Dopamine for motor recovery after stroke: where to from here?

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See **Articles** page 530

Pharmacological drugs are important in the prevention of stroke and its acute management, but they currently play no part in stroke rehabilitation. Much of stroke rehabilitation is aimed at improving motor function, which is crucial for regaining independence. Preclinical studies and small clinical trials provide some evidence that drugs that increase dopamine concentrations in the brain might enhance motor recovery after stroke. However, evidence is scarce for the use of these drugs in clinical practice. Some systematic reviews have identified the need for more basic research to better understand the role of dopamine in neural plasticity and motor recovery after stroke,[1,2] while others concluded that large studies of drugs that modulate dopamine neurotransmission are needed.[3] In *The Lancet Neurology*, Gary Ford and colleagues[4] now report the Dopamine Augmented Rehabilitation in Stroke (DARS) trial, the largest trial to date of dopaminergic treatment during stroke rehabilitation.

The DARS trial randomly assigned 593 patients within an average 18 days after stroke onset and tested co-careldopa versus placebo in addition to routine occupational and physical therapy. The sample size was larger than the combined samples of all previous studies of dopaminergic treatment for patients with stroke, which is an impressive accomplishment. The primary outcome was independent walking at 8 weeks after randomisation, assessed with the patient-reported Rivermead Mobility Index. The proportion of patients walking independently at 8 weeks did not differ significantly between the co-careldopa and placebo groups. The authors conclude that adding co-careldopa to routine stroke rehabilitation does not improve walking outcomes. However, this conclusion is less certain in light of some of the trial's limitations, which are freely acknowledged by the authors. Useful lessons can be gained for future stroke rehabilitation drug trials.

The DARS trial was designed so that motor therapy would occur during the time window of co-careldopa's peak effect. The protocol required that the drug or placebo was administered 45–60 min before therapy sessions, which were delivered as part of standard care and intended to involve at least 20 min of motor therapy. However, difficulties with achieving this treatment timing and therapy dose meant that less than 10% of participants were eligible for the prespecified per-protocol analysis. Ford and colleagues acknowledge that the intensity of physical therapy might have been insufficient to capitalise on the presumed plasticity-enhancing effects of co-careldopa treatment. They also acknowledge that the intermittent treatment regimen might have been suboptimal. Previous studies have found that once daily levodopa treatment and physical therapy can benefit motor performance after stroke,[5] but not a single dose and therapy session.[6] Additionally, the intensity and duration of therapy intended to benefit the primary outcome of independent walking was not reported. The therapy delivered in the DARS trial could be any active physical treatment aimed at improving motor skills, which could include upper limb activities not involving mobilisation. This inclusion of non-specific motor activities is important because most studies have found that dopamine treatment enhances learning of specifically practiced tasks, rather than having a generalised effect.[7] Administering co-careldopa once daily and increasing the intensity and controlling the content of therapy, might have allowed detection of the hypothesised benefits of dopamine in motor learning.

Stroke rehabilitation is a complex intervention and stroke rehabilitation trials are challenging. Patients can be difficult to enrol into a rehabilitation study within days of stroke, and maintaining intervention fidelity as participants move between acute and rehabilitation settings and then into the community can also be challenging. The DARS trial illustrates these difficulties, with patients recruited up to 59 days after stroke and low treatment protocol fidelity. The DARS trial has some similarities to trials of acute stroke treatments, such as a large sample size and a binary primary outcome measure. However, more sensitive measures of neurological impairment might be needed to detect the effects of a drug administered over several weeks to interact with the complex neurobiological mechanisms of recovery. DARS also differs from most trials of acute stroke treatments in that it did not use any biomarkers for patient selection. Genetic, neuroimaging, or neurophysiology biomarkers might have allowed the DARS

trial to identify patients who are most likely to benefit,[7,8] as noted by the authors.

What lessons might DARS offer for the design of future stroke rehabilitation drug trials? Experience-based therapy needs to be of sufficient intensity to interact with the tested drug and structured in a way that is synergistic with the drug's mechanisms of action. It is unlikely that a single drug will enhance recovery for all patients, and biomarkers could help to identify subsets of patients who are more likely to benefit. Testing rehabilitation drugs on a scale that allows for high treatment fidelity and sensitive outcome measures will produce more certain conclusions. Stroke recovery and rehabilitation are highly heterogeneous processes and are more likely to be improved by precision medicine than herd medicine.

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I declare no competing interests.

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The uncertain role for phosphodiesterase inhibitors in stroke prevention

See **Articles** page 539

Cilostazol has been an approved drug for the treatment of intermittent claudication in North America and Japan for more than 20 years, but not for stroke. Cilostazol is an oral phosphodiesterase (PDE) inhibitor, similar in mechanism of action to dipyridamole. Key pharmacological differences are that cilostazol inhibits PDE-3 with greater effect on intracellular cyclic-AMP concentrations and lesser effect on cyclic-GMP than dipyridamole. Dipyridamole inhibits PDE-5, which has a dominant effect on increasing intracellular cyclic-GMP concentrations; cyclic-GMP then inhibits PDE-3. Cilostazol is also an adenosine reuptake inhibitor that further increases intracellular cyclic-AMP and potentiates its action. In vascular smooth muscle, cilostazol results in vasodilation, has a 10 h half life, is primarily excreted renally, and its metabolism is influenced by cytochrome P450 enzyme variants (CYP3A4 and CYP2C19), the same as clopidogrel.[1,2]

Previous studies with cilostazol for stroke prevention have been completed. From 1992 to 1996, 1085 patients from Japan were enrolled in a double-blind study (the CSPS-1 trial)[3], and randomised to cilostazol or placebo, with a significant benefit accruing to cilostazol for stroke prevention. A pilot study enrolling 720 patients in China showed no difference in stroke recurrence between aspirin versus cilostazol as a single antiplatelet therapy.[4] A second study (CSPS-2 trial),[5] that enrolled 2757 patients in Japan, compared cilostazol 100 mg twice per day with aspirin 81 mg once per day in a non-inferiority design.[5] The study yielded borderline results; the annual rate of recurrent stroke was 2·8% in patients randomly allocated to cilostazol and 3·7% in those allocated to aspirin (HR 0·74, 95% CI 0·56–0·98), meeting the criteria for non-inferiority. There are parallels with findings from the trials of dipyridamole for stroke prevention, the ESPS-1,[6] ESPS-2,[7] and ESPRIT[8] trials, all of which initially suggested benefit for dipyridamole, despite design or execution concerns. The results of the PROFESS trial,[9] that enrolled 20 232 patients, confirmed that dipyridamole was not non-inferior and had similar outcome rates to clopidogrel alone.[9]

The Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) by Toyoda and colleagues,[10]