Amphetamine Trials and Tribulations

Larry B. Goldstein, MD, FAAN, FAHA

Background—Laboratory experiments conducted since the 1940s show that amphetamine combined with task-relevant experience improves postbrain injury behavioral outcomes. Several small clinical trials evaluated the approach as a means of improving poststroke recovery.

Results of Review—In laboratory studies, the effect of amphetamine on recovery depends on the location and extent of brain injury, the dosing and timing of amphetamine, and the type, intensity, and timing of concomitant behavioral training. The small clinical trials conducted to date vary considerably in critical aspects of their designs and are largely negative.

Conclusion—The question of whether d-amphetamine combined with physiotherapy is of any clinical value remains unanswered. (Stroke. 2009;40[suppl 1]:S133-S135.)

Key Words: amphetamine ■ stroke ■ recovery ■ humans

Reports suggesting that the administration of d-amphetamine improves functional outcome when given after brain injury date to at least the 1940s.1 Interest renewed with a provocative 1982 report describing experiments in which a single dose of d-amphetamine given 24 hours after unilateral sensorimotor cortex ablation in the rat led to an enduring enhancement of motor recovery.2 The observation has since been replicated in numerous laboratories in a variety of different species with a range of brain injuries.3–5 These experiments elucidate several important principles. First, the dose-effect relationship for amphetamine-promoted motor recovery has an inverted “U” shape. The drug is relatively ineffective at lower and higher doses. Second, the effects of certain drugs (eg, amphetamine) on recovery are dependent on concomitant behavioral experience. Third, the timing of the drug administration/experience intervention is critical and also varies with the number and frequency of treatment sessions. Fourth, some drugs (eg, haloperidol) impair recovery.

Several double-blind placebo-controlled clinical studies have evaluated the effects of amphetamine on poststroke motor recovery in humans (Table). In one of the first such studies, 8 subjects were given a single dose of either d-amphetamine (10 mg, a dose approved by the Food and Drug Administration for other indications) or placebo within 10 days of ischemic stroke.6 All had targeted physiotherapy for 45 minutes within 3 hours of drug or placebo administration. When assessed the next day, motor performance improved in the amphetamine-treated group, whereas there was little change in those given placebo. The study provided a “proof of principle”—amphetamine combined with physiotherapy could positively affect poststroke motor performance, at least in the short term.

Extending this finding has proven challenging, in part because of the multiple factors that laboratory studies indicate may be critical. A second trial compared the recoveries of subjects given 10 mg of d-amphetamine daily for 14 days followed by 5 mg for 3 days with those given placebo (n=21)7 Treatment began more than 1 month after stroke. Drug/placebo administration was not tightly linked with physiotherapy. There was no benefit, possibly attributable to the dosing regimen, treatment window, or a lack of a tightly coupled drug-physiotherapy regimen.

Another trial compared d-amphetamine with placebo given once every 4 days for 10 sessions beginning 16 to 30 days after stroke with physiotherapy given during the “peak of drug action,”8 a schedule based on experiments in cats.9 Subjects given d-amphetamine had greater improvements compared to placebo-treated subjects as long as 1 year later. A second trial using a similar regimen included patients up to 6 weeks (mean, 3.5 weeks) after stroke and found no effect.10 dL-amphetamine (10 mg twice-weekly tied to physiotherapy) was tested in subjects beginning 5 to 10 days after stroke with outcomes measured after 3 months.11 There was no effect of treatment, possibly because of the reduced potency of the l-stereoisomer.

Another study randomized 30 subjects with severe ischemic strokes within 96 hours of symptom onset to 5 to 10 mg of d-amphetamine once or twice daily (depending on alertness) plus 30 to 45 minutes of physiotherapy twice-daily or a maximum of 15-minutes of physiotherapy each day for 5 consecutive days (ie, both groups received amphetamine and...
the intensity of physiotherapy varied).12 There was no difference between the groups. In addition to the dosing regimen, interval, and duration, treatment began soon after stroke and included only the severest subjects.

In the largest study reported to date, 71 patients were randomized to 10 sessions of physiotherapy coupled with either 10 mg of \textit{d}-amphetamine or placebo twice weekly beginning 5 to 10 days after stroke.13 Although there was no overall difference between the groups, the addition of \textit{d}-amphetamine accelerated the recovery of arm motor function among those with moderate deficits.

A preliminary study combined robot-assisted arm physiotherapy with or without \textit{d}-amphetamine and found early benefit only with \textit{d}-amphetamine.14 The NIH-sponsored Amphetamine-Enhanced Stroke Recovery (AESR) trial is in progress and is evaluating the impact of the timing and duration of therapy.

Amphetamine can have a variety of cardiovascular side effects that might limit its use. One study evaluated the safety of 3 doses of \textit{d}-amphetamine (2.5, 5, or 10 mg twice-daily for 5 days) compared to placebo in 45 subjects enrolled within 72 hours of stroke.15 Blood pressure and heart rate increased, but there was no difference in adverse events. Of the 99 subjects enrolled to date in the AESR trial, only 12% did not complete planned treatment with none withdrawn because of events potentially attributable to \textit{d}-amphetamine.

