Dopamine Augmented Rehabilitation in Stroke (DARS): a multicentre double-blind, randomised controlled trial of co-careldopa compared with placebo, in addition to routine NHS occupational and physical therapy, delivered early after stroke on functional recovery

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Declared competing interests of authors: Gary A Ford received personal fees from Lundbeck Ltd, Boehringer Ingelheim, Pfizer and AstraZeneca, and grants and personal fees from Athersys outside the submitted work. Alastair Cozens had equity in Skene Software Ltd and other financial activity outside the submitted work for SiLCK Clinical Solutions Ltd. David Meads is a member of the Health Technology Assessment (HTA) Elective and Emergency Specialist Care (EESC) Panel. Catherine M Sackley is a member of Health Services and Delivery Research researcher-led board. Amanda J Farrin is a member of the HTA Clinical Evaluation and Trials Board and the HTA Commissioning Strategy Group.

Published July 2019
DOI: 10.3310/eme06050

Scientific summary

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Efficacy and Mechanism Evaluation 2019; Vol. 6: No. 5
DOI: 10.3310/eme06050

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

In England, there are 110,000 new cases of stroke annually and 900,000 stroke survivors, of whom 300,000 are moderately or severely disabled. Physical therapy (PT) and occupational therapy (OT) promote the recovery of function following stroke and early access to multidisciplinary rehabilitation is recommended for all patients to improve function and quality of life; however, many patients remain disabled and unable to walk despite PT.

Most rehabilitation interventions focus on the patient's ability to learn or relearn motor skills. Studies of the brain structures involved in learning suggest that the basal ganglia and dopamine play a key role in the acquisition of motor skills. Dopamine is a key modulator of striatal function and may contribute to the selection and termination of motor programmes for skilled movements. This suggests that pharmacological manipulation of neurotransmitter systems could be used to enhance the reacquisition of motor skills after stroke.

A number of drugs increase brain dopaminergic activity, but some, such as amphetamines, are associated with significant adverse effects. Levodopa is an orally administered precursor of dopamine that crosses the blood–brain barrier before being metabolised to dopamine. Co-careldopa (Sinemet®, Merck Sharp & Dohme Ltd) is a combined preparation of 100 mg of levodopa with a peripheral DOPA decarboxylase inhibitor, carbidopa. Carbidopa reduces peripheral levodopa metabolism, thereby maximising the central bioavailability of levodopa, and is a well-established treatment for Parkinson's disease, a condition associated with marked reductions in basal ganglia dopamine activity.

Seven small trials of dopamine agonists after stroke, with a combined total of 249 patients, have provided equivocal evidence on motor recovery, and a larger trial to establish the effects of increasing dopaminergic activity after stroke on motor recovery is required. Administering oral levodopa prior to motor therapy to enhance brain dopamine concentrations during therapy is a logical strategy to optimise efficacy of dopaminergic therapy and minimise adverse effects. This approach requires co-ordination of drug administration with planned therapy, and differs from that used for treatment of Parkinson's disease and drug administration in most clinical trials. This novel approach of co-ordinating drug administration with motor therapy was utilised in the Dopamine Augmented Rehabilitation in Stroke (DARS) trial.

Aim and objectives

Aim

To determine if combining co-careldopa with routine PT and OT during early rehabilitation in people with new stroke admitted to a stroke unit enhances the effect of conventional rehabilitation treatments in terms of physical functioning.

Primary objective

The primary objective compared the proportion of patients in both treatment groups walking independently at 8 weeks post randomisation.

Secondary objectives

Secondary objectives were to assess the impact on physical functioning, mood and cognition at 8 weeks, 6 months and 12 months post randomisation, comparing between treatment groups:

- proportion of patients walking at 6 months and 12 months
- activities of daily living, mobility and dependency
- psychological distress/mood
- carer burden.

Additional objectives were to:

- Determine the cost-effectiveness of co-careldopa and conventional rehabilitation treatment compared with usual care within NHS stroke services.
- Investigate potential moderators and mediators of effect at 8 weeks, namely (1) whether or not baseline patient clinical characteristics and investigations predict those who might benefit from co-careldopa-augmented rehabilitation, and (2) whether or not fatigue, concurrent musculoskeletal symptoms, signs and pain, and cognitive function influence the short- and long-term effect of co-careldopa on physical functioning.
- Investigate the feasibility of implementation of timed drug administration with therapy within routine NHS services.
- Assess the adverse event (AE) profile associated with co-careldopa administered with NHS stroke motor rehabilitation therapy.
- Investigate the practical implications of delivering this intervention within routine NHS acute and early community care of people with stroke.
- Assess the acceptability of co-careldopa treatment to stroke patients.

