

**Title page:****Speeding stroke recovery ?****A systematic review of amphetamine after stroke.****Nikola Sprigg and Philip MW Bath**

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## Abstract

**Introduction:** The use of drugs to enhance recovery ('rehabilitation pharmacology') has been assessed. Amphetamine can improve outcome in experimental models of stroke, and several small clinical trials have assessed its use in stroke.

**Methods:** Electronic searches were performed to identify randomised controlled trials of amphetamine in stroke (ischaemic or haemorrhagic). Outcomes included functional outcome (assessed as combined death or disability/dependency), safety (death) and haemodynamic measures. Data were analysed as dichotomous or continuous outcomes, using odds ratios (OR), weighted or standardised mean difference, (WMD or SMD) using random-effects models with 95% confidence intervals (95% CI); statistical heterogeneity was assessed.

**Results:** Eleven completed trials (n=329) were identified. Treatment with amphetamine was associated with non-significant trends to increased death (OR 2.78 (95% CI, 0.75 to 10.23), n=329, 11 trials) and improved motor scores (WMD 3.28 (95% CI -0.48 to 7.04) n=257, 9 trials) but had no effect on the combined outcome of death and dependency (OR 1.15 (95% CI 0.65 to 2.06, n=206, 5 trials). Amphetamine increased systolic blood pressure (WMD 9.3 mmHg, 95% CI 3.3 to 15.3, n=106, 3 trials) and heart rate (WMD 7.6 beats per minute, 95% CI 1.8 to 13.4, n=106, 3 trials). Despite variations in treatment regimes, outcomes and follow-up duration there was no evidence of significant heterogeneity or publication bias.

**Conclusion:** No evidence exists at present to support the use of amphetamine after stroke. Despite a trend to improved motor function, doubts remain over safety and there are significant haemodynamic effects, the consequences of which are unknown.

## INTRODUCTION

Stroke units save lives and, coupled with effective treatments such as thrombolysis and improved hyperacute care, more patients are surviving stroke. This, in the presence of an ageing population, has increased the number of stroke survivors, among whom the burden of stroke is high, with many patients left with significant disability. The brain's ability to regenerate and undergo plastic change has long been exploited by rehabilitation; however, now the potential to exploit neuroplasticity with pharmacological agents seems to be a real possibility.<sup>1,2</sup>

Amphetamine, a sympathomimetic drug that leads to the release of noradrenaline and possibly dopamine and serotonin, acts as a stimulant, both centrally and peripherally.<sup>3</sup> In experimental models of stroke, when given in conjunction with task specific practice, amphetamine has been shown to accelerate the recovery of motor function.<sup>4-6</sup> Improved recovery is only seen when amphetamine is given with training related activity suggesting that in addition to modulation of central neurotransmitters, amphetamine may enhance long term potentiation. Further, amphetamine can result in neural sprouting and enhanced synaptogenesis<sup>7</sup> and augmentation of dendritic length and density, perhaps reflecting enhanced synaptic connectivity.<sup>8</sup>

In healthy volunteers, amphetamine can modulate use dependent plasticity, as measured by task specific training performance and simultaneous transcranial magnetic stimulation evoked electromyographic responses.<sup>9</sup> Similarly, in volunteers undergoing functional MRI, increased regional cerebral activation was seen, suggesting that amphetamine may lead to recruitment of neuronal units and/or increased activation within these units.<sup>10</sup>

Several small trials have assessed the use of amphetamine after stroke and we sought to perform a systematic review to assess its effects on functional outcome and haemodynamic measures.

## **METHODS**

### **Search strategy**

Electronic searches were performed in the Cochrane Stroke Group Trials Register (last searched June 2008), Cochrane Controlled Trials Register (Cochrane Library, Issue 2, 2008), MEDLINE (1966-July 2009), EMBASE (1980-June 2008), and Science Citation Index (1992-June 2008). The reference lists of all relevant articles and reviews were also checked to identify suitable studies.

The following search strategy was used for MEDLINE and adapted for the other databases:

1. Exp amphetamine
2. (\$amphetamine or amphetamine\$ or d-amphetamine or dexamphetamine or dextroamphetamine or methamphetamine).tw
3. (amphetam\$).tw
4. or/1-3
5. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebrovascular accident/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or intracranial arteriovenous malformations/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or vasospasm, intracranial/ or vertebral artery dissection/
6. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
7. ((brain\$ or cerebral or cerebell\$ or intracranial or subarachnoid) adj5 (haemorrhage or hemorrhage or hematoma or haematoma or bleed\$ or aneurysm)).tw.
8. or/5-7
9. 4 and 8
10. limit 9 to human

### **Data collection and analysis**

Randomised controlled trials of amphetamine in stroke (ischaemic or haemorrhagic) were selected for inclusion. Trial quality was assessed using standard criteria <sup>11</sup> including determining methods of randomisation, double blinding, participants lost to follow up, generation of random numbers, and allocation concealment. Data were independently extracted from publications, this including outcome measures (by intention-to-treat), ideally at end-of-treatment and at end-of-follow up.