The variable and largely negative clinical trial results could be attributable to design factors related to stroke location and extent, the dosing and timing of the drug, and the type, intensity, and timing of physiotherapy. We turned back to the laboratory to evaluate some of these factors. In one experiment, young adult rats housed in complex environments had unilateral surgical ablation of the fore- and hind-limb sensory-motor cortex. After 5 days, a plaster-of-Paris cast was applied to half of the rats to restrain the unimpaired (ie, ipsilateral) forepaw. Similar but nonrestraining casts were placed on controls. Beginning the next day, the rats were given a single dose of either \textit{d}-amphetamine, haloperidol, or vehicle placebo each day for 5 days and immediately returned to their cages. In this way, the casted rats received a combination of intensive exercise of the affected (ie, non-casted) forepaw in combination with drug or placebo. The casts were removed after 7 days, and the animals tested twice weekly for an additional 3 weeks. Forepaw function was assessed with a variation of Schallert “cylinder test” in which the number of forepaw contacts with the walls of a transparent cylinder occurring over 3 minutes was recorded by an observer unaware of drug group or the experimental hypothesis. The time required to traverse a narrow elevated beam was used as a measure of locomotor function (assessing primarily hindlimb function). The Figure gives preliminary results based on a final behavioral assessment (approximately 5 weeks after cortex injury). The top panel summarizes data for forepaw touch and shows an overall difference among the groups \((\text{ANOVA}_5,28 \ F=2.62, P=0.046)\). Consistent with prior work, uncasted amphetamine-treated rats had better recoveries (ie, higher scores) than uncasted controls with uncasted haloperidol-treated rats having the poorest recoveries. Forelimb-casted rats had better recoveries than sham-casted rats, regardless of drug treatment. The effect of casting attenuated the benefit of amphetamine (control-casted versus amphetamine-casted) and partially reversed the harmful effect of haloperidol. These results suggest that it is critical to control the intensity of physiotherapy in clinical trials of amphetamine or similar drugs in humans, and that intensive physiotherapy might obviate the effect of the drug. The bottom panel summarizes data for locomotor recovery in the same rats and shows no overall difference among the groups \((\text{ANOVA}_5,28 F=0.54, P=0.74)\); the effect of fore-limb casting does not generalize to hind-limb deficits; shorter times reflect better function). This, too, is consistent with previous experiments showing drug treatment needs to be given in conjunction with task-relevant experience.

A meta-analysis concluded that there is no indication for the routine use of amphetamines to improve poststroke recovery and that further research is needed.16 Given the potentially critical differences in trial designs, however, the interpretation of the results of this meta-analysis is not clear. Regardless, despite decades of animal experimentation and several small clinical trials, the question of whether \textit{d}-amphetamine combined with physiotherapy is of any clinical value remains unanswered.

### Table. Comparative Clinical Trials of the Effects of Amphetamine on Poststroke Motor Recovery

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Stroke-Treatment Interval</th>
<th>\textit{d}-Amphetamine Dose/Treatment Frequency</th>
<th>Drug-Therapy Session Interval (Duration)</th>
<th>Outcome Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cristostomo et al, 1988⁶</td>
<td>8</td>
<td>&lt;10 days</td>
<td>10 mg, one session</td>
<td>&lt;3 hour (45 minutes)</td>
<td>1 day</td>
</tr>
<tr>
<td>Reding et al, 1995⁷</td>
<td>21</td>
<td>&gt;1 month</td>
<td>10 mg daily for 14 days, then 5 mg daily for 3 days</td>
<td>Same day (75 minutes)</td>
<td>1 month</td>
</tr>
<tr>
<td>Walker-Batson et al, 1995⁵</td>
<td>10</td>
<td>16–30 days</td>
<td>10 mg every 4 days for 10 sessions</td>
<td>“Peak of drug action” (75 minutes)</td>
<td>1 week and 1 year</td>
</tr>
<tr>
<td>Sonde et al, 2001¹¹</td>
<td>39</td>
<td>5–10 days</td>
<td>10 mg twice weekly*</td>
<td>1 hour (30 minutes)</td>
<td>3 months</td>
</tr>
<tr>
<td>Martinsson et al, 2003¹²</td>
<td>30</td>
<td>&lt;96 hours</td>
<td>5 or 10 mg once or twice daily for 5 days</td>
<td>Same day (15 minutes vs 30–45 minutes)</td>
<td>3 months and 1 year</td>
</tr>
<tr>
<td>Treig et al, 2003¹⁰</td>
<td>24</td>
<td>&lt;6 weeks</td>
<td>10 mg every 4 days for 10 sessions</td>
<td>1 hour (45 minutes)</td>
<td>90 days and 1 year</td>
</tr>
<tr>
<td>Gladstone et al, 2006¹³</td>
<td>71</td>
<td>5–10 days</td>
<td>10 mg twice weekly for 10 sessions</td>
<td>90 minutes (1 hour)</td>
<td>6 weeks and 3 months</td>
</tr>
</tbody>
</table>

*\textit{d}-amphetamine.
**Duration of physiotherapy varied (both groups received \textit{d}-amphetamine).
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Disclosures

None.

References

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