

UCLA

UCLA Previously Published Works

Title

Should Body Weight-Supported Treadmill Training and Robotic-Assistive Steppers for Locomotor Training Trot Back to the Starting Gate?

Permalink

<https://escholarship.org/uc/item/6qw8n31r>

Journal

Neurorehabilitation and Neural Repair, 26(4)

ISSN

1545-9683

Authors

Dobkin, Bruce H
Duncan, Pamela W

Publication Date


2012-05-01

DOI

10.1177/1545968312439687

Peer reviewed

Should Body Weight–Supported Treadmill Training and Robotic-Assistive Steppers for Locomotor Training Trot Back to the Starting Gate?

Neurorehabilitation and
Neural Repair
26(4) 308–317
© The Author(s) 2012
Reprints and permission: <http://www.sagepub.com/journalsPermissions.nav>
DOI: 10.1177/1545968312439687
<http://nnr.sagepub.com>


Bruce H. Dobkin, MD¹, and Pamela W. Duncan, PT, PhD²

Abstract

Body weight–supported treadmill training (BWSTT) and robotic-assisted step training (RAST) have not, so far, led to better outcomes than a comparable dose of progressive over-ground training (OGT) for disabled persons with stroke, spinal cord injury, multiple sclerosis, Parkinson’s disease, or cerebral palsy. The conceptual bases for these promising rehabilitation interventions had once seemed quite plausible, but the results of well-designed, randomized clinical trials have been disappointing. The authors reassess the underpinning concepts for BWSTT and RAST, which were derived from mammalian studies of treadmill-induced hind-limb stepping associated with central pattern generation after low thoracic spinal cord transection, as well as human studies of the triple crown icons of task-oriented locomotor training, massed practice, and activity-induced neuroplasticity. The authors retrospectively consider where theory and practice may have fallen short in the pilot studies that aimed to produce thoroughbred interventions. Based on these shortcomings, the authors move forward with recommendations for the future development of workhorse interventions for walking. In the absence of evidence for physical therapists to employ these strategies, however, BWSTT and RAST should not be provided routinely to disabled, vulnerable persons in place of OGT outside of a scientifically conducted efficacy trial.

Keywords

locomotion, walking, motor activity, central pattern generators, stroke rehabilitation, spinal cord injury rehabilitation, physical therapy modalities, exercise therapy, robotics, clinical trials

Body weight–supported treadmill training (BWSTT), robotic-assistive step training (RAST), and associated techniques for locomotor training (LT) have not proven superior to exercise and progressive over-ground gait training (OGT) to improve walking for motor impaired patients with stroke, spinal cord injury (SCI), multiple sclerosis, Parkinson’s disease, and cerebral palsy. This conclusion, based on scientifically conducted, randomized clinical trials (RCTs), is most disappointing.¹

The authors bet heavily on BWSTT as a neurophysiologically sound strategy for moderate to severely impaired patients after SCI² and stroke.³ After over a dozen years of mostly uncontrolled pilot studies and underpowered trials, we initiated and completed an adequately powered, multicenter RCT of BWSTT plus OGT for patients with recent traumatic, incomplete SCI who could still not walk without maximal assistance by 6 weeks after onset. We compared this strategy with conventional progressive OGT.⁴ In a second RCT, also supported by peer review and funding from the National Institutes of Health, we compared BWSTT

with progressive exercise in the home that did not include any formal practice for walking, starting at either 2 or 6 months after stroke in highly disabled (walking speed <0.4 m/s) and moderately disabled (initial walking speed 0.4 to <0.8 m/s) hemiparetic participants.⁵ The participants were identified at the time of their inpatient rehabilitation, unlike earlier pilot studies of BWSTT, in which subjects were usually a convenience sample drawn from volunteers in the community. Baseline variability among groups in the Spinal Cord Injury Locomotor Trial (SCILT) and the Locomotor Experience Applied Post Stroke (LEAPS) trial was negligible, because the entry criteria had been well defined. The technique for the

¹Geffen UCLA School of Medicine, Los Angeles, CA, USA

²Wake Forest University, Winston-Salem, NC, USA

Corresponding Author:

Bruce H. Dobkin, MD, Geffen UCLA School of Medicine, Reed Neurologic Research Center, 710 Westwood Plaza, Los Angeles, CA 90095, USA

Email: bdobkin@mednet.ucla.edu

experimental intervention, BWSTT and OGT, was developed and applied by the therapists who came to refer to this strategy as LT.⁶ Outcomes were assessed at 6 and 12 months after 36 sessions of each intervention had proceeded for 3 months after entry.

