Stroke

CONTROVERSIES IN STROKE

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High-Dose, High-Intensity Stroke Rehabilitation: Why Aren't We Giving It?

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INTRODUCTION

Current doses and intensities of poststroke rehabilitation therapy provided as usual care are paltry compared to the magnitudes needed to drive large behaviorally relevant reductions in neurologic impairments. There is convergent evidence indicating that high-dose, high-intensity rehabilitation is effective for improving outcomes after stroke with large effect sizes compared to usual care. Here, we highlight some of this evidence (focusing on studies of upper extremity motor rehabilitation) and then ask the simple question—why are we not delivering high doses and intensities of rehabilitation in clinical practice? We contend that reasons for the lack of implementation of high-dose, high-intensity rehabilitation have to do with questionable conceptual, ideological, and economic assumptions. In addition, there are practical challenges, which we argue can be overcome with technology. Current practice (we refer primarily to the context of US health care) in stroke rehabilitation is itself built on very little evidence, indeed considerably less than the cumulative evidence indicating that high-dose, high-intensity rehabilitation would be more effective. Our hope is that this perspective will help persuade multiple stakeholders (neurologists, physiatrists, therapists, researchers, patients, policymakers, and insurance companies) to advocate for higher doses and intensities of rehabilitation. There is certainly more research to be done on new ways to deliver high-dose, high-intensity neurorehabilitation, as well as zeroing in on its best timing and dosing and how to best combine it with drugs and physiological stimulation. In the meantime, our view is that a large body of convergent evidence already justifies seeking to incorporate higher doses and intensities of therapy into current clinical practice as the new standard of care.

WHY IS HIGH DOSE, HIGH INTENSITY REHABILITATION NEEDED NOW?

Despite impressive advances in acute stroke therapy, stroke remains an enormous cause of worldwide disability. The health and economic impacts of the disease are staggering, and the resulting disability crisis is only projected to increase in the coming years.[1,2] In contrast to acute stroke therapy, advances and clinical translation in stroke rehabilitation have been much slower. Indeed, neurorehabilitation is at a critical impasse. On the one hand, research is steadily accumulating evidence that high-dose, high-intensity rehabilitation—delivered either by increasing the hours of regular occupational, physical, or speech therapy or by using novel, technologically driven approaches—is effective for improving outcomes with large effect sizes compared with usual care.[3–5] On the other hand, the incorporation of high-dose, high-intensity rehabilitation into clinical practice has been frustratingly slow.[6] The reasons for limited implementation of high-dose, high-intensity neurorehabilitation despite convincing research findings are myriad and include problematic conceptual, ideological, and economic assumptions. The conceptual (mis)assumption is the failure to appreciate the capacity for continued and meaningful recovery, even in chronic phases of stroke,

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if substantially high doses and intensities of rehabilitation are provided.[7–9] The ideological (mis)assumption is that behavioral interventions will always be a suboptimal stopgap until either magic-bullet drugs or technological innovations come along that leapfrog over the need for time-consuming behavioral protocols. The economic (mis)assumption is that more rehabilitation necessarily implies more money spent.[10] Current reimbursement in the United States for stroke rehabilitation is fee-for-service, and, as a result, insurance status significantly impacts access to rehabilitation services.[11] This upfront cost way of thinking ignores the potential cost savings that result from better rehabilitation outcomes, for example, through reduced rehospitalization rates, less dependence on home health, decreased caregiver burden, and increased return to work.[12]

Our central thesis is that the evidence for high-dose, high-intensity rehabilitation improving outcomes after stroke is substantial, and thus, given the tremendous societal burden of stroke-related disability, there is an urgent need to address ways to deliver it. Our intent is not a meta-analysis or systematic review, but rather to discuss conceptual issues and highlight studies that report successful delivery of high doses and intensities of rehabilitation. Our focus is on arm and hand motor impairments and their rehabilitation. Given the conceptual emphasis of this article, we expect that the ideas presented will generalize to other stroke-related impairments (ie, gait, language, and cognition). The focus is on stroke rehabilitation in the United States; comparing stroke rehabilitation systems across different counties is beyond our scope, but we also cite selected studies from outside the United States.

WHAT ARE DOSE AND INTENSITY IN THE CONTEXT OF REHABILITATION?

How does one specify the dose and intensity of poststroke rehabilitation? There are many reasonable approaches to doing so.[13,14] In this perspective, we define dose as the number of hours of rehabilitation delivered, and intensity as the time period (ie, weeks) over which these hours are delivered. Thus, the dose and content of a poststroke rehabilitation program are defined by X hours of task-oriented practice or impairment-oriented therapy delivered over Y weeks. We acknowledge that this does not fully account for the content delivered during rehabilitation sessions (ie, time moving versus resting, the types and numbers of the movements practiced, or degree of the challenge presented). We also acknowledge that systematic frameworks for defining and quantifying dose, intensity, and content in stroke rehabilitation[3,5,14–16] are critical to advancing both research trials and clinical care (metrics such as time on task during sessions will be valuable for prescribing clinicians). Emerging technology such as wearable sensors combined with machine learning approaches will undoubtedly aid the classification and quantification of upper extremity movement.[17,18]

WHAT DOSES AND INTENSITIES OF POSTSTROKE REHABILITATION ARE CURRENTLY BEING DELIVERED IN CLINICAL PRACTICE?