Methods

The DARS trial was a multicentre, randomised, double-blind, placebo-controlled trial with stroke patients who were randomised, while inpatients, to receive 6 weeks of co-careldopa or placebo in combination with physical occupational rehabilitation.

Participants had new or recurrent clinically diagnosed ischaemic or haemorrhagic stroke within 5 to 42 days prior to randomisation, could not independently walk $\geq$ 10 metres indoors [Rivermead Mobility Index (RMI) score of $<$ 7 points], did not have Parkinson's disease and required rehabilitation.

A total of 51 UK NHS stroke services with an acute inpatient stroke rehabilitation unit and a service allowing rehabilitation treatments within the community setting participated in the DARS trial.

Patients were randomised to receive either co-careldopa or a matched placebo tablet, taken before receiving routine NHS PT and OT involving motor therapy for 6 weeks. Patients were required to take the study drug 45–60 minutes before PT or OT sessions. Patients were randomised in permuted block sizes balanced for centre, type of stroke and baseline RMI score. Treatment adherence and therapy sessions received were recorded.

The primary outcome was the proportion of patients walking independently at 8 weeks (RMI score of $\geq$ 7 points). Secondary outcomes assessed physical functioning [Nottingham Extended Activities of Daily Living (NEADL), Barthel Index (BI), ABILHAND Manual Ability Measure (ABILHAND) and modified Rankin Scale (mRS)], pain (musculoskeletal – symptoms/signs and pain manikin), cognition [Montreal Cognitive Assessment (MoCA)], mood [General Health Questionnaire 12-item version (GHQ-12)], fatigue [Fatigue Assessment Scale (FAS)] and carer burden [Carer Burden Scale (CBS)] at 8 weeks, 6 months and 12 months.

The sample size calculation of 572 patients was based on the proportion of people walking independently at 8 weeks reported in previous Levodopa and placebo studies and it provided 90% power at 5% significance to detect a 50% relative difference between the placebo and active treatment groups in the proportion of participants independently walking at 8 weeks.

Ongoing monitoring during the trial indicated that the combined death rate and loss to follow-up was likely to exceed the assumed rate of 10%; therefore, a decision was taken to increase the required sample size to 590 to account for this.

Potential predictors of response to co-careldopa via moderators and mediators were explored. Moderator analyses explored whether or not the size of the treatment effect depended on baseline characteristics of the patients. Mediator analyses explored the extent to which the treatment effect could be explained by an intermediate mechanistic outcome. Analyses focused on RMI at 8 weeks. Potential mediator variables related to the period prior to the outcome but post randomisation and included therapy sessions received, study medication taken, and assessments of fatigue, pain, cognitive function and activities of daily living.

A health economic analysis was undertaken using quality-adjusted life-years (QALYs) as the main outcome measure, captured using the EuroQol-5 Dimensions at baseline, 8 weeks, 6 months and 12 months after randomisation. Health-care resource utilisation was captured using questionnaires covering primary and secondary care use over the trial period. The primary health economic analysis was a cost–utility analysis with a secondary cost-effectiveness analysis.

Results

Between May 2011 and March 2014, 593 patients [mean age 68.5 years, 187 (61%) male] and 165 carers (mean age 59.7 years) were recruited; 308 patients were randomised to co-careldopa and 285 to placebo at a median of 15 days (range 3–59 days) following stroke onset. Most participants had cerebral infarction: 270 (87.7%) in the co-careldopa group and 238 (83.5%) in the placebo group. A total of 91 participants withdrew from the trial: 58 (18.8%) in the co-careldopa group and 33 (11.6%) in the placebo group. The mean number of therapy sessions that included motor activities was 23.2 in the co-careldopa group and 24.8 in the placebo group, with a mean length of 43 minutes in both groups. The mean number of investigational medicinal product (IMP) doses taken was 20.6 in the co-careldopa group and 22.4 in the placebo group, and the IMP was taken as per protocol in 55% of therapy sessions.