Our horses did not win. Both the SCILT⁴ and the LEAPS⁵ trials showed that the more conventional OGT in SCILT and home-based exercise for LEAPS produced similar results in strength, walking speed and distance, physical functioning–related quality of life, and dependence on assistive aids (SCILT). Participants with greater motor control in SCILT and LEAPS did perform better than those with less selective movement and strength, regardless of the intervention. A futility analysis for SCILT revealed that >1000 participants would be needed to possibly show a difference between the interventions. Of course, SCILT and LEAPS did not address the question of whether BWSTT can enhance gains in patients who are more than 1 year beyond onset and still not able to walk in the home or community.

RAST was touted, at first, as a strategy to exceed the effects of BWSTT and other motor learning strategies. It would enable more intensive practice of stepping without placing high physical demands on physiotherapists, along with offering more normalized movement trajectories of the legs than hands-on therapy during BWSTT might provide.⁷ In addition, robotic therapy was expected to be less expensive, because it took several more therapists to provide BWSTT.

Despite a long series of pilot studies that strongly suggested the potential for efficacy of BWSTT, subsequent meta-analyses,⁸⁻¹⁰ systematic reviews,¹¹⁻¹⁴ and additional recent RCTs for SCI,^{15,16} stroke,¹⁷⁻¹⁹ and cerebral palsy²⁰ have revealed equivalence. The related strategy of using RAST plus OGT for stroke,²¹ Parkinson's,²² and multiple sclerosis²³⁻²⁶ also revealed no better than similar outcomes when compared with equal intensity of more conventional therapy. An RCT with a design similar to SCILT, but deploying the Lokomat (Hocoma, Zurich, Switzerland), is in progress.²⁷ If this trial does not reveal a strong, clinically important improvement by RAST over conventional training for early SCI, robotics, like BWSTT, should go back to the starting gate until new strategies for functional practice with devices are developed.

We examine how plausible hypotheses that favored these experimental approaches for gait retraining led to pilot studies that sent the horses out to the community track before they were ready to be crowned. We perform a reality check on the racetrack record of properly designed RCTs. We find that the ostensible thoroughbreds of BWSTT, RAST, and LT appear more like solid plow horses than elite winners. We conclude by considering the biases that can breed failure, but can also teach us how to place better bets in the future.

Hypotheses With Surface Plausibility

The conceptual bases for BWSTT included the responsiveness of lumbar central pattern generators (CPGs) to segmental afferent input, despite the loss of most or all supraspinal input to the lumbar motor pools. In addition, BWSTT seemed to epitomize the new icons of neurorehabilitation for motor learning—task-oriented training, progressive practice, and activity-dependent neuroplasticity. The same concepts supported the development of cleverly engineered, electromechanical RAST devices.

Central Pattern Generators

Animal models of complete low thoracic spinal cord transection strongly suggested that interneurons in the lumbar cord formed circuits for automatic, coordinated, alternating hind-limb flexion-extension.²⁸⁻³¹ The spinal transected rats and cats could be trained to perform hind-limb stepping on a treadmill (TM) belt. This was accomplished with partial weight support via a body sling, often accompanied by initial rectal stimulation or pulling down on the tail to elicit leg extensor activity. The moving belt optimized hip extension of one limb at the end of stance and extensor loading in mid-stance of the other to drive automatic stepping. Electromyographic (EMG) activity and flexor-extensor muscle group kinematics kept pace with faster treadmill speeds in the mammals, consistent with the impact of peripheral sensory stimulation on CPGs. Later studies used epidural electrical stimulation as sensory input in spinalized rodents to elicit automatic steplike activity as well.³²