In the United States, patients admitted to inpatient rehabilitation facilities after stroke are mandated to receive a minimum number of hours of rehabilitation therapy (generally 3 hours per day for 5 d/wk, often divided as 1 hour each of physical, occupational, and speech therapy).[19,20] Access to these facilities, offering even this low amount of rehabilitation, varies widely based on social, racial, ethnic, and geographic factors.[21,22] In a study of Medicare claims between 2010 and 2013, 59% of patients did not see an occupational or physical therapist in the first month poststroke.[23] At 3 months after stroke, one recent study showed that 35% of patients with stroke receive no physical therapy, 48.8% no occupational therapy, and 61.7% no speech therapy; 1 in 3 patients do not receive any form of rehabilitation.[24] Although data on the nature and severity of deficits were not available in these studies, those who saw rehabilitation therapists were less likely to be readmitted to the hospital.[23] Furthermore, the length of stay for stroke patients at inpatient rehabilitation facilities is short (on average 15 days)[25] and driven by insurance reimbursement. Even when rehabilitation therapy after stroke is prescribed, doses and intensities received by patients are strikingly low. One classic observational study found that the average number of active upper limb movements per stroke rehabilitation therapy session was 32.[26] Another study found that treatment time during rehabilitation sessions averaged 36 minutes (in our framework for dose intensity, this would be 0.5 hours per session). In addition, there was considerable variability in the number of movements practiced (still averaging ≈30), and active practice of functional movements (versus passive stretching) was minimal.[27] A recent systematic review found that time on task during usual care upper limb motor interventions varied from 8 to 44 minutes per session.[20] Overall, current poststroke rehabilitation therapy is characterized by inconsistent delivery, and, when delivered, it is generally given at doses and intensities that are too low.

Standard of care rehabilitation poststroke is so variable and nonprotocolized that it is nearly impossible to incorporate it into clinical trials as the control arm. As a result, control therapy delivered in the context of clinical trials is almost invariably given at higher doses and intensities than usual care. For example, in the recent, pivotal VNS trial (Vagus Nerve Stimulation) for upper extremity motor stroke recovery, both groups (experimental and sham control group) received 27 hours over 6 weeks of

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"high-repetition, task-based, functional, individualized, and progressive upper limb exercises."[28] Given that participants in the study had varying degrees of functional capabilities, the exact number of movements and tasks varied across individuals and sessions, but it was estimated that there were >300 movements per session; 10 times the amount provided in usual care.[26] Thus, there is, at the very least, tacit recognition that new neurotechnological approaches for stroke rehabilitation (eg, VNS) need to be delivered with a rehabilitation training dose that is considerably higher than usual care. Unfortunately, when neurotechnological devices become commercially available, they almost invariably revert back to being used alongside usual care rather than being implemented with the high-dose, high-intensity training given in the original trial context. This all-too-common pattern leads to 3 conclusions. First, usual care as it is currently practiced is inadequate as a control. Second, the potentiating effects of new technologies depend on a higher level of behavioral training than usual care. Third, outside of a clinical trial, providing higher doses of training beyond usual care is currently a huge logistical challenge.

WHAT CONSTITUTES HIGH-DOSE, HIGH-INTENSITY STROKE REHABILITATION?

In the context of upper extremity stroke rehabilitation, we recommend not using the term repetition because it is misleading from both motor learning and rehabilitation perspectives. Effective practice is deliberate,[29] and learning implies acquiring feedback-control policies, not just feedforward memorization of an action sequence.[30] In animal studies, hundreds of upper extremity movements are required to induce behaviorally relevant plastic changes after stroke.[31–33] The number of trials required in human motor learning studies is in the same range, ranging from 300 to 800 practice movements per session[34,35]; this amount is an order of magnitude greater than the ≈30 upper extremity movements delivered during current poststroke rehabilitation.[26] Few studies have translated rehabilitation dosing parameters (including time, scheduling, and intensity) from preclinical to clinical studies—an area ripe for translation.[36–38]

WHAT IS THE EVIDENCE FOR THE EFFICACY OF HIGH-DOSE, HIGH-INTENSITY STROKE REHABILITATION?

In this section, we discuss 3 examples of programs that deliver high-dose, high-intensity rehabilitation (≈100 hours or more over weeks) through an increase in the number of hours patients had access to therapists.

1. **The Queen Square Program** (developed by Ward et al[39] at the Queen Square Neurological Institute) is a structured 3-week outpatient behavioral intervention program that delivers 6 hours of therapy per day for 5 days per week (a total of 90 hours over 3 weeks). The program includes an initial evaluation of movement and performance in activities of daily living, followed by therapy with the goal of both impairment reduction and functional improvement. The program content includes twice-daily individual sessions with a therapist focused on repetitive task-practice and movement quality supplemented with robotic training, sensory retraining, dynamic and functional orthoses, neuromuscular electrical stimulation, and group work. Clinical criteria warranting admission to the program are broad and focused on whether staff feel that they would be "able to help patients achieve their goals for the affected upper limb." Plegia, shoulder pain, severe spasticity, or contractures are exclusions. One recent cohort study of chronic stroke patients who underwent this clinical program[39] showed a median 6-point improvement (interquartile range, 3–9) in the upper extremity Fugl-Meyer (UE-FMA) from admission to completion of the 3-week program and continued to make gains (median 9-point UE-FMA change, interquartile range, 4–12) up to 6 months, as well as corresponding improvements across a range of functional and patient-reported outcome measures.[40] Importantly, this study demonstrates that high-dose, high-intensity upper limb therapy can improve outcomes even in patients with chronic stroke. It should be noted that along with the actual therapy, the Queen Square Program also emphasized a comprehensive and multidisciplinary approach including psychosocial interventions.[41] The Queen Square study was not a clinical trial, as it lacked both a control group and blinded assessments. Nevertheless, it demonstrated that real-world implementation of high doses and intensities of upper limb therapy is feasible. Indeed, it is unclear if a clinical trial replicating the Queen Square Program could feasibly be set up—hundreds of patients traveling and staying in a hotel for 3 weeks only to get standard of care if they were randomized into the control group. They would almost certainly need to subsequently be offered a crossover to the high-dose, high-intensity intervention. From an economic standpoint, this program comes under the National Health Service in the United Kingdom, which means it is free to patients. It is unclear whether this model can scale even in the United Kingdom, and it is not obvious how it could be implemented or paid for in the United States outside of a concierge model.
2. **Constraint-induced movement therapy (CIMT,** developed by Taub and colleauges[42]) is an example of a focused rehabilitation intervention

