

What's the Perfect Dose for Practice to Make Perfect?

Neurologists and clinician-scientists interested in stroke recovery frequently do not know the details of the rehabilitative therapy that their patients receive. However, patients' and caregivers' expectations of getting the best possible therapy will put more demands on health care providers to understand not only the ingredients of rehabilitation, but also the patient's potential for recovery. Some of the crucial questions are when to provide traditional and/or experimental therapy (acute vs subacute vs chronic phase), how intense it should be, its frequency and duration per session, how many sessions in total, what activities it should include (relearning of skills vs compensatory skill learning), and whether or not it is coupled with plasticity enablers and enhancers (such as pharmacological agents, brain stimulation, or multi-sensory feedback). Lang et al, in this issue of *Annals of Neurology*, have taken up this challenge by rigorously investigating one of these variables: repetition of movements within a fixed number of sessions.¹

Lang et al showed that gains in upper-limb function did not improve as a function of dose— for task-specific therapy in patients, beginning 6 months or more poststroke. Treatment consisted of supervised practice of functional tasks that were graded and progressive for each participant by study therapists. Therapy dose was quantified in terms of repetitions of upper-limb movement and delivered 1 hour per day, four days per week, for 8 weeks (a total of 32 hours). A strength of the study design was the provision of four levels of dose, including an “individualized maximum” (IM) level. The IM group received the highest dose, 300 repetitions per session, but also continued beyond 8 weeks until the outcome plateaued, which, on average, occurred approximately 1,200 repetitions beyond the week 8 total. The lowest dose delivered was 3,200 repetitions. Modest gains in function with improvements were realized at a rate of just under 1 point per week on the Action Research Arm Test (ARAT), with no differences between groups (dose) to indicate that more movement training results in better functional outcomes. In fact, the group that performed 6,400 repetitions did not improve over the study period. Within each group, there was considerable variation in response, characteristic of many stroke rehabilitation trials.

The ARAT was the primary outcome. The ARAT measures the ability to perform tasks and is comparable to the Wolf Motor Function Test. Although there is a concern about practice effects with repeated assessments, advancing in the ARAT generally means ability to perform a new task, because of its hierarchical Guttman scale design.² The statistical analysis used for the main outcome was sophisticated and mitigated the relatively small sample size in each group. Change in outcome over the course of the intervention was best modeled by a linear growth curve and significance of group assignment on growth curves assessed with hierarchical linear modeling. Permutation tests and bootstrapping completed the rigorous analysis and provide some assurance of reliability. Of course, there is no guarantee that random differences among groups did not mask, in some way, the specific effect of an intervention.

Since there was no dose-response effect, one might wonder whether there was any effect of therapy, saturation of effects at the lowest dose, or whether the improvements may reflect a practice effect from the weekly assessment alone or an expectation bias that therapy helps. A no-therapy control, and use of multiple baseline assessments before treatment, could usefully be included in future trial designs. It is understandable that such a control was omitted in this study, given that it had a singular goal of measuring the effect of dose, and it can be impractical to expect frequent visits for assessment when therapy is withheld. But if a null control had been included, it would have answered the interesting question of whether the 3,200 dose was an effective and efficient treatment compared to no treatment.

The lack of improvement of the 6,400 group is curious. For example, it is unknown whether this group by chance had more patients with lower potential for therapy response, as might have been evident if biomarkers of functional or structural corticospinal tract integrity were obtained.^{3,4} Such biomarkers, which have been shown to correlate highly with clinical measures of impairment and recovery predictions,^{5–7} were not used to stratify patients at study inception and may indeed have accounted for variation in treatment response within and across groups. In fact, in comparison to the other groups, the 6,400 group was more heavily male, left-handed, discordant (nondominant hand affected),

and had the fewest purely subcortical strokes (only one), even though only concordance was significantly different by statistical comparisons. Stratification on multiple features cannot succeed when sample size is too small, but inclusion of biomarkers that help to stratify patients at the beginning and predict ability to recover can be helpful in such trials.

The study reminds us of the potential value of “bursts” of therapy at the chronic stage, even if the functional gains achieved are modest for some. Lang et al found that 90% of patients in their study reported a meaningful perception of change in performance and satisfaction over time—an effect that did not depend on dose and was not borne out by differences in functional outcomes. How long these perceived benefits might last is questionable and perhaps better answered once a robust treatment effect is found. The EXCITE trial, which included patients across a wider range of time poststroke, also demonstrated the effectiveness of a burst of therapy on functional ability.⁸

It is not surprising that patients improve slightly after re-engaging in therapy at the chronic stage. Over time, deterioration of paretic upper-limb function occurs alongside factors such as learned nonuse. Although plasticity is increased in experimental stroke models at the acute and subacute phase, at the chronic stage plasticity seems to normalize to prestroke levels, such that task specificity of both compensatory responses in chronic stroke, and skill learning in healthy individuals, possibly rely on the same “garden variety” plasticity.⁹ However, it seems unlikely that task-specific therapy alone, no matter how high the dose, will ever exceed the magnitude of effect observed. The jury remains out until the limitations of everyday plasticity are overcome by some other means. This is why pharmacological agents,^{10,11} methods to provide multisensory feedback (eg, auditory, and visuomotor coupling),¹² and interventions, such as noninvasive brain stimulation,^{13,14} continue to be explored as possible plasticity enhancers and adjuvants to stroke rehabilitation.

The form of therapy in chronic stroke may need to differ substantially from the current individually guided and supervised practice paradigm to produce a more-robust treatment effect. There is some evidence in support of this idea from trials of robotic-guided therapy.^{15,16} The number of repetitions in such trials is substantially higher than even the highest dose in this one, but repetitions of elementary movements using a robot may not be equivalent to practice of a relevant task and may not generalize to nonpracticed activities. The patients who are motivated to enter a clinical trial are likely to be the ones that have already practiced activities of daily living on their own. For these patients, only a therapy substantially different than task-based practice could offer any hope of reversing impairment or improving function. This is analogous to plateaus commonly observed in sporting performance, where regular

repetitive practice leads to no further improvement. In sport, as in rehabilitation, progression and variation are key concepts in continued improvement.

It has long been claimed that individual performance differences in music and sports reflects differences in the amount of deliberate practice, culminating in reports that musicians entering professional conservatories have practiced far more than 10,000 hours. However, a recent meta-analysis suggested that deliberate practice only explains 18% to 21% of the variance in performance in music and sports.¹⁷ Clearly, more is good, but it is not always better.

Lang et al’s study does not encourage more trials of conventional supervised task-based practice in the chronic phase. A conceivable next step identified by the investigators is to examine dosing along other dimensions, such as intensity and also frequency. For example, a recent secondary analysis of the AVERT trial suggested that more-frequent, shorter intervention periods might have a beneficial effect.¹⁸ Arguably, intensity would be more difficult to quantify than repetition. Nevertheless, we envision that future recovery and rehabilitation trials will explore dimensions such as repetition, intensity, and frequency of novel therapies. These trials will need to use biomarkers of recovery potential, explore methods to enhance plasticity (such as pharmacological agents, multisensory feedback, and noninvasive brain stimulation) alongside therapy, and be conducted in a motivating and rewarding environment.

Author Contributions

W.B., G.S., and G.W. contributed equally to the writing of this editorial.

Potential Conflicts of Interest

Nothing to report.

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