These animal studies did not determine how many of the lumbar motor pools to leg muscles were activated by CPGs. Were there enough to enable OG walking? Supraspinal inputs are necessary, of course, to initiate walking and set the level of activity of lower motor neurons needed for locomotion, as well as to manage equilibrium, adaptations to the environment, and coordinate thoughts and other goal-directed movements during gait. Not surprisingly, then, none of the trained mammals walked OG. They needed the drive of the TM belt, even though they could load their forelimbs to aid attempts at quadrupedal locomotion. So CPGs are a remarkable way to reduce the conscious neural work of the motor network, but experiments have not grappled with the likely insufficiency of isolated CPGs to manage bipedal OG gait. Indeed, recent rodent experiments suggest that BWSTT may only improve OG locomotion in the presence of spared descending fibers.³³

Evidence of conservation of CPGs in humans was found in occasional patients with clinically complete or severe SCI. When supine, these subjects demonstrated spontaneous lower extremity alternating flexor and extensor activity at about 0.5 to 1 Hz, often in association with hip pain,

pinch, or other external stimulation.³⁴ The amplitude and coordination of firing of motor units in leg muscles were also found to increase after considerable BWSTT in people with complete and incomplete chronic SCI.^{35,36} The animal and human studies led to the suggestion that BWSTT might tap into this CPG subsystem and contribute to enable walking in highly impaired patients.

A recent case study also supported a human CPG as a target for rehabilitation. A subject with a chronic, motor complete SCI (sensation present below C7) spent 107 hours getting BWSTT in 175 sessions over 2 years.³⁷ He was still unable to take steps. Then the research group implanted an epidural electrical pulse stimulator. By 80 sessions later, the device elicited enough tonic EMG firing during weight-supported standing to enable full weight support in a standing frame. Some low-amplitude EMG was then elicitable in the leg flexors and extensors during fully assisted stepping with BWSTT, but the subject did not take steps. Remarkably, when supine, the subject was now able to produce, only during electrical stimulation, voluntary flexion on command at the hip, knee, and ankle, but not against gravity. Mechanisms for this regained movement include residual supraspinal or propriospinal input that was brought into play by increasing the excitability of just enough of the lower motor neuron pools to produce these movements, much as practice increases excitability in less impaired persons.³⁸ If indeed the exogenous stimulation unmasked such pathways, the experiment also points to the clinical limitations in detection of residual descending axons in paralyzed patients. On the other hand, greater spinal motor pool excitation from electrical stimulation could have simply augmented the ability of the subject to initiate a flexor reflex with, for example, abdominal strain. Much more work needs to be carefully carried out before an RCT of invasive epidural stimulation should go forward to augment training in highly impaired patients. The notion of the CPG as a target for BWSTT and RAST, however, does gain credence from all of these studies.

Task-Oriented Massed Practice

BWSTT and RAST also seemed to offer an ideal method to facilitate massed practice of stepping and allow patients to focus on the kinematics of gait. Motor learning, in contrast to compensatory approaches to rehabilitation, stresses reusing the affected neural networks and spared pathways that contribute to motor control.³⁹ Supporting the patient in an upright position that would not collapse a paretic leg during stance, for example, and engraining the timing of gait by the moving TM belt might enable greater practice of stepping.

Practice intensity is surprisingly modest under usual rehabilitation training⁴⁰ and could be considerably greater.⁴¹⁻⁴³ Although the quantity of practice appears to increase the effect size of a walking intervention, few trials incorporate repetition of task practice based on prior dose-response

studies.^{44,45} Thus, how much repetition is enough goes undocumented. In addition to task-specific repetition, sensory feedback^{46,47} and feedback about performance⁴⁸ are thought to enhance the effects of practice. These aspects of training were not specified in pilot studies.

Task-related, task-specific, and task-oriented training sound like the optimal strategy to improve a specific motor skill. This approach represents how we learn to hit a tennis ball, by practice with a tennis racquet rather than practice hitting golf balls with a club. Task-oriented training is not necessarily the same as task-specific training, however. Even in learning to play tennis, better footwork, an important component of play, can be practiced without a racquet and ball, by moving about playing basketball, squash, or boxing. Unfortunately, clinicians do not know all the components that make up a motor skill, especially within the context of reduced neural substrate. Thus, the components of task-oriented training need to be better described to be able to judge their contributions; multiple interventions may be needed to hone those components.⁴⁹

