

Getting the right prescription for rehabilitation after stroke

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Clinicians working with stroke survivors believe that poststroke rehabilitation works, but the evidence base to convince a wider audience is lacking. There are several contributory factors for this. First, we do not know how much of an intervention to provide, although the differences in outcome due to an extra 30 hours¹ compared to 300 hours² of upper limb treatment suggests more is better. Second, we are not sure when to intervene, although the heightened effect of training due to injury-induced biological events seen early after stroke in rodent models (so-called spontaneous biological recovery³) suggests earlier is better. Third, because clinical trials in neurorehabilitation are often not based on mechanistic principles, they lack the appropriate stratification that might identify the appropriate subgroups where large clinically meaningful effect sizes are possible.⁴ In other words, there are clues but they often seem to be ignored. Consequently, it appears difficult to move past the proof of principle study and the failure to translate advances in neuroscience into improved stroke outcomes continues.⁵ This all adds up to a challenging time for those interested in promoting recovery after stroke.

As a consequence, the A Very Early Rehabilitation Trial for Stroke (AVERT) trial⁶ was greeted with enthusiasm. Here was a thoughtfully designed study asking whether earlier and more rehabilitation is better. Specifically, the rationale of the original AVERT study was that at least 3 additional sessions of sitting, standing, and walking activity started within 24 hours of stroke would improve favorable outcome 3 months after stroke (defined as a modified Rankin Scale score of 0–2). It was reasoned that earlier, more frequent, and higher amounts of out of bed activity after stroke could reduce immobility-related complications and take advantage of spontaneous biological recovery to improve outcomes. The flip side was that impaired cerebral autoregulation might lead to reduced cerebral perfusion with an increase in upright posture, thereby exacerbating ischemia. The AVERT results were published last year and demonstrated that 3-month

outcomes were better in the usual care group than in those mobilized early. The possible reasons for this, including mortality due to stroke recurrence or progression, have been discussed elsewhere.⁷ Furthermore, although described as a trial of activity, this interpretation ignores the obvious point that increased activity can be achieved while patients remain in bed,⁸ which in fact may be more beneficial to upper limb recovery.

AVERT took 8 years to recruit and the results were much anticipated. After publication of the primary results, there was a general sense of disappointment that there was no green light to earlier and more aggressive physical therapy, which many had suggested was needed to augment recovery. There was some concern that the results would be used to cut back “unnecessary” early neurorehabilitation teams.

However, AVERT has more insights regarding early poststroke rehabilitation, as investigators delved further into their results. Crucially, the investigators were careful to record details of all interventions, thereby allowing for prespecified “dose” response analyses to examine the effect of (1) time from stroke onset to first mobilization out of bed, (2) number of out-of-bed sessions per patient per day, and (3) minutes of out-of-bed activity per patient per day. In this issue of *Neurology*®, Bernhardt et al.⁹ report that additional sessions (given constant time to first mobilization and minutes of out-of-bed activity) improved the odds of achieving a favorable outcome (defined as a modified Rankin Scale score of 0–2). However, increasing the amount of time spent in out-of-bed activity (given constant number of sessions and time to first mobilization) reduced the odds of a favorable outcome. Taken together, these findings indicate that short, frequent sessions of mobilization may be preferable for many stroke survivors in the first weeks after stroke, a result that is altogether more clinically useful than the primary analysis.

AVERT was aimed at increasing sitting, standing, and walking, so does this study tell us anything about rehabilitation of stroke more generally? It is tempting

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to suggest that the results might generalize. In the upper limb, for example, newly learned skills are more likely to be retained when there are frequent and longer rest periods between training sessions.¹⁰ The authors are cautious about the results, suggesting that each of these factors (number and length of treatment sessions) will need to be assessed prospectively in randomized clinical trials. The implications for early upper limb training, while supine or upright, are also likely to require separate investigation.

For now, however, this study provides clinically useful data that help to fill an important gap in our knowledge about the optimal dose (frequency and timing) of mobilization in the early stages after stroke. Importantly, it completely changes the narrative that had begun after the publication of the primary outcomes. It highlights the complexity of decision-making that is involved in stroke rehabilitation, and reminds us that therapy schedule, not just the total amount and timing, matters. The design of future clinical trials needs to take this into account by investigating whether these principles apply to all neurorehabilitation interventions in general. This further analysis of the AVERT study provides further clues to finding the right prescription for early rehabilitation after stroke.

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