that features high doses of movement training. In CIMT, the nonparetic upper extremity is restrained with a sling and mitten while simultaneously, the patient is asked to engage in shaping and task-oriented practice with the stroke-affected arm and hand.[42] The CIMT protocol also has a transfer package to promote the generalization of motor gains to the patient's real-world environment.[43] Evidence for the efficacy of CIMT for patients after stroke comes from the EXCITE trial (Extremity Constraint Induced Therapy Evaluation),[44] a single-blind, randomized study that enrolled 222 patients with stroke 3 to 9 months prior and moderate arm motor deficits. Patients were randomized to up to 6 hours of CIMT daily for 2 weeks versus usual care. In addition, patients in the CIMT group were encouraged to wear the mitt on their nonparetic upper extremity for a goal of 90% of waking hours during the 2-week intervention period. Significant benefits were found for the primary end points—Wolf Motor Function Test (52% reduction in time to complete its tasks) and Motor Activity Log (76%–77% increase in self-reported quantity and quality of affected arm use)—at 1 year. Gains were retained at 2 years posttherapy.[45] Since the EXCITE trial, CIMT has been studied extensively,[46–48] and it is currently considered one of the most effective therapy regimens to improve outcomes of the upper limb.[49]. Clinical adoption of CIMT, however, has been limited because of restrictive inclusion (patients must fit within a narrow range of paretic limb motor deficits to qualify), and it is currently challenging to pay for the extra therapist time to administer it. Additional barriers to adoption include the need to provide education about CIMT and strategies for its implementation to therapists, stroke survivors, and caregivers.[50]

3. **The recovery of arm function in chronic stroke study** (by Daly et al conducted within the US Department of Veterans Affairs system) implemented a 5-hour-per-day, 5-day-per-week, over 12 weeks outpatient rehabilitation therapy research program (300 hours over 12 weeks) for chronic stroke patients with moderate-severe upper extremity impairment. The program involved a core upper limb training protocol based on a sequential program going from single-joint to functional multi-joint movements. The result was clinically significant improvements (post-pre) in both the Arm Motor Ability Test (primary end point) and the Fugl-Meyer score (secondary end point, ≈10-point gain).[51] A follow-up study found similar results at 12 weeks, and when outcomes were analyzed at the midpoint of the study, after 150 hours of therapy, the gains in Fugl-Meyer were correspondingly halved (5 points).[52] That is, the effects at 300 hours of therapy were twice that at 150 hours, indicating no mid-treatment plateau and suggesting a linear relationship between dose intensity received and treatment-related motor gains in chronic stroke. Taken together, these 3 programs show that high-dose, high-intensity motor rehabilitation (≈100 hours) improves outcomes, even for patients with moderate-severe motor impairment and even in chronic stroke, a time period when many clinicians assume recovery has hit a plateau[7,53] (Table).

WHERE MIGHT THERE BE CONFUSION ABOUT HIGH-DOSE, HIGH-INTENSITY REHABILITATION?

1. **There is confusion about stroke rehabilitation goals, approaches, and outcome measures.** Therapy goals[54] can be classified based on the World Health Organization International Classification of Functioning, Disability, and Health[55] schema. This schema organizes functioning and disability into 3 levels: (1) body structure/function (impairment), (2) activity limitation (formerly disability), and (3) participation restriction (formerly handicap). For upper extremity hemiparesis after stroke, this would be therapy focused on improving (1) motor control or encouraging return to more normal movement patterns, (2) better function in activities of daily living (ADLs), and (3) social involvement, life roles, employment, and quality of life.

Current standard rehabilitation prioritizes activity (ie, International Classification of Functioning [ICF] level 2); with the scant number of hours available to them, therapists prioritize ADLs (ie, eating with a fork, dressing, and bathing), at times using adaptive equipment and approaches to bypass the motor behaviors typically used to perform the activity pre-stroke. Correspondingly, ADL training is the dominant rehabilitation framework in current practice.[56] This approach is distinct from impairment minimization, whereby therapists coach their patients to practice a high number of normal movement patterns, encouraging restitution of body structure/function.[57,58] An extreme case to illustrate this ADL-impairment dichotomy is training the nonparetic arm to maximize the performance of ADLs as opposed to training the affected arm—therapy achieves independence in feeding oneself but without return of paretic arm control. A less extreme but still illustrative example is allowing for compensatory strategies (maximizing trunk movements and residual muscle and joint effectors with non-normal movement