### **Types of outcome measures**

The primary outcome was functional outcome at end-of-follow up as assessed by combined death or disability/dependency, defined as a modified Rankin Scale (mRS) >2 or Barthel Index (BI) <60. Secondary outcomes included measures of impairment, function and haemodynamic measures, the latter including blood pressure (mmHg) and heart rate (beats per minute).

### **Data synthesis**

Data were analysed by 'intention-to-treat' where available, tested for heterogeneity using  $I^2$ , and a weighted estimate calculated for the typical treatment effect across trials. Improvement scores were calculated, where possible, to assess change following treatment. Random effects models were used since between-trial sources of heterogeneity were expected, e.g. due to differences in type of treatment regime, outcome scales, and clinical and statistical differences between the trials. Treatment effects were determined using the odds ratio (OR) for dichotomous data and weighted mean difference (WMD) for continuous data, and 95% confidence intervals (CI) calculated. Where different assessment scales were being analysed (such as Fugl-Meyer and Rivermead Motor Assessment Scale) standardised mean difference (SMD) was calculated. The Cochrane Collaboration's Review Manager software, RevMan 4.2.7, was used for data entry and analysis. Publication bias was assessed visually using a funnel plot and statistically using Eggers plot.

## RESULTS

### Trials

Eleven completed trials (329 patients) were identified and included in the analysis (figure 1). One ongoing trial was identified,<sup>12</sup> and two trials had recently been terminated early due to problems recruiting patients.<sup>13 14</sup> All but two trials limited inclusion to ischaemic stroke, and recruitment time ranged from within 72 hours to 6 weeks following stroke onset (table 1). Trial quality overall was good; one trial was single blind due to safety concerns, but all had blinded assessment of outcomes. Of the eleven trials, 2 are published only in abstract format.<sup>15, 16</sup> A variety of outcome scales were used: motor impairment - Fugl-Meyer Scale (FMS), Rivermead Motor Assessment Scale or TEMPA test; neurological deficit - Scandinavian Stroke Scale (SSS); mood - Zung Depression score; and communication - Sheffield Screening test or Porch Communication Ability test.

### Death or disability/dependency

The combined outcome of death or dependency was only reported in 5 trials (n=206 patients) and treatment with amphetamine did not alter it, OR 1.15 (95% CI 0.65 to 2.06) (figure 2). No change in disability (BI) was seen, WMD 0.12 (95% CI, -4.26-4.61). All 11 trials provided data on mortality and there was a trend for more deaths at the end of follow-up with amphetamine, OR 2.78 (95% CI, 0.75 to 10.23) (figure 3).

### Impairment

Motor impairment was the primary outcome in several trials and was recorded in 9 studies (n=257); a trend to better motor scores was present in patients treated with amphetamine, WMD 3.28 (95% CI - 0.48 to 7.04). Similarly, analysing change in motor scores from baseline to end-of-trial showed a trend to a better motor score improvement with amphetamine, SMD 0.28 (95% CI, -0.08 to 0.64) (figure 4).

Neurological impairment was assessed in 2 studies (n=67 patients);<sup>17, 18</sup> there were trends to better neurological score (SSS), WMD 2.43 (95% CI, -4.41 to 9.28), and greater change in score between baseline and end-of-treatment, WMD 3.96 (95% CI, -1.23 to 9.15) in the amphetamine group (figure 9).<sup>17, 18</sup>

### Other outcomes

Two studies analysed language,<sup>19 18</sup> with no difference in language function as assessed by the Porch Communication Score or Sheffield screening score, SMD 0.11 (95% CI, -0.45 to 0.67). Language was the primary outcome in one of these studies<sup>19</sup> and, using a different method of analysis, a statistically significant improvement was seen in language ability. Mood, as assessed with the Zung depression score, did not improve in the amphetamine group, WMD 0.87 points (95% CI, -3.33 to 5.07), in the 2 studies in which it was assessed.<sup>15, 18</sup>

### **Haemodynamics**

Haemodynamic data was available in 3 studies (n=106 patients).<sup>17, 18, 20</sup> Systolic and diastolic blood pressure both showed significant increases after dexamphetamine, WMD 9.29 (95% CI, 3.26 to 15.32) (figure 5) and WMD 5.13 (95% CI, 1.61 to 8.64) respectively. Heart rate was also significantly increased with amphetamine, WMD 7.61 (95% CI 1.78 to 13.43) (figure 6).

### **Heterogeneity and publication bias**

Despite variations in treatment regimes, outcomes, and follow-up duration, there was no evidence of significant heterogeneity in any of the analyses. Additionally, there was no evidence of publication bias, either visually or statistically ( $p= 0.125$ ).

