

Project Title:	Does Levodopa (3,4-dihydroxy-L-phenylalanine) drug treatment in combination with routine NHS occupational and physical therapy, delivered early after stroke within a stroke service, improve functional recovery including walking and arm function?
Project Ref:	08-43-61
Cost:	£1,408,286
Lead Applicant & Institution:	Professor Bipinchandra Bhakta Department of Rehabilitation Medicine University of Leeds
Start Date:	20 January 2010
Plain English Summary:	<p>Despite clear benefits of organised stroke care, a third of people with stroke are left with significant physical disabilities. Physical and occupational therapies have been shown to benefit people but residual disability for a large proportion of patients still remains a key issue in regaining full independence. There is promising research evidence emerging from pilot studies which indicate that combining certain drugs with physical and occupational therapy may improve the recovery of arm and leg movements essential day to day activities such as walking and getting dressed. These improvements are in addition to the benefits gained from physiotherapy and occupational therapy alone. These studies suggest that the nerve circuits in the brain responds better to the usual therapy when they are also exposed to drugs such as dopamine at the same time as having occupational or physiotherapy. A lot of this evidence comes from small studies. We feel that it is important to study this effect properly in larger scale studies as some of the scientific issues cannot easily be addressed in small studies. If this approach is beneficial it will revolutionise rehabilitation treatment for people with stroke worldwide. It will have a major impact of recovery and independence after stroke for a significant number of people.</p> <p>In this present study we will find out if combining L-dopa (a widely available and inexpensive drug that is widely used to treat Parkinson's Disease) with routine occupational and physical therapy enhances the effect of the therapy and further improves recovery of functionally useful arm and leg movement in people with first ever stroke. A total of 572 people with stroke will be randomly allocated to receive either active drug (L-dopa+carbidopa) or a placebo tablet about one hour before their physiotherapy or occupational therapy treatment session. All study participants will receive the usual stroke care within their hospital rehabilitation setting. Those suitable to take part in this study will be identified at two weeks after admission to hospital with stroke. We will provide detailed information about the study and seek their consent to participate. Those providing consent will be randomly allocated to one of two groups. Group 1 will</p>

	<p>receive the active drug approximately 60 minutes before their routine physical and occupational therapy sessions (up to two sessions per day) for up to 6 weeks. Group 2 will receive a placebo drug in combination with routine physical and occupational therapy. The medication will be continued at home if the person is still having rehabilitation treatment after discharge from hospital.</p> <p>People with stroke who are recruited to this study will be assessed on pre determined outcome measures such as their ability to walk and use their arms for functional activities at baseline (2 weeks), 8 weeks, 6 months and 12 months after stroke by an independent researcher.</p>
<p>Abstract:</p>	<p><u>Design:</u> A multicentre prospective randomised double blinded placebo controlled trial. 572 people with new stroke admitted to acute stroke services will be recruited.</p> <p><u>Setting:</u> At least 8 UK stroke services within Stroke Local Research Networks(LRN) that have an acute inpatient rehabilitation facility and a service that allows rehabilitation treatments to be continued within the home setting.</p> <p><u>Target population:</u> People with new stroke aged ≥ 18 years, Rivermead Mobility Index (RMI) score < 7 at time of recruitment (7-14 days post stroke). Exclusion criteria: Unlikely to survive more than 1 month, those requiring palliative care as advised by treating physician; Parkinson's disease; contraindications to L-dopa; unable to walk prior to stroke due to pre-existing co-morbidities(e.g. osteoarthritis). LRN staff will identify participants and consent.</p> <p><u>Inclusion criteria:</u></p> <ol style="list-style-type: none"> 1. New clinically diagnosed ischaemic or haemorrhagic (excluding subarachnoid haemorrhage) stroke in the 2 weeks* prior to randomisation 2. Cannot walk 10 metres (may use an aid if necessary but with no standby help) 3. Expected to need ongoing rehabilitation treatment after randomisation* 4. Aged 18 years or above 5. Able to give informed consent 6. The patient is able to access continuity of rehabilitation treatment (i.e. without a break of > 3 working days following discharge from hospital (e.g. through early supported discharge scheme) 7. Expected to be able to comply with treatment schedule post randomisation (e.g. swallow tablets/capsules) <p><u>Exclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Not expected to survive for 2 months following stroke 2. Diagnosis of Parkinson's disease, dementia, severe systemic illness, severe psychosis or glaucoma 3. Known hypersensitivity to Co-careldopa 4. Patients taking Monoamine-Oxidase Inhibitors (MAOIs), dopaminergic or sympathomimetic agents, 5. Symptomatic postural hypotension <p><u>Intervention:</u> L-dopa 100mg + carbidopa 25mg(as co-careldopa) will be given to patients as a single oral tablet 45-60 minutes before physical therapy or occupational therapy sessions focused on motor skills(e.g. walking, dressing). Participants will be randomised equally between study drug and placebo within 7-14 days after stroke(stratification see section 5.1). Individual participant randomisation will be undertaken by the Leeds</p>

