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## Poststroke Treatment:

### Lost in Translation

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Stroke research has primarily focused on prevention and acute treatment. Yet, there is a window of opportunity to provide treatments that will increase functional recovery by capitalizing on the brain's neural plastic responses during postacute and chronic periods.<sup>1,2</sup> Papadopoulos and colleagues' study in this issue of *Stroke* is consistent with decades of research demonstrating that coupling of D-amphetamine administration with motor practice can enhance motor recovery after brain injury in animal models.<sup>3,4</sup> This study elegantly shows that short-term, postacute administration of D-amphetamine sulfate combined with focused physical activity and housing in an "enriched" environment improves motor recovery markedly. These improvements are associated with increased axonal sprouting in corticoefferent pathways to the red nucleus and cervical spinal cord from the contralesional forelimb sensorimotor cortex.

Prior animal experiments provide considerable evidence that even a single dose of D-amphetamine induces enduring motor improvements after various types of brain injury.<sup>5</sup> Likewise, some clinical studies show that amphetamine administration can be beneficial<sup>6,7</sup> and that drugs that have pharmacological effects opposite to that of amphetamine may be harmful.<sup>8</sup> Several clinical trials, however, have failed to show a benefit of poststroke amphetamine administration.<sup>9–12</sup> One positive<sup>7</sup> and one negative<sup>12</sup> trial involved similar patients who were treated under similar protocols. It is therefore not surprising that a recent Cochrane report analyzing 10 studies involving 287 patients concluded that there are still no conclusive data showing that amphetamine treatment is of clinical benefit.<sup>13</sup> Why is there such a discrepancy?

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### Disclosures

None.

The fact that amphetamine effects can be so robust in animal models<sup>14</sup> and yet so variable in human clinical trials<sup>13</sup> should not discredit amphetamine's potential treatment value. Instead, the translation from animal studies to human trials must closely weigh the potential impact of even subtle differences in the timing of treatment, different stroke etiologies, stroke location variability, differences in the type of amphetamine and doses, varying levels of infarct severity, differences in the type and intensity of physiotherapeutic interventions, different outcome measures, age, and the effects of a host of concomitant medications used to treat a variety of comorbid conditions.<sup>3,13,15</sup> These are far more easily controlled in the laboratory than in the clinic. There are no clear or straightforward ways to control for the differences between these 2 settings, factors that may in part have contributed to the long list of promising putative neuroprotective drugs that had no benefit when tested in stroke patients.<sup>16</sup> Nevertheless, this is exactly the task facing clinical stroke investigators. One possible approach is to introduce the same challenges in preclinical studies expected in clinical trials, including the use of older animals and variability in the location and size of the infarcts. If these features result in a lost or reduced benefit of treatment in animal models, then clinical trial failures would make more sense. There likely are no "magic bullet" treatments that will benefit all patients with stroke equally. This has led to the notion of "proof of concept" Phase 2 clinical trials that first try to determine whether a biological effect expected from preclinical studies occurs in an ideally matched human population.

There are too few treatment options available for people living with the consequences of stroke to dismiss the promise raised by the extensive body of laboratory work indicating the potential for D-amphetamine coupled with specific training to enhance the recovery process. Studies such as that of Papadopoulos and colleagues that contribute to our understanding of the basic neurobiology underlying the interaction between experience and drug administration are critical.

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