## DISCUSSION

Amphetamine was not associated with improvement in the combined outcome of death or dependency after stroke, in keeping with a previous smaller review<sup>21</sup>. Additionally, whilst there were trends to motor and neurological improvement, none of the effects were significant. Furthermore, there remains insufficient data to draw any conclusions regarding the effects of amphetamine on mood or communication or quality of life. This current analysis included data from newly published trials or data not previously available, doubling the available sample size in comparison to earlier review.<sup>21</sup>

There are many potential explanations for the lack of treatment effect seen. First, the varying outcome measures limited analysis and may have underestimated or concealed any potential effect. Wide confidence limits highlight the limited available data and make it difficult to draw firm conclusions. Similarly, many of the outcome measures demonstrate ceiling effects, although some studies excluded patients with mild weakness in an attempt to overcome this.<sup>22-25</sup> Second, enrolment in a number of studies was completed early due to a low recruitment rate<sup>25 18</sup> so the intended sample size was not achieved thereby leading to a potential type II error. Difficulties recruiting into acute stroke trials with multiple exclusion criteria are well recognised.<sup>26</sup> In two other studies, enrolment was terminated prematurely and the results remain unpublished.<sup>13, 14</sup>

Third, amphetamine may not be effective at improving outcome using the dose regimes tested in the available trials. The optimal treatment regime remains uncertain, with data from experimental stroke showing that a 'bell-shaped' dose response exists,<sup>5</sup> i.e. both low and high doses, as well as early administration, are associated with a poor outcome.<sup>4, 27</sup> In this respect, clinical trials tested lower and less frequent dosing than experimental models, presumably with the aim to reduce potential adverse effects.<sup>4, 5, 28, 29 4, 27, 30</sup> Discrepancy between pre-clinical experiments and clinical trials is well documented in stroke studies and pre-clinical data needs rigorous assessment when utilised in the development of new treatments for stroke.<sup>40</sup>

Fourth, it is feasible that baseline imbalances in stroke severity (with more severe stroke in the treatment group) may have concealed a treatment effect. This hypothesis is strengthened by the observation that the treatment effect appears to be greater when assessed in terms of improvement, thus taking into account any baseline imbalance. Unfortunately, limited sample sizes prevent stratification of data by prognostic baseline factors such as stroke syndrome, severity or time to recruitment. Similarly, no clinical study has taken into account the nature of ischaemic lesion, its size and location, which may help target interventions to selected groups of patients.<sup>31</sup>

Fifth, significant haemodynamic effects may increase risk factors for a poor outcome with lack of treatment effect reflecting a balance between potential benefit and harm. Both elevations in blood pressure and heart rate are associated with poor outcome after stroke,<sup>32 33</sup> as is impaired baroreceptor sensitivity, with increased cardiac events and arrhythmias.<sup>34</sup> Despite this, the relationship between drug induced haemodynamic changes and outcome remains unclear. Experimental data supporting



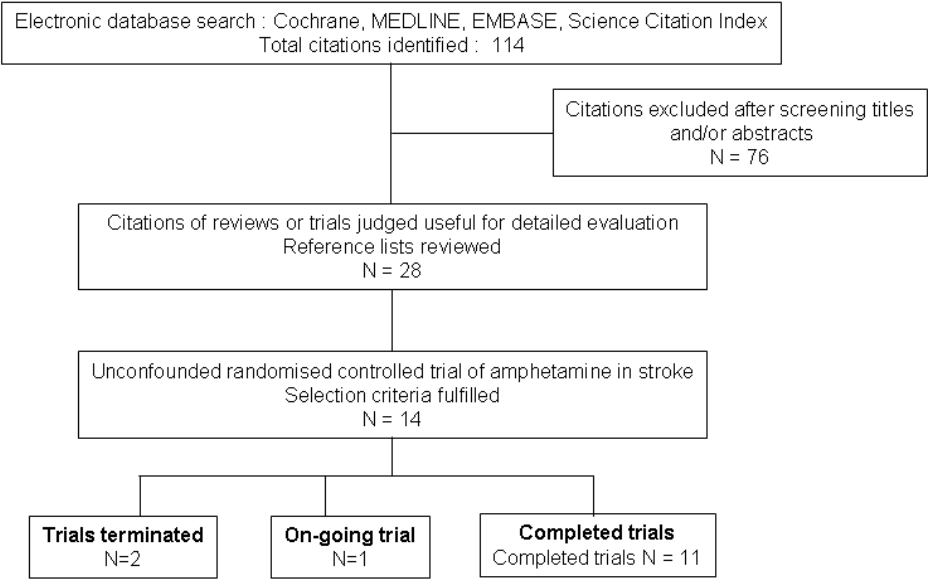
the use of amphetamine, where no tendency to harm has been demonstrated, have involved healthy volunteers.<sup>9, 35, 36</sup> This is in contrast to clinical studies where stroke patients are older and often have multiple co-morbidities. Similar to results utilising amphetamine in animal stroke models, data derived from the use of amphetamine in healthy volunteers needs cautious interpretation.

