54 allocated to placebo had a modified Rankin score (mRS) of 0 to 2 (no dependency on other people) at three months, odds ratio (OR) of 3.8 (95% confidence interval (CI) 1.2 to 10.7) (Chollet 2011).

How the intervention might work

In animals, SSRIs have several potentially beneficial effects on both normal and diseased brain. First, SSRIs have a neurotrophic effect. Neurotrophins are a family of proteins that are involved in embryogenesis (formulation of an embryo) and organogenesis (development of organs). They control neural plasticity (ability to change, or easily changed or shaped) in adults, regulate synaptic activity and neurotransmitter synthesis and are essential for the regeneration of nerves (Lang 2004). Adult neurogenesis is generally restricted to specific areas of the brain, namely the subependymal cells of the ventricular system and the subgranular zone of the dentate gyrus in the hippocampus (Ming 2005). SSRIs increase neurogenesis and expression of neurotrophic or growth factors in the adult hippocampus (Schmidt 2007) and this is likely to account for the behavioural benefits of antidepressants in animals (Santarelli 2003). Importantly, several studies have shown that migration of new neurones to damaged areas of brain may occur (Wiltrout 2007) and that neurogenesis can also occur within areas of damaged brain in patients with ischaemic stroke (Taupin 2006). Secondly, fluoxetine may have a neuroprotective effect associated with its anti-inflammatory effect (for example repression of microglia activation) (Lim 2009) and enhancement of specific protein expression (hypoxia inducible factor-1 alpha, hemeoxygenaste-1) (Shin 2009). Thirdly, SSRIs can indirectly affect the adrenergic system through upregulation (that is increase a cellular component of a cell, such as ribonucleic acid (RNA) or protein, in response to an external variable) of beta1 receptors (Palvimaki 1994). In healthy humans, functional magnetic resonance imaging studies have demonstrated that fluoxetine can modulate cerebral motor activity (Loubinoux 1999). In eight patients with pure motor stroke given fluoxetine, there was hyperactivation in the ipsilesional (that is on the same side as the stroke lesion) primary motor cortex during a motor task; moreover, fluoxetine significantly improved motor skills of the affected side (Pariente 2001). Zittel et al investigated the effects of a single dose of 40 mg citalopram in eight chronic stroke patients; dexterity was significantly improved (Zittel 2008).

Why it is important to do this review

It is rare for treatments for neurological diseases such as stroke to have a dramatically favourable effect, such as that of fluoxetine on recovery after stroke as suggested by the FLAME trial (Chollet 2011). Treatments for stroke are far more likely to have a modest treatment effect, at best, which can nevertheless be clinically worthwhile. If modest but worthwhile treatment effects are to be reliably detected or refuted, then any errors in the evaluation of their effectiveness need to be much smaller than the effect of the treatment itself, otherwise the errors may nullify the effect of the treatment and lead to a false negative result. Similarly, if the treatment is not effective, substantial errors could lead to a false positive result, or an exaggerated positive result.

The common sources of error in studies of interventions are systematic error (bias) and random error. Systematic errors can be minimised by proper randomisation, analysis by allocated treatment, evaluation of outcome evaluation blinded to the allocated treatment, emphasis on the overall primary results, and publication of all studies irrespective of the results; whereas random error can really only be minimised by studying the effect of the treatment compared with a control on a large number of major outcomes, and therefore in all studies. It is therefore important to systematically review all the relevant studies that have evaluated the effect of SSRIs on recovery after stroke (published and unpublished) to

minimise systematic and random error in our estimates of the potential effects of SSRIs on recovery after stroke. Although a review of fluoxetine in stroke has already been undertaken and published (Yi 2010), the searches were done in 2009 and so the review did not include the FLAME trial (Chollet 2011); and the review was limited to fluoxetine rather than all SSRIs (Yi 2010). Furthermore, although the authors of the existing review considered some important aspects of study quality, the Cochrane risk of bias tools were not used so the reviewers may have missed some sources of bias. Thus, there is a need to produce an updated, methodologically robust systematic review incorporating all the relevant trials that have examined the role of all SSRIs for stroke recovery.

If a simple, inexpensive drug such as one of the SSRIs is shown to improve stroke recovery, this would have major implications for patients, carers, health services, social care services and the economy.

OBJECTIVES

Our objective is to determine whether SSRIs improve recovery after stroke.

METHODS

Criteria for considering studies for this review

Types of studies

The review will be restricted to all relevant randomised controlled trials (RCTs) in patients with a clinical diagnosis of stroke (Hatano 1976) where an SSRI has been given within the first three months of stroke onset. We will exclude trials using a cross-over design, or where two or more of the interventions were compared against each other rather than a placebo or standard care group. We will include identified trials in all languages. There will be no restriction on the eligibility of RCTs on the basis of sample size or duration of follow-up. We will consider unpublished reports, abstracts, brief and preliminary reports for inclusion on the same basis as published reports. If we find studies meeting all the criteria for inclusion but not presenting any outcome data, and if such data are not available from the authors, the studies cannot be used to contribute data to any pooled estimate of effect. We will list these studies in an additional table.