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Table. Selected Stroke Rehabilitation Studies Investigating and Delivering High-Dose, High-Intensity Rehabilitation

Study	Dose, intensity	Study design, population	Therapy content	Main findings	Key lessons
Investigation of high-dose, high-intensity therapy					
Queen Square Upper Limb Program (2019)	90 h over 3 wk	Cohort study of 224 chronic stroke patients	Comprehensive upper extremity-focused rehabilitation targeting all levels of ICF.	Improvements across a range of outcome measures (including a median 9-point improvement in the UE-FMA).	High-dose, high-intensity rehabilitation can have substantial effects on outcomes in chronic stroke.
EXCITE (2006)	60 h over 2 wk*	RCT of 222 chronic stroke patients	Constraint-induced movement therapy vs usual care.	Wolf motor function test and motor activity log improved in the CIMT group compared with usual care.	High-dose, high-intensity rehabilitation delivered in the form of CIMT improves outcomes beyond usual care in chronic stroke.
Recovery of arm function in chronic stroke (2015)	300 h over 12 wk	RCT of 39 chronic stroke patients	Robotics + motor learning vs functional electrical stimulation + motor learning + motor learning. All 3 groups received the same dose and intensity. Motor learning treatment involved high-repetition practice focusing on normal movement patterns.	All 3 groups demonstrated clinically significant differences in AMAT and UE-FMA (10 points). No difference across groups. A follow-up study demonstrated that halving the number of hours (150 h) reduced the motor gains by half.	High-dose, high-intensity rehabilitation is required for motor function improvements in chronic stroke, and there is a linear dose-response relationship between therapy and motor gains.
Technology as a mode to deliver high-dose, high-intensity therapy delivery					
Telerehabilitation (2019)	42 h over 6 wk	RCT of 124 subjects	Telerehabilitation vs in-clinic, dose-matched therapy.	Compliance with telerehabilitation was high. Both groups showed clinically significant gains in the UE-FMA across ICF domains, as well as on global function (modified Rankin Scale).	Telerehabilitation is a feasible and efficacious way to deliver high doses and intensities of rehabilitation.
SMARTS2 (2021)	30 h over 3 wk	RCT of subacute stroke patients.	Neuroanimation (3D movements of a paretic arm by controlling the movement of a virtual dolphin) vs dose-matched conventional therapy. Both groups received this therapy in addition to usual care.	Both the neuroanimation group and the dose-matched therapy group showed greater recovery on ARAT as compared with historical controls.	Neuroanimation is a feasible and novel way to deliver a behavioral intervention focused on training high-quality movements.
VIGoROUS (2022)	20 h over 3 wk	Pragmatic RCT of chronic stroke patients	Video game play (15 h) driven by sensor-detected movements of the paretic arm.	Self-managed motor practice at home combined with behaviorally focused therapist sessions had similar outcomes on MAL and Wolf Motor Function compared with intensive in-clinic therapy.	Video games are a promising method to deliver high-dose, high-intensity rehabilitation, thus freeing therapist time to focus on behavior and lifestyle coaching.

3D indicates 3-dimensional; AMAT, Arm Motor Ability Test; ARAT, Action Arm Research Test; CIMT, constraint-induced movement therapy; EXCITE, Extremity Constraint Induced Therapy Evaluation; ICF, International Classification of Functioning; MAL, Motor Activity Log; RCT, randomized control trial; SMARTS2, Study to Enhance Motor Acute Recovery With Intensive Training After Stroke; UE-FMA, upper extremity Fugl-Meyer; and VIGoROUS, Video Game Rehabilitation for Outpatient Stroke.

*In addition to 6 hours of therapy each weekday for 2 weeks (60 hours), participants in the intervention group wore a mitt on their less impaired upper extremity, which encouraged use of their more impaired arm and hand for a goal of 90% of waking hours.

patterns) or introducing adaptive equipment (eg, customized eating utensils) to accomplish activities of daily living.[59,60] ADL training and impairment minimization are not mutually exclusive (therapists often work on shaping movements toward more normal patterns during ADL tasks), but ADL completion is often emphasized over movement quality given the severe time constraints of usual care.

Another misconception that needs to be dispelled is that if current rehabilitation goals are primarily focused on ICF level 2 (ADLs) rather than ICF level 1 (impairment), focusing on high doses and intensities is less important. In fact, high doses and intensities matter at all levels of the ICF. The key is clarity with respect to rehabilitation goals. For example, if the patient has severe impairment in the chronic phase, then high doses of ADL retraining (ICF level 2) might be preferable with assessment at the activity level. But regardless of whether ADL retraining or impairment is targeted, the rules of practice always apply—more is better if training is of appropriate quality.