Despite concerns regarding increasing heart rate and blood pressure, up to a fifth of acute stroke patients have low blood pressure, and hypotension is also associated with poor outcome.<sup>37</sup> Elevation of systemic blood pressure in the presence of dysfunctional cerebral autoregulation (as occurs in acute ischaemic stroke) might lead to augmentation in cerebral blood flow and, potentially, enhance recovery.<sup>31</sup> Changes in cerebral blood flow with amphetamine have been demonstrated previously,<sup>38</sup> although these appeared to be region-specific and may represent cortical activation rather than systemic augmentation. Monitoring of treatment effects with functional imaging may provide further information on potential mechanisms of amphetamine action, as is being studied in normal volunteers.<sup>39</sup>

## **Conclusions**

Despite a trend to improvement in motor scores, there is no evidence that amphetamines improve outcome in ischaemic stroke. Furthermore, there are significant haemodynamic effects, the consequences of which remain unclear but may have implications on prognosis. As such, doubt persists regarding the safety of amphetamine treatment. Further clinical trials are needed to further assess safety, and if appropriate, to define an optimal treatment regime.<sup>21</sup>

**Figure 1** Search strategy and selection process for identifying clinical trials of amphetamine in stroke



**Figure 2** Death and dependency by treatment group

**Figure 3** Death at end of trial by treatment group

**Figure 4** Improvement in motor score by treatment group

**Figure 5** Blood pressure by treatment group

**Figure 6** Heart rate by treatment group

**Table 1** Characteristics of included studies

Author Date	Subjects Control/ Active	Dose regime	Therapy intervention	Type of patients	Time post stroke	Length of follow-up	Primary outcome
Crisostomo 1988	4/4	Single dose of 10 mg dexamphetamine	45 mins physio session within 3 hrs of treatment	Ischaemic stroke with motor weakness	Up to 10 days	3 days	Motor (FM)
Reding 1995	12/9	Dexamphetamine 10 mg for 14 days then 5mg/day for 3 days	Standard in- patient therapy	Ischaemic stroke requiring rehabilitation	7-45 days	3 weeks	Motor (FM), Function (BI), Mood (ZDS)
Walker- Batson 1995	5/5	10 doses of 10 mg dexamphetamine at 3-4 day intervals	Physio session 1 hour after treatment	Ischaemic stroke with hemiplegia	16-30 days	1 year	Motor (FM),
Sonde 2001	19/12	10 doses of 10 mg d,l- amphetamine at 3-4 day intervals	30 mins physio 1 hour after treatment	Ischaemic and haemorrhagic stroke with paresis	5-10 days	3 months	Motor (FM), Function (BI)
Vachalathiti 2001	14/13	10 mg metamphetamine for 7 days	Unknown	Ischaemic stroke	0-10 days	3 weeks	Motor (FM)
Walker- Batson	9/12	10 doses of 10 mg dexamphetamine at	1 hour speech therapy 45	Ischaemic stroke with mod-severe	16-45 days	6 months	Communication (PICA)

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2001		3-4 day intervals	mins after treatment	aphasia			
Martinsson 2003	15/30	2.5-10 mg dexamphetamine twice daily for 5 days	1 therapy session during the 5 day Rx period	Ischaemic stroke motor weakness	<72 hours from onset	90 days	Safety (AE) Haemodynamics Neurological (SSS) Functional (BI)
Treig 2003	12/12	10 doses of 10 mg dexamphetamine at 3-4 day intervals	Physio within 60mins of treatment	Ischaemic stroke with BI 0-50	Up to 6 weeks	360 days	Motor (RMAS), Function (BI)
Platz 2005	13/18	10 doses of 10 mg d-amphetamine at 3-4 day intervals	Therapy 2 hours after dose	Ischaemic stroke mild arm paresis	3 weeks to 6 months	1 year	Motor (TEMPA test time)
Gladstone 2006	37/34	10 doses of 10 mg dexamphetamine at 3-4 day intervals	1 hour therapy session 90 mins after dose	Ischaemic or haemorrhagic stroke with moderate hemiparesis	5-10 days	3months	Motor (FM), Function (BI)
Sprigg 2006	16/17	Initial 5mg then 10 doses of 10 mg dexamphetamine at 3-4 day intervals	Routine inpatient therapy	Ischaemic stroke motor weakness	3-30 days	90 days	Motor (FM), Neurology (SSS), Function (BI, mRS), Haemodynamics (BP, HR, CBF)

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