Types of participants

We will include any person who has had a stroke (Hatano 1976) in the previous three months. We will include those with subarachnoid haemorrhage. We will exclude trials that included mixed populations (such as stroke and head injury or other central nervous system disorders) unless separate results for patients with stroke are available.

Types of interventions

We will include any drug classified as a SSRI (for example fluvoxamine, fluoxetine, sertraline, citalopram and paroxetine). We will include any dose or mode of delivery, given for any duration and for any reason, for example to aid neurological recovery, to treat depression or anxiety or emotionalism, or to prevent depression or anxiety or other mood disorders. We will not include drugs that have mixed effects that include SSRI actions.

Types of outcome measures

Primary outcomes

Disability (measured, for example, by the Barthel Index, Functional Independence Measure) and dependence (measured by the modified Rankin score, for example).

Secondary outcomes

Impairments, depression, anxiety, quality of life, fatigue, healthcare cost, death, adverse events, leaving the trial early.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module.

Electronic searches

We will search the following electronic bibliographic databases:

- Cochrane Stroke Group Trials Register;
- Cochrane Depression Anxiety and Neurosis Group Trials Register;
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue);
- MEDLINE (from 1948) (Appendix 1);
- EMBASE (from 1980);
- CINAHL (from 1982);
- AMED (Allied and Complementary Medicine) (from 1985);
- PsycINFO (from 1967);
- PsycBITE Pyschological Database for Brain Impairment Treatment Efficacy (www.psycbite.com/).

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Trials Search Co-ordinator and will adapt it for the other databases. We will search for relevant trials in all languages and arrange for translation of trial reports published in languages other than English.

Searching other resources

In an effort to identify further published, unpublished and ongoing trials, we will:

1. search the online Clinical Trial Results and Clinical Trial Registries for Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Organon, Pfizer, Roche, and Wyeth;
2. search the following ongoing trials registers:
   i) Stroke Trials Registry (www.strokecenter.org/trials),
   ii) ClinicalTrials.gov (www.ClinicalTrials.gov),
   iii) ClinicalStudyResults.org (www.Clinicalstudyresults.org),
   iv) Current Controlled Trials (http://www.controlled-trials.com),
   v) EU Clinical Trials Register (https://www.clinicaltrialsregister.eu);
3. search reference lists of included studies and relevant reviews;
4. use Science Citation Index Cited Reference Search for forward tracking of important references (i.e. of included trials and reviews);
5. contact authors and researchers in the field.

We will search for relevant trials in all languages and arrange for translation of trial reports published in languages other than English.

Data collection and analysis

Selection of studies

One review author (GM, MH, MK, MB or RL) will perform the electronic searches, read titles and available abstracts and exclude obviously irrelevant studies. We will obtain the full text of all remaining studies. One experienced review author (GM or MH or GH) and one less experienced review author (MK, RL or MB) will independently scrutinise each full text article and decide whether they fulfil study inclusion criteria. Should any disagreements arise, we will ask a third review author for an opinion and a consensus will be reached.

We will include a study flow diagram which will include the number of unique references identified by the searches, the number of records excluded after preliminary screening of titles and abstracts, and the number of records retrieved in full text. We will take appropriate notes during the search process to ensure that the flow diagram can be completed correctly.

Data extraction and management

We will develop a paper data extraction form based on the one used for previous Cochrane reviews in depression. It will be piloted on three papers and modified as appropriate. Two review authors (an experienced and a less experienced one) will independently extract data from each study. Any disagreements will be resolved by discussion.

We will extract data on the following:

1. the report: author, year and source of publication;
2. the study: sample characteristics, social demography;
3. the participants: stroke sequence (first ever versus recurrent), social situation, time since stroke onset, prior history of psychiatric illness, current neurological status, stroke severity, whether people with aphasia were recruited, the proportion with depression at baseline (if recorded by trialists). We will not extract information on location or size of lesion as this is unlikely to have been recorded by the trialists, and brain imaging often does not show a visible lesion, particularly for patients with minor strokes;
4. the research design and features: adherence, non-response and length of follow-up;
5. the intervention: type, duration, dose, timing and mode of delivery;
6. the effect size: sample size, nature of outcome, estimate and standard error.

We will store the data electronically. We will obtain missing information from the primary investigators, if possible.

Assessment of risk of bias in included studies

We will assess risk of bias using The Cochrane Collaboration's risk of bias tables. For each study, we will determine whether there was allocation concealment; how randomisation was performed (including how sequences were generated); whether there was blinding of patient, personnel and outcome assessors; whether there were incomplete outcome data and whether there was selective outcome data reporting.

We will also record whether there was an imbalance in baseline characteristics, whether there was minimisation or stratification based on baseline variables, and early stopping of the intervention.

Measures of treatment effect

We will carry out statistical analysis using the Review Manager software, RevMan 5.1 (RevMan 2011). We will calculate a summary statistic for each outcome measure used to describe the observed treatment effect. All summary statistics reported in this review will refer to effects at either: (1) the end of intervention, or (2) the end of follow-up.