The treadmill⁵⁰ and available commercial robotic devices⁵¹ include task components that do not necessarily replicate the lower extremity biomechanics of walking OG. For example, some lateral sway is inevitable on a TM with BWS, so this aspect of training differs from OGT. Visuospatial and optic flow signals are also quite different compared with OGT.⁵² The amount of force delivered by the hand of the therapist to extend the knee or prevent toe drag at the initiation of swing will vary across therapists. How well, in terms of learning, the subject responds to cues from a therapist while being assisted in BWSTT is uncertain. Most important, studies have not demonstrated that therapists have teased out how the training of component tasks on a belt or device can be translated into OG practice and vice versa, that is, how temporal and spatial components of walking and postural control⁵³ that seem impaired OG can be retrained on a TM or robot. Indeed, BWSTT and present-day adjustments of the parameters that can be manipulated for RAST seem to rely on the same observations that therapists ordinarily use to cue patients during OG practice—foot clearance, knee extensor support in stance, timing of hip flexion for swing, and so on. Thus, it may not be so surprising to find that the devices offer no greater opportunity for motor learning than thoughtful OG physical therapy, despite the potential for more step repetitions. Most important, the trainers of patients receiving BWSTT and present-day robotics cannot easily judge how engaged each subject remains during practice sessions. The belt or robotic keeps moving and the hands of therapists or the motors of devices keep churning, even when disabled subjects do not concentrate, self-assess, and put themselves into a state to learn. Progress in rehabilitation requires procedural and declarative learning and both demand attention. Inattention may be easier to spot during OG training.

Neuroplasticity

Skills practice and exercise have received much support from animal models and functional imaging studies of patients with stroke, multiple sclerosis, and SCI. Practice produces neural network adaptations, usually in association with gains in function or motor control.⁵⁴⁻⁵⁶ These findings were also found after training on a TM or robotic device.^{38,54,56-61} The brain-behavior changes, however, do not necessarily have a causal relationship. Thus, cortical adaptations after training may suggest that the motor network was engaged by training, but neural representational plasticity itself is not evidence for efficacy of the training. Too many rehabilitation pilot studies claim to alter plasticity, as if plasticity is an acceptable surrogate for functional gains.

Early Races

Initial pilot studies in the early 1990s chose patients who had very limited stepping ability after an American Spinal Injury Association Impairment Scale (AIS) C SCI or hemiplegic stroke. Participants who were trained on a TM with BWS seemed to do better than expected compared to the prior experience of the investigators or to historical controls who had received conventional rehabilitation with parallel bar support, bracing, assistive devices, and OGT.⁶²⁻⁶⁵ These and many other pilot studies, however, suffered from the usual confounders of early proof-of-concept studies, including participant selection bias; small sample sizes; absence of an active comparison intervention for control subjects; varied outcome measures; widely different subgroups in terms of amount of impairment and disability and the cause of a myelopathy or location of a stroke; variations in the intervention across research sites; lack of blinded outcomes, treatments, or assessments; statistical methods that compared pretesting and posttesting within groups rather than between a treated group and a control group; and multiple outcome measures without statistical correction for multiple tests of inference.⁶⁶

In addition, patients with chronic SCI or stroke were often chosen as participants in pilot studies, based on the assumption that chronic impairment means an unchanging level of impairment and disability. These participants were likely to have been sedentary with subsequent loss of strength and conditioning over time. They may not have been practicing ways to improve their mobility after the end of formal rehabilitation, months to years earlier. Thus, providing structure and progressive therapy for walking, strengthening, and conditioning or balance and gait training to improve standing and walking could have helped a chronically impaired person to make modest gains. This notion of disuse deterioration that can be quickly reversed by any form of rehabilitation would be especially likely in patients who retain some motor control and capacity for motor learning. Without a control intervention group, an

investigator cannot assume that a gain is specific to the experimental intervention.

Among other issues in early studies, the measure of test-retest gains made by participants may have reached statistical significance but may not have improved the number of bouts and distances walked during daily activities. Indeed, by improving the degree of independence in walking a short distance (measured by the oft-used Functional Ambulation Classification) or revealing a modest gain in walking speed over 10 m or in the distance walked in a fixed time (2-6 minutes), an investigator still has not shown that these outcomes necessarily move the participant to a higher level of home or community walking ability and daily activity.⁶⁷ In addition, outcomes that are statistically significant have higher odds of being fully reported than studies that do not reveal superiority.⁶⁸ Also, during these pilot studies, the investigators could not assess how much more than usual their subjects practiced beyond the time of formal BWSTT. Motivation to increase daily activity simply by participating in a study may have been a critical component for progress in chronically impaired persons.