2. **It is sometimes assumed that significant recovery from impairment is not achievable by rehabilitation.** It has long been appreciated that the largest degree of recovery occurs early after stroke and that this appears to be a repair process that is independent of regular rehabilitation, although it may benefit from some level of rehabilitation to optimally express itself. This repair process is referred to as spontaneous biological recovery. A recovery process is by definition a change. During a longitudinal study to assess the relationship between baseline impairment and subsequent change in impairment for the upper limb, the proportional recovery rule was discovered.[61] The proportional recovery rule, as originally introduced, stated that in the subacute stroke

recovery period, most patients recover ≈70% of their maximal potential reduction in impairment. That is, a stroke patient with 40 points of potential to recover on an impairment-based recovery scale (ie, scores 26 on the initial Fugl-Meyer out of a total score of 66) will recover 28 points (to a Fugl-Meyer outcome of 54), on average. Proportional recovery has since been applied to a broad range of stroke impairments, including lower limb paresis,[62] aphasia,[63] and neglect.[64] There has been robust statistical debate over the applications, implications, and interpretations of proportional recovery.[65–69] The current consensus appears to be that proportional recovery does hold and accounts for more variance in the recovery of the UE-FMA than any other model, but that it does not predict to the high degree that was originally surmised.[69–71] It remains a clue as to how spontaneous recovery of the upper limb mechanistically unfolds.[72,73] Indeed, the proportional recovery rule was developed as a model to explain recovery from motor impairment after stroke, not as an individual-level prediction rule.[69] Future clinical predictive models of impairment reduction will need to incorporate other factors along with the proportional recovery and use predictive diagnostics for external model evaluation. With all this said, the proportional recovery rule in no way implies that behavioral interventions (ie, high-dose, high-intensity rehabilitation) in the subacute period cannot do better than spontaneous recovery.

3. **It is sometimes assumed that too much rehabilitation is detrimental.** Epochs of time post-stroke can be divided into hyperacute/acute (hours through 7 days), subacute (1 week through 6 months), and chronic (6 months onward) based on tissue response and the biological processes that emerge during these time windows.[74] (Mis)interpretation of the results from 2 prior studies has led to the erroneous conclusion that delivering too much rehabilitation too early can lead to worse outcomes. In the multicenter Efficacy and safety of very early mobilization within 24 h of stroke onset (AVERT [A Very Early Rehabilitation Trial]) trial, which recruited 2104 patients with ischemic or hemorrhagic stroke, intensive mobilization within 24 hours of stroke was associated with reduced odds of a favorable outcome at 3 months.[75] It is critical to differentiate rehabilitation therapy dose and timing from out-of-bed upright mobilization, the latter of which was the focus of AVERT. The therapy group spent more time out of bed than the usual care group because the intervention was specifically focused on out-of-bed activities such as sitting, standing, and walking. Early postural shifts after stroke are likely to have a detrimental effect on cerebral perfusion in a subset of patients, especially those with larger strokes, large artery stenoses, and intracerebral hemorrhages.[76] AVERT cautions that early intensive upright out-of-bed mobilization may worsen outcomes, especially in patients with larger strokes and hemorrhages.[77] Importantly, AVERT was not designed to provide generalizable lessons about the dose, intensity, and timing of rehabilitation and, of course, did not address the upper limb, which can be trained while sitting or supine.

The VECTORS trial (Very Early Constraint-Induced Movement during Stroke Rehabilitation) compared traditional therapy (1 hour of ADL retraining and 1 hour of UE bilateral training activities) to dose-matched (2 hours of shaping therapy and wearing a padded constraint mitten for 6 hours per day) or high-intensity (3 hours of shaping therapy and wearing a mitten for 90% of waking hours per day) CIMT during acute inpatient rehabilitation, on average 10 days from stroke onset.[52] While dose-matched CIMT did not change functional outcomes, high-intensity CIMT resulted in worsened motor outcomes at 90 days. However, some puzzling aspects of the VECTORS study should be noted. The difference in the 2 doses of CIMT was only 1 hour, and the putative negative effects of this dose increase occurred at a considerable delay (30 days), results is incongruent with the original rodent studies that first inspired the trial. In addition, this 52-participant trial had baseline differences across groups in sex balance, number of prior strokes, and dominant limb involvement (eg, 63% in the high-intensity CIMT group had their dominant limb affected versus only 32% in the low-dose CIMT group, which could contribute to differences in group outcomes).[78] Overall, it is hard to conclude that activity-dependent excitotoxicity is the explanation for the VECTORS result, and, thus, current evidence is simply too inconclusive to decide that high-dose, high-intensity early after stroke is detrimental.

A closely related cousin to the misconception that high doses and intensities of rehabilitation worsen outcomes early after stroke is the idea that therapy in chronic stroke cannot reduce impairment. The studies discussed above suggest otherwise—90 hours of therapy over 6 weeks,[39] 60 hours over 2 weeks,[44] and 300 hours over 12 weeks[51,52] of rehabilitation therapy all led to significant reductions in upper extremity motor impairment.

A recent well-designed study, CPASS (Critical Period After Stroke Study), explicitly tested whether therapy provided early after stroke was more effective than the same dose provided in the chronic stroke setting.[79] The result did indeed confirm the hypothesis: 20 extra hours of self-selected, task-specific motor therapy (over and above usual care) was more effective at improving scores on the Action Arm Research Test (an ICF level 2

measure) when received within the first 3 months after stroke as compared with after 6 months. Here, for the first time, in humans, we see, from a well-designed hypothesis-driven study, the demonstration of a critical period—the same dose and intensity of upper limb rehabilitation delivered early after stroke yielded better results than when delivered later. Thus, rehabilitation therapy appears to be more effective early poststroke, but high doses and intensities of rehabilitation are still effective in any phase of recovery, including chronic stroke. There is certainly more work to be done to find the optimal dose and time for rehabilitation therapies after stroke. That said, given the extent of stroke-related disability and in light of already available data, we contend that higher doses and intensities of therapy should be incorporated into current clinical practice while, in parallel, conducting additional research studies.

WHY HAVE NOT WE IMPLEMENTED HIGH-DOSE, HIGH-INTENSITY REHABILITATION IN USUAL CARE?