The proportion of patients who can walk independently at 8 weeks was 40.6% in the co-careldopa group and 44.6% in the placebo group [odds ratio (OR) 0.78, 95% confidence interval (CI) 0.53 to 1.15], indicating no statistical evidence of a significant difference between the treatment groups. At 8 weeks, the follow-up rate in the co-careldopa group was 88.0% and in the placebo group was 91.6%. The results at 6 months and 12 months also failed to demonstrate any statistically significant differences between the groups [51.6% (co-careldopa) vs. 53.3% (placebo) and 51.6% (co-careldopa) vs. 56.8% (placebo) at 6 and 12 months, respectively]. The ability to walk independently did not differ between males and females. Participants who suffered an infarction were significantly less likely to walk independently than those who had a primary haemorrhage [206 (40.6%) vs. 46 (54.1%), respectively; OR 0.382, 95% CI 0.219 to 0.667]. Sensitivity analyses confirmed the results of the primary end-point analysis of no evidence of a statistically significant difference between the treatment groups.

There was no significant difference between the two groups in the number of AEs reported: in the co-careldopa group, 195 participants (63.3%) reported a mean of 3.5 AEs each and in the placebo group 170 participants (59.6%) reported a mean of 3.6 AEs each. Fifty-seven participants (18.5%) in the co-careldopa group reported 74 serious adverse events (SAEs) and 50 participants (17.5%) in the placebo group reported 58 SAEs. The majority of SAEs reported in both the co-careldopa group and the placebo group were not suspected to be related to the IMP. Thirty-nine participants (6.6%) died within 12 months of randomisation: 22 (7.1%) in the co-careldopa group and 17 (6.0%) in the placebo group. The median

number of days from randomisation to discharge was 25 in the co-careldopa group and 27 in the placebo group, with the majority of participants discharged to their own home or a relative's home: 174 (56.5%) in the co-careldopa group and 170 (59.6%) in the placebo group.

There was no evidence of statistically significant differences between treatment groups in NEADL, BI, ABILHAND or mRS, pain or fatigue at any time point. MoCA scores did not significantly differ between groups; the majority of participants had cognitive impairment at baseline (77% with a score of < 26 points), which improved during the 12-month follow-up period (41% with a score of < 26 points). No statistically significant differences were observed in GHQ-12 scores between groups at 8 weeks and 12 months but, at 6 months, those in the co-careldopa group reported significantly better general health [mean difference (MD) –1.33 points, 95% CI –2.57 to –0.10 points]. Mortality at 12 months was not significantly different between groups (7.1% in co-careldopa vs. 6.0% in placebo). SAEs occurred in 18.5% of the co-careldopa group and 17.5% of the placebo group. Carers in the placebo group reported statistically significantly greater burden at both 6 months and 12 months (MD 5.05 points, 95% CI 0.10 to 10.01 points and MD 7.52 points, 95% CI 1.87 to 13.18 points, respectively) on the CBS.

In the health economic analyses, co-careldopa patients incurred higher costs and gained fewer QALYs than placebo patients, indicating that co-careldopa is not cost-effective. The mean number of QALYs was 0.397 [standard deviation (SD) 0.002] for the co-careldopa group and 0.420 (SD 0.002) for the placebo group.

Conclusions

There is no evidence that co-careldopa administered before routine NHS PT or OT during stroke rehabilitation in NHS services is clinically effective or cost-effective in improving walking, physical functioning, mood or cognition in the first year following stroke, and it would not be a cost-effective therapy.

The DARS trial is larger than all previous randomised controlled trials to evaluate dopaminergic drug therapy during recovery from stroke. In that context, the DARS trial has established that there is no case for administering co-careldopa during rehabilitation of stroke patients who do not have Parkinson's disease.

Recommendations for future research

Future clinical trials of other pharmacotherapies that act on motor learning should consider comparing strategies of continuous dosing and intermittent dosing prior to motor therapy and different doses of drug therapy. Clinical trials of pharmacotherapy to improve stroke recovery may need to consider using a greater intensity of therapy than was used in the DARS trial. Future research should consider incorporation of emerging imaging markers, such as functional magnetic resonance imaging, as proof-of-concept biomarkers into early-phase trials of pharmacotherapy to improve recovery from stroke. Future research is needed into the development of more sensitive clinical markers of motor recovery that would demonstrate proof-of-concept efficacy on neurological impairment in early-phase trials before undertaking large pragmatic trials using disability measures as the primary trial outcome.

Trial registration

This trial is registered as ISRCTN99643613.

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research partnership.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by the EME programme as project number 08/43/61. The contractual start date was in January 2010. The final report began editorial review in November 2015 and was accepted for publication in February 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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