Clinical Trials Research Unit (CTRU). The placebo will be given as an oral tablet 45-60 minutes before rehabilitation treatment. Routine physical and occupational therapy will be administered to all patients in both groups.

Outcomes:

Primary outcome:

The proportion of participants walking as defined by a score of 7 or above on the Rivermead Mobility Index (RMI), in the L-dopa and control intervention groups.

Secondary outcomes:

(a) Barthel Index, self care dependency in stroke; (b) Motor Activity Log-28(AOU), functional upper limb activities; (c) Northwick Park Nursing Dependency measure, physical dependency from which care costs can be estimated; (d) Nottingham Extended Activities of Daily Living Scale, measures activities such as outdoor mobility and household tasks; (e) General Health Questionnaire 28, measures depression; (f) Caregiver Burden Index, measures carer strain; (g) EQ-5D, measure of health status for economic evaluation; (h) a proforma will be developed to record study drug adherence as part of rehabilitation treatment, type of rehabilitation treatment given, (i) Modified Rankin Scale to relate this study data to other clinical trials (see National Stroke Trials database), (j) RMI change score to capture changes in posture and movement, (k) Baseline routinely collected clinical data will be used to allow Edinburgh case mix adjuster to be completed and ensure that the the baseline clinical characteristics are comparable across the active and control groups. Data on concomitant medication will be recorded. We will also collect data on lesion location identified from routinely undertaken Brain CT scans at time of admission to stroke unit. We anticipate that this data would be available for the majority of patients recruited to the study.

(b) Impact on physical functioning and mood at 8 weeks, 6 months and 12 months

- To compare the proportion of patients who are walking at 6 and 12 months post-randomisation in the two groups, as measured by a score of 7 or higher on the Rivermead Mobility Index
- To compare activities of daily living and dependency (Barthel Index, Northwick Park Dependency Score, Nottingham Extended Activities of Daily Living Scale, ABILHAND) between groups.
- To compare psychological distress / mood between the two groups (General Health Questionnaire 12)
- To compare carer burden between groups using the Caregiver Burden Scale
- To investigate cost effectiveness of Co-careldopa and conventional rehabilitation treatments (EQ-5D, Northwick Park Dependency Score to quantify care costs)

Investigate potential moderators and mediators of effect at 8 weeks, 6 months and 12 months

- To investigate whether baseline patient clinical characteristics and investigations (e.g. routine Brain CT scanning) help to predict those who might benefit from L-dopa augmented rehabilitation
- To investigate whether key factors (e.g. fatigue (Fatigue Assessment Scale), concurrent musculoskeletal symptoms, signs and pain (using the MSK SSP manikin)) influence the short and long term effect of L-dopa on physical functioning

Investigation of implementation within NHS

- To assess the adverse event profile associated with combination treatment (NHS stroke rehabilitation treatment linked with oral Co-

	<p>careldopa)</p> <ul style="list-style-type: none"> • To investigate the practical implications of delivering this intervention within routine NHS acute and early community care of people with stroke • To assess acceptability of Co-careldopa treatment to stroke patients (study drug adherence will be measured and a semi structured interview will be undertaken with participants at the week 8 assessment) <p><u>Follow up:</u> Baseline assessments (prior to randomisation), 8 weeks (primary) after randomisation; 6 and 12 months after randomisation.</p> <p><u>Sample size:</u> A sample size of 572 patients will provide 90% power at 5% significance to detect a smaller improvement of 50% (i.e. 26% vs 39%) in the proportion walking independently (see above) at 8 weeks.</p> <p><u>Project timetable</u> Total study time 45 months</p>
ISRCTN: (if applicable)	99643613
Project Protocol:	www.eme.ac.uk/projectfiles/084361protocol.pdf
Project website: (if applicable)	To follow
URL of this Page:	www.eme.ac.uk/projectfiles/084361info.pdf