Given the mounting evidence for high-dose, high-intensity rehabilitation, why has it not become the standard of care? In addition to the conceptual confusion discussed above, there are also more pragmatic answers to this question.

1. **Therapists, especially those who trained in stroke, are a scarce resource.** One study showed that demand for therapy services outpaces supply in the majority of the United States.[80] The shortage of therapists is also true internationally[81] and has been shown to contribute to the inability to provide services to meet minimum dose and intensity requirements in the United Kingdom.[82] Among rehabilitation therapists trained specifically in stroke, those trained to deliver high doses and intensities of rehabilitation are in even more limited supply.[56]
2. **Some call for more definitive trials of high-dose, high-intensity rehabilitation before implementation.** The studies covered thus far in this Perspective provide convergent evidence for the following points: more rehabilitation is better regardless of time after stroke, and many more hours beyond current usual care stroke rehabilitation are required for large effect sizes. Some might ask, given this prelude, why not conduct additional randomized controlled trials, testing high-dose, high-intensity rehabilitation versus usual care? We would be the first to advocate for more rehabilitation research trials incorporating high doses and intensities of therapy. These could include mechanistic studies with rigorously defined end points[83] to better understand the generalizable mechanisms of rehabilitation, dose-finding, and dose-ranging studies to determine specifically how much rehabilitation is needed,[84] as well as later-phase trials focusing on patient-centered outcomes, care delivery, and cost-effectiveness. However, we do not think that the implementation of high-dose, high-intensity rehabilitation into usual care should await these trials given the available evidence, which is far superior to the near nonexistence of evidence for the 1 hour of each per day approach to current rehabilitation care. There are many areas of medicine in which a pressing need justifies clinical decisions with incomplete evidence. Consider management decisions in acute stroke care—telestroke consultation to guide administration of intravenous tissue-type plasminogen activator; blood pressure augmentation and head positioning in ischemic stroke patients with posture- and blood pressure-dependent examinations; and hyperosmolar therapy for patients with brain swelling associated with large strokes.[85] None of these examples have level I evidence supporting them. In stroke rehabilitation, the modern practice patterns within inpatient rehabilitation units (generally 1 hour per day of therapy from each discipline) have been grandfathered in, with few supportive phase 3 trials.[86,87] So, what are we to do when there is a major medical crisis (stroke disability) for which current practice is built on insufficient evidence, and there is strong scientific plausibility in favor of a new approach? Our perspective is that given the strong evidence in favor of high-dose, high-intensity rehabilitation, the time for clinical implementation is now; the implications for not doing so are discussed further below.
3. **There is a lack of implementation research in rehabilitation.** One study showed that only ≈2% of published stroke rehabilitation research evaluated the implementation of evidence-based interventions in health care practice.[88] Thus, despite the evidence that high-dose, high-intensity rehabilitation works, there is little knowledge about how to deliver it in clinical practice.
4. **The insurance reimbursement model for rehabilitation therapy is challenging.** In the United States, for therapy to be reimbursed by insurance, patients need to demonstrate continued progress on outcome measures that therapists report. This is problematic for a few reasons. First, commonly agreed-upon stroke outcome measures are ADL rather than impairment-based.[89,90] Second, the timing during which individual patients show therapy-related motor gains is variable—just because a patient does not demonstrate gains early in therapy does not preclude further rehabilitation potential.[91]

5. **Finally, poststroke rehabilitation has not yet embraced a value-based care model.** Societal costs related to stroke are staggering: between 2012 and 2030, total direct annual stroke-related medical costs in the United States are expected to increase from $71.55 to $184.13 billion. Real indirect annual costs (attributable to disability and lost productivity) are projected to rise from $33.65 to $56.54 billion over the same period. Overall, total annual costs of stroke are projected to increase to $240.67 billion by 2030, an increase of 129%.[92] In the United States, inpatient and outpatient stroke rehabilitation services operate on a fee-for-service model: there is a default limit on hours of rehabilitation services and a need to justify additional hours of therapy to insurance companies. Moreover, the fee-for-service model contributes to the fragmentation in poststroke care. For the stroke patient, clot retrieval, inpatient rehabilitation, outpatient rehabilitation, and chronic stroke-related medical care are reimbursed separately. A value-based care model,[12] in which health outcomes are used as the basis for health care payment, would lead to greater integration of postacute care services and emphasis on therapy to improve stroke outcomes, which would, in turn, lead to the implementation of higher doses and intensities of rehabilitation.

WHAT ARE POTENTIAL WAYS TO DELIVER HIGH-DOSE, HIGH-INTENSITY REHABILITATION?

When therapists are a scarce resource, alternative models of delivering rehabilitation should be explored. Group therapy, including circuit class training,[93,94] can be used in both inpatient[56] or community settings[95] to make therapist time per patient more efficient. Another option is for stroke survivors to complete self-directed therapy programs[96,97] outside of formal rehabilitation sessions. We focus on the promise of technology to be used as a vehicle to help deliver high-dose, high-intensity rehabilitation, and in particular robots, telerehabilitation, and gaming.[98]

Rehabilitation robots, in principle, could allow patients to make many more movements with varying degrees of assistance or resistance.[99,100] Two-dimensional (or planar) robots have a manipulandum that can constrain and guide movements along a specified trajectory. In 3 dimensions, an exoskeleton is needed to provide trajectory guidance. In assistive mode, robots hold and move the limb, similar to a therapist providing hands-on encouragement. Unfortunately, as has been demonstrated in a recent meta-analysis,[101] the promise of robotics for stroke rehabilitation has not been borne out.[102–104] The effects on impairment are consistently low, and there is no generalization to activities. The reasons for this failure, as Krakauer[105] has argued, are conceptual and not technical in nature. These will not be discussed here, but the simplistic notion of repetition is 1 culprit: hundreds of rote, assist-as-needed, 2-dimensional reaching movements are not likely to lead to either restitution or return of function. Both impairment- and ADL-level gains necessitate deliberate, contextual, and challenging practice. Thus, while rehabilitation robots were, in principle, designed to deliver high doses and intensities of movement, clinical trials have been disappointing, and current robots are expensive. In our opinion, they require a complete conceptual rethink as well as cost reduction before they can deliver on their promise for stroke rehabilitation.