Unit of analysis issues

We anticipate that most of the trials will have a simple parallel group design where each individual will be randomised to one of

two treatment groups. However, there may be trials where each individual can be randomised to one of three (or more) possible groups, including different doses of SSRIs. We will deal with this by performing subgroup analyses to explore the influence of the dose of a drug on the outcome.

Dealing with missing data

We will approach primary investigators for missing data. When missing data are not available, we will perform sensitivity analyses to determine the influence of including trials with missing data.

Assessment of heterogeneity

We will investigate statistical heterogeneity by the Chi^2 test and the I^2 statistic, available in RevMan. If there is evidence of statistical heterogeneity ($I^2 > 50\%$), we will use a random-effects model and perform subgroup and sensitivity analyses as appropriate.

Assessment of reporting biases

We will assess publication bias by a funnel plot. We will try to avoid language bias by including all studies, irrespective of language, and seek translation where needed. We will check for selective reporting of results by scrutinising the aims and methods of the trials and comparing these with outcomes reported. Should we find similar papers by the same authors, we will contact the authors to ensure that the publications are not duplicates.

Data synthesis

For dichotomous data, we will report risk ratios (RR). For ordinal scales, where there is a well-recognised cut-point in the scale (for example modified Rankin) we will analyse the data as a dichotomous outcome (dependent or independent). For ordinal scales with no recognised cut-point, we will analyse the data as continuous data. The data required for meta-analyses of continuous data in RevMan are means and standard deviations (SD). When extracting continuous data from the study reports we will take precautions by checking whether standard error (SE) was mistakenly reported as SD. We will use SE or 95% CI to compute SD when SDs are missing.

For ordinal scales and continuous data, we will calculate standardised mean differences (SMD) because we expect different scales to be used for the same outcomes (for example Barthel Index and Functional Independence Measure for disability). It should be noted that the SMD does not correct for differences in the direction of the scale. If some scales increase with disease severity and others decrease, we will multiply the mean value from one set of studies by -1. An example of this is the National Institute of Health Stroke Scale (where a low score represents a less severe stroke) and the Scandinavian Stroke Scale (where a low score indicates a more severe stroke).

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses: depression versus no depression at entry, motor versus non-motor deficits, dose of drug, type of SSRI, brand of drug.

Sensitivity analysis

We will perform sensitivity analyses to explore the influence of the key aspects of trial quality that we identified during our assessment of risk of bias. For example, if some trials do not include blinded outcome assessment (perhaps relying instead on self-report), we will exclude these trials from the analyses in order to explore whether this makes any different to effect sizes.

ACKNOWLEDGEMENTS

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Zittel 2008

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Medline search strategy

MEDLINE (Ovid)

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. exp Gait Disorders, Neurologic/
8. or/1-7
9. exp Serotonin Uptake Inhibitors/
10. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhib$).tw.
11. SSRI$1.tw.
12. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw.
13. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).nm.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. exp animals/ not humans.sh.
17. 15 not 16
18. Randomized Controlled Trials as Topic/
19. random allocation/
20. Controlled Clinical Trials as Topic/
21. control groups/
22. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
23. Clinical Trials Data Monitoring Committees/
24. double-blind method/
25. single-blind method/
26. Placebos/
27. placebo effect/
28. cross-over studies/
29. Multicenter Studies as Topic/
30. Therapies, Investigational/
31. Drug Evaluation/
32. Research Design/
33. Program Evaluation/
34. evaluation studies as topic/
35. randomized controlled trial.pt.
36. controlled clinical trial.pt.
37. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
38. multicenter study.pt.
39. (evaluation studies or comparative study).pt.
40. meta analysis.pt.

41. meta-analysis as topic/
42. random$.tw.
43. (controlled adj5 (trial$ or stud$)).tw.
44. (clinical$ adj5 trial$).tw.
45. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
46. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
47. ((multicenter or multicentre or therapeutic) adj5 (trial$ or stud$)).tw.
48. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
49. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
50. (coin adj5 (flip or flipped or toss$)).tw.
51. latin square.tw.
52. versus.tw.
53. (cross-over or cross over or crossover).tw.
54. placebo$.tw.
55. sham.tw.
56. (assign$ or alternate or allocat$ or counterbalance$ or multiple baseline).tw.
57. controls.tw.
58. (treatment$ adj6 order).tw.
59. (meta-analy$ or metaanaly$ or meta analy$ or systematic review or systematic overview).tw.
60. or/18-59
61. 17 and 60

HISTORY

Protocol first published: Issue 11, 2011

CONTRIBUTIONS OF AUTHORS

Dr Mead, Dr Hackett and Professor Hankey wrote the protocol. All authors read the protocol and approved it. All authors will contribute to the searches, selection of studies and data extraction. Dr Mead and Dr Hackett will perform the analyses. All authors will contribute to writing the review.

DECLARATIONS OF INTEREST

Maree Hackett and Graeme Hankey are co-principal investigators on a study designed to access the impact of fluoxetine on disability and dependency after stroke. It is envisaged that the results of this trial would be eligible for inclusion in this review.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.