These potential biases in pilot studies put the wind behind the horses of BWSTT and later RAST. Still, the conceptual bases for BWSTT and its cousin, robotic steppers, were and continue to be scientifically reasonable. By informed intuition, both strategies looked like sure winners, perhaps unbeatable racehorses. Rehabilitation strategies, however, should only gain acceptance when a well-defined experimental intervention is better than an active therapeutic intervention in a controlled RCT with blinded outcomes. Indeed, several such trials are usually necessary before the treatment is crowned. Instead, despite the shortcomings of early pilot studies, commercial BWS systems and electromechanical robotic steppers became widely available and adopted for routine use in clinics. SCILT and LEAPS, along with nearly all RCTs that included at least 25 subjects in each arm, however, found no clear advantage of BWSTT or robotics. Are bets being placed, then, after the race is over?

One recent report did find a higher Functional Ambulatory Category (FAC) for patients with subacute stroke who practiced on the electromechanical GaitTrainer (Rehastim, Berlin, Germany).⁶⁹ Unfortunately, the FAC reflects only an untimed 25-foot walk. Another RCT included 12 subjects in each of 4 subgroups in a 2 × 2 matrix: higher versus lower Motricity Index and RAST versus conventional training for the initial 4 weeks of a 100-day inpatient stroke rehabilitation stay.⁷⁰ The lower Motricity Index robotic group improved more by the FAC, but both the conventional and the robotic groups still had low walking speeds of <0.4 m/s at completion 4 months poststroke. So, perhaps the most impaired subjects, who still retain some as yet uncertain level of motor control, could be a subgroup that may benefit from BWSTT or RAST, but a 24-subject comparison is no more than a pilot study.

Other trials have also searched for predictors of potential responders to BWSTT and RAST. When your horse does not come into the money, it is a natural response to seek reasons other than the fact that the other horses that won or tied were better or as good as yours. For example, does severity of walking impairment or the time from onset to intervention matter? LEAPS was designed to test both higher versus lower severity based on initial walking speed (<0.4 m/s and <0.8m/s), as well as the optimal timing of BWSTT (starting 2 months or 6 months after onset). The home-based exercise program was similar to BWSTT in all outcome measurements of this 400-subject trial. Only half leaped to a higher walking classification, and those who did so initially walked at speeds that were closest to the 0.4 or 0.8 m/s boundaries. As in other trials after stroke⁷¹ and SCI,⁷² a higher initial level of motor control was the best predictor of achieving independent walking at a faster walking speed. Behavioral measures of motor control after stroke and SCI could benefit from better physiological or anatomical information about the amount of spared corticospinal tract⁷³ at the level of the internal capsule⁷⁴ or perilesional cord. An objective measure would augment the sensorimotor examination to better stratify subjects in an RCT.

Although not documented in reports of trials, our personal experience from pilot studies is that subjects with stroke or SCI who do not practice beyond therapy times with either BWSTT or RAST will be far less likely to improve compared with those who practice at home. Carryover for any walking intervention seems essential for better home and community walking. Fear of falling also inhibits practice unless addressed. Patients with visuospatial and visual field deficits, spatial inattention or hemineglect, cognitive impairment that causes poor recall and planning, aphasia that impairs comprehension, and hemisensory loss have usually been eliminated by clinical trial entry criteria. Unfortunately, many such disabled persons need better strategies to recover independent walking. Inherent in their exclusion is the fact that generalization of the results of BWSTT and RAST to date to the general population of patients who walk poorly is moot.