Given that patients spend most of their time at home, especially in the chronic stroke phase, approaches to bring rehabilitation to the home environment are needed to increase dose and intensity. **Telerehabilitation** extends access to rehabilitation to the home via communication technologies.[106] A recent study[107] found telerehabilitation to be comparably effective to in-clinic therapy for improving stroke-related impairment (the primary outcome was the change, from baseline to 4 weeks after the end of therapy, in UE-FMA, with a noninferiority margin of 30%). Notably, in this trial, telerehabilitation was delivered via a computer with a table, chair, and gaming input devices that were provided to participants. There were synchronous sessions, which consisted of videoconferencing during which therapists guided games and exercises on the computer system. There were also asynchronous sessions, which consisted of the same gaming and exercise content but without therapist contact. A total of 124 subjects (≈4 months poststroke, late subacute phase of recovery) were randomized to receive 36 sessions (42 hours delivered over 6 weeks; for both in-clinic and telerehabilitation groups, half of the sessions were synchronous and half were asynchronous; note the dose-intensity was much higher than usual care) of arm motor therapy either in the home using the telerehabilitation system or in the clinic (dose-matched). Compliance with telerehabilitation was high (98.3%), and patients performed an average of 1031 arm movements per treatment session. Both groups showed clinically and statistically significant gains in the primary outcome, the UE-FMA, as well as on activity level (ie, Box and Blocks) and participation-level (ie, Stroke Impact Scale) outcomes; gains in global function (ie, modified Rankin Scale score) were also substantial.[108] For broad adoption of telerehabilitation, some questions remain, including the specific patients (age, severity, and type of stroke deficits) that would benefit most, cost-effectiveness, the role of caregivers, and equitable access to supporting infrastructure (computers, internet, and integration into health records).[109,110] The optimal ratio of synchronous to asynchronous therapy time is a key parameter that is

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important to further elucidate. Given the limited pool of stroke-trained therapists, to substantially boost therapy hours and achieve high-dose, high-intensity therapy, the amount of asynchronous rehabilitation time will need to expand. However, our view is that regular synchronous therapy (direct interaction with a licensed therapist via videoconference) is absolutely critical for best results—telerehabilitation does not compete with therapists; it extends how they treat patients with stroke.

Video games can be used to deliver therapy with immersive, stimulating, and mood-enhancing experiences. Games can be further enhanced with augmented reality or virtual reality, in which special equipment such as head-mounted displays provide users with immersive interactions with 3-dimensional images or environments.[98] A recent study, SMARTS2 (Study to Enhance Motor Acute Recovery With Intensive Training After Stroke), used a video game to test high doses of non-task-based training in an enriched environment setting. The dose intensity featured in the study was 30 hours delivered over 3 weeks. This was in addition to the standard of care. A total of 24 subacute stroke patients (<6 weeks from stroke) were randomized to either this dose of novel neuroanimation therapy or dose-matched (ie, high dose) occupational therapy. The neuroanimation therapy group made 3-dimensional movements of their paretic arm by controlling the movement of a virtual dolphin while being coached by a licensed physical or occupational therapist. The a priori hypothesis was that the video game would provide patients with an enriched and immersive environment to explore and train high-quality movements that would drive a reduction in impairment. Results showed that there were no differences in the primary end point (UE-FMA) between groups or compared with historical controls (who only received 30 minutes of upper limb therapy per day), but that both the neuroanimation group and the dose-matched (high dose) therapy group showed greater recovery on the Action Arm Research Test (secondary end point that measures activity limitations). The pilot results are promising as they suggest a feasible way to use gaming to deliver a behavioral intervention focused on training high-quality movements.[111] Two points must be made here about these results. The first is that failure to see an additional change in the UE-FMA beyond usual care, while initially puzzling, is likely due to the fact that changes in the UE-FMA, in the subacute period, are largely driven by recovery from weakness,[112] which was not the impairment targeted by the videogame. The second is that the Action Arm Research Test changes seen in this study were likely driven by true motor control improvements and not just compensation. These points highlight the limitations of traditional outcome measures and point to the need to incorporate better assessment tools (ie, kinematics) to quantify recovery after stroke, particularly when behavioral changes are fine-grained and at the level of motor control.

