AFFINITY
Assessment of fluoxetine in stroke recovery

ASSESSMENT OF FLUOXETINE IN STROKE RECOVERY (AFFINITY) TRIAL

Formal title: An Australasian, investigator-driven, NHMRC funded, multi-centre, prospective, randomised, parallel group, double-blind, placebo-controlled trial to establish the effect(s) of routine administration of fluoxetine (20 mg once daily) in patients with recent stroke

Study Protocol Summary

Version 4, 18th November 2015

If you are interested in collaborating on the trial or if you would like more information please contact:

AFFINITY Trial Coordinating Centre

Stroke Research Group
Harry Parkins Institute of Medical Research
2nd Floor, QQ Block
Sir Charles Gairdner Hospital
6 Verdun Street
Nedlands, Western Australia 6009
Ph: 08 6151 1061
Fax: 08 6151 1028
Email: AFFINITY@health.wa.gov.au
Website: www.affinitytrial.org

Australian Government
National Health and Medical Research Council

Government of Western Australia
Department of Health

Royal Perth Hospital

The University of Western Australia
Achieve International Excellence

The University of Sydney

The George Institute for Global Health

SUMMARY

Title	An Australasian, investigator-driven, NHMRC funded, multi-centre, prospective, randomised, parallel group, double-blind, placebo-controlled trial to establish the effect(s) of routine administration of fluoxetine (20 mg once daily) in patients with recent stroke
Short title	**A**ssessment o**f** **f**luoxet**in**e **i**n s**t**roke recove**r**y (**AFFINITY**) Trial
Acronym	AFFINITY
Clinical phase	IIIb (i.e. fluoxetine is an established drug for depression, but not for stroke recovery; hence, possible new indication)
Trial Co-Principal investigators	Associate Professor Maree Hackett, The George Institute for Global Health & The University of Sydney Professor Graeme Hankey, The University of Western Australia & Sir Charles Gairdner Hospital.
Primary Research Question	Does treatment with fluoxetine, 20mg once daily, started 2-15 days after stroke onset and continued for 180 days, improve functional outcome at the 180 day assessment?
Trial design	Parallel group, randomised, placebo-controlled clinical trial.
Setting	Australian and New Zealand hospital stroke units and rehabilitation centres.
Eligibility criteria	*Inclusion Criteria* Men or women aged ≥ 18 years with all of the following: • Clinical diagnosis of stroke 2-15 days previously (Day of stroke onset = Day 0, randomise on Day 2-15) • Brain imaging consistent with ischaemic or haemorrhagic (intracerebral and/or subarachnoid) stroke (including normal CT brain scan) • Persisting measurable focal neurological deficits (e.g. motor, somatosensory, visual, language, cognitive) present at randomisation and severe enough to produce a modified Rankin Scale (mRS) score of ≥1 and to warrant treatment from the perspective of patient or carer(s) *Exclusion Criteria* Any of the following: • History of epileptic seizures • History of bipolar disorder • History of drug overdose or attempted suicide • Ongoing treatment with any selective serotonin reuptake inhibitor (SSRI) • Allergy or contra indication to fluoxetine including ➢ Hepatic impairment (serum alanine aminotransferase [ALT] >120 U/l), ➢ Renal impairment (creatinine > 180micromol/l or eGFR < 30ml/min/1.73m^2), ➢ Hyponatremia (sodium < 125mmol/L) despite treatment of the cause and confirmed on repeat testing, • Use of medications that may interact seriously with fluoxetine ➢ Proposed use of a monoamine oxidase inhibitor (MAOI), or use of a MAOI within 14 days prior to randomisation ➢ Current treatment with an antipsychotic drug (neuroleptic), pimozide, tamoxifen, or tramadol, unless the patient, doctor and if possible prescribing doctor believe it is appropriate to discontinue use. • Not available for follow up over the next 365 days e.g. no fixed home address • Life-threatening illness (e.g. advanced cancer) that is likely to reduce 365 day survival • Pregnant, breast-feeding or of child-bearing potential and not using contraception

	• Enrolled in another interventional clinical research trial involving an investigational product (medicine) or device.
Randomisation	Randomisation is by means of a password protected, computerised central randomisation service available 24 hours a day, using a minimisation algorithm to achieve balance between the two treatment groups for the following four prognostic factors: • Time from stroke onset (2-8 vs 9-15 days) • Presence of a motor deficit • Presence of aphasia • Predicted probability of survival free of dependency at 6 months (0-15% vs 16-100%).
Interventions	Participants are randomly assigned to 180 days treatment with either: • Fluoxetine, 20mg capsules, to be taken once daily, or • Placebo capsules that match the fluoxetine capsules once daily. For patients unable to swallow, the contents of an opened capsule can be given via enteral tube.
Outcome measures	*Primary outcome* • Functional outcome as measured by the mRS using the simplified modified Rankin Scale questionnaire (smRSq) at 180 days after randomisation. *Secondary outcomes at 180 and 365 days after randomisation* Survival, Mood (Patient Health Questionnaire-9 item [PHQ-9]), Cognitive function (Telephone Interview of Cognitive Status [TICSm]), Communication (Stroke Impact Scale [SIS]); Motor function (SIS); Overall health status (SIS); Health-Related Quality of Life (HRQoL) (EuroQol [EQ-5D-5L]); and Functional recovery (smRSq) at the 365 day assessments.New diagnosis of depression requiring treatment with antidepressants; Fatigue (vitality domain of the SF-36); Serious adverse events at any time during follow-up and which are also recorded as secondary outcomes: • New Stroke, ischaemic or haemorrhagic [not the qualifying event leading to enrolment] • Acute coronary syndrome [MI confirmed by ECG and/or raised serum Troponin] • Upper gastrointestinal bleed requiring blood transfusion and/or endoscopy • Other major bleed (i.e. not upper GI or intracerebral) - requiring blood transfusion or procedural intervention • Fall • New fracture [confirmed on X ray] • Epileptic seizure [focal or generalised] • Symptomatic hypoglycaemia [blood sugar < 3mmol/l] • Symptomatic hyperglycaemia [blood sugar > 22mmol/l] • New hyponatremia [Na < 125mmol/l] • Attempted suicide/self-harm • Death

	Cost of health care over the first year Cost-effectiveness.
Follow up	At 28, 90, 180 and 365 days after randomisation. Participants are assessed by the site investigator 28 days and 90 days after randomisation, in the hospital ward, outpatient clinic or via telephone. Participants are followed-up at 180 and 365 days after randomisation by the trial coordinating centre, by telephone or postal questionnaire.
Sample size estimate	90% power to detect an absolute increase in the proportion of patients with an mRS of 0-2 at 6 months from 50% to 57.5%
Number of participants	1,600 (800 in each group)
Statistical methods	An ordinal logistic regression analysis of the mRS adjusted for baseline variables included in minimisation algorithm
Trial duration	2013-2018