Another application of video gaming is to encourage self-management of motor practice at home. That is, video games can provide a venue through which high doses and intensities of motor practice are self-managed at home, freeing valuable therapist time to focus on behavioral coaching and protocol design. The VIGoROUS trial (Video Game Rehabilitation for Outpatient Stroke) specifically tested this hypothesis; the goal was to determine the effect on everyday arm use of allocating therapist time differently (ie, on behavioral coaching versus motor practice) by leveraging self-delivered video games.[113] Chronic stroke patients were allocated to self-managed gaming versus traditional therapy groups. The gaming groups received a total of 5 hours of in-clinic therapy time focused on behavioral coaching and 15 hours of self-managed gaming (video game play was driven by sensor-detected movements of the paretic arm) over 3 weeks. The dose intensity-matched control group received 15 hours of CIMT and also 5 hours of behavioral coaching. Results showed that self-managed motor practice with video games at home combined with behaviorally focused therapist sessions had similar outcomes on the amount and quality of everyday arm use (Motor Activity Log) and the Wolf Motor Function Test (activity-limitation measure) to intensive in-clinic therapy. This pragmatic trial demonstrates 1 promising method to deliver high-dose, high-intensity rehabilitation when therapist time is scarce—use video games to deliver high doses of motor practice and free up the therapist to be the behavioral coach.

The discussion above focuses on how to deliver high doses and intensities of therapy for the upper limb. For technological approaches in particular, the cost of these approaches should be valued relative to efficacy; more cost-effectiveness research evaluating technology in rehabilitation is needed, as was done in a recent multicenter stroke robotics study.[103] We can also extrapolate these issues of scale to other domains of clinical practice (lower extremity therapy, language, and cognition) with particular attention to how scalable modes of delivery interact with stroke-related deficits. For example, for aphasia after stroke, Apps that augment in-person speech therapy have shown substantial promise.[114–116] For gait deficits after stroke, self-directed rhythmic auditory stimulation has shown recent success.[117,118]

For all modes of therapy delivery (in-person therapy, remote, and technology-augmented), high-dose, high-intensity rehabilitation will require more time with therapists and familiarization with new technologies. This implies that motivation and engagement will be critical factors for successful adherence to these programs.[119–122] Furthermore, careful planning of session content, including building in periods of rest, will be important.

WHICH REHABILITATION CONTENT IS OPTIMAL TO DELIVER?

While a central thesis of this editorial is that high-dose, high-intensity rehabilitation is effective and helpful at all levels of the ICF, it is important to discuss which therapy content, at a given dose intensity, provides the highest yield and greatest gains across ICF domains. Impairment reduction should be a primary goal when possible because large reductions in impairment will lead to the highest likelihood of generalization to better function. Adding further functional gains once impairment reduction has been maximized can be accomplished with ADL-focused training (eg, the transfer package with CIMT[43]) as well as attention to personal factors, psychological conditions, and social issues.

What are optimal strategies to bring about the largest reductions in impairment? For upper extremity recovery, there are specific evidence-based rehabilitation therapy programs that primarily emphasize restitution of motor control.[39,44,57,58,123] However, these require large amounts of in-person therapy (and therapist) time. Neurotechnological approaches—telerehabilitation and gamified rehabilitation through immersive environments[111] and, in particular, nervous system stimulation strategies[28,124–126]—have great promise for impairment reduction.

Thus, an optimal strategy would be for therapist-coached, neurotechnology-enhanced, behavioral training to promote impairment reduction, and then in a serial fashion, for task-specific practice to ensue to maximize functional gains. That is, train to reduce impairment and then practice to enhance function, with different types of neurotechnology in each phase, and always under therapist supervision. Societal reintegration and participation outcomes are additional major and important goals that should be emphasized in parallel. Given that stroke-trained rehabilitation therapists are in limited supply and the barriers to in-person therapy, bringing these rehabilitation strategies to patients' homes via a combination of telerehabilitation and technology-enhanced, gamified exercises is going to be key.

WHAT HAPPENS IF WE DO NOT DELIVER ON HIGH-DOSE, HIGH-INTENSITY STROKE REHABILITATION?

If we fail to deliver higher doses and intensities of stroke rehabilitation, clinical outcomes in stroke rehabilitation will likely continue to be marginal. This would lead to increased nihilism, which would in turn contribute to increased clinician burnout. The provision of rehabilitation will worsen further, as additional cost-cutting will appear justified. For rehabilitation research, clinical trial conditions will continue to bear little relation to what happens in the real world. As discussed above, the control group in clinical trials (when the control group receives a dedicated therapy program, ie, in the VNS trial[28]) usually receives much higher doses and intensities of therapy than usual care.[127,128] Rehabilitation research trials are especially challenging and expensive to design for this reason.[128] Finally, there are novel nervous system stimulation technologies (VNS,[129] spinal cord stimulation,[124] and deep brain stimulation[125]) that promise to drive large reductions in impairment after stroke. All technologies require a background of high-dose, high-intensity training to maximize their rehabilitative effects. That is, without high-dose, high-intensity rehabilitation as the new standard of care, cutting-edge technologies have little chance to deliver on their translational promise of improving stroke outcomes.

WHERE DO WE GO FROM HERE?

Current doses and intensities of rehabilitation therapy poststroke are simply too low. There is mounting evidence that high-dose, high-intensity rehabilitation improves stroke outcomes across all levels of the ICF. The first step for adoption is acknowledgment, alignment, and advocacy for higher doses and intensities of rehabilitation from clinical stakeholders (neurologists, physiatrists, and therapists), researchers, patients, policymakers, and insurance companies. Second, there is an urgent need to create business models to implement and reimburse high-dose, high-intensity rehabilitation. Third, there should be continued emphasis on translational research focused on mechanisms of stroke recovery and how to reproduce or enhance this recovery with novel high-dose, high-intensity training protocols that leverage various forms of neurotechnology.

ARTICLE INFORMATION

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