Additional uncontrolled, multicenter, observational studies were recently reported but do not answer any of the important questions about the utility of BWSTT or RAST. A wide range of subacute and chronic AIS C and D patients in the Reeve Foundation's NeuroRecovery Network were given the most updated version of LT and BWSTT from the therapy group that managed the SCILT and LEAPS trials.^{75,76} The 7 sites provided their standardized BWSTT and OGT interventions for 20 to 250 sessions starting 28 to 650 days after onset. The AIS C group improved its walking speed from an initial 0.05 to a mean 0.18 ± 0.3 m/s, and the AIS D group improved from an initial 0.44 to a mean 0.68 ± 0.5 m/s. The results confirm that less impaired subjects, those graded AIS D, are likely to improve more than AIS C

subjects, but little else. Aside from losing the opportunity to produce an RCT to determine the efficacy of their demanding intervention, the investigators did not examine the functional impact of their training in this very heterogeneous but very large convenience sample of 176 participants. In a trial of RAST that also lacked a conventionally managed control group, investigators randomly assigned 46 participants to the Lokomat and 84 to the GaitTrainer. The subjects had AIS C or D myelopathies, most <1 year duration, and received 40 training sessions over 8 weeks.⁷⁷ As in the NeuroRecovery participants, about half did not have a traumatic SCI, which puts the baseline stability of the subjects in question. Mean walking speeds increased from an initial <0.1 to a final 0.26 m/s in the 2 groups. Unfortunately, these 2 quasiexperimental studies with a total of 300 subjects offer no new information about whether BWSTT or robotics can be better or equivalent to OG training alone, despite the fact that they consumed the considerable time and cost of therapists and disabled patients.

In the absence of studies demonstrating the superiority of the NeuroRecovery Network's LT, proponents continue to position this therapy as one that should be embraced in practice. They continue to offer training and certification of therapists in the delivery of BWSTT and LT, along with case reports and a manual/textbook disseminating methods and recommendations for practice.⁷⁶ This approach is a throwback to the days of the self-described experts who endorsed and taught Rood or Bobath therapy and begs us to reconsider the definition of evidence-based practices by clinicians. We trust that no further uncontrolled trials will be undertaken.

Thoroughbred or Workhorse?

We thought we had a thoroughbred intervention with BWSTT, but the races to date reveal just another workhorse. The same holds for RAST. Great excitement in rehabilitation circles was generated initially by the notion that this style of therapy incorporated the new icons of CPGs, task-oriented practice, repetition, and neuroplasticity. Indeed, along with constraint-induced movement therapy for the upper extremity that was drawn from an unrelated animal model, researchers and practitioners in the 1990s rediscovered that their interventions had a scientific basis. As Einstein is attributed to have said, however, "Not everything that can be counted counts, and not everything that counts can be counted."

In retrospect, much was not taken into account. Here are some persisting questions. How can progressive, repetitive practice on devices augment how a therapist trains skills and problem-solving for walking? Massed practice of the same action has its limitations. Novel situations and feedback about components of errant stepping, as well as global feedback about performance, are likely to drive learning.

Do BWSTT and RAST enable learning? How can motor learning opportunities be incorporated within the peculiar constraints of device training? For example, can future robotic control algorithms be altered from moving the legs through a kinematically normal pattern to a more physiologically meaningful path that permits errors of balance and step pattern that subjects can try to correct to better enable motor learning? Can the participation and cognitive engagement of the patient be better assured so that BWSTT and RAST effectively push the challenge point for motor learning? For example, the more sophisticated RAST machines employ assist-as-needed controllers, but no simple solution exists so far to ensure that the subject is not merely riding along.⁷⁸ When engagement of CPGs was the primary goal of RAST, cognitive aspects of motor learning were not considered to be crucial.

Can gait deviations detected during over-ground walking, such as the timing and angle of hip flexion for swing or the extent of knee extension with loading during single-limb stance, be manipulated and improved during BWSTT and RAST? Also, what is the therapeutic bridging strategy between the device and OGT? The interaction of LT with BWSTT, for example, has not paid off to date. Could the context of training on mechanical devices negatively affect the extension of what is being trained for the challenges of walking and balance in daily activities? Studies have yet to show that patients can respond to feedback about any aspect of the step cycle while the legs are being moved electromechanically or by hand. In our experience, for example, participants with hemiplegia on the Lokomat could not respond quickly enough to a feedback signal that aimed to cue them to initiate hip flexion at the moment of toe-off.

As for all neurorehabilitation interventions, can we establish specific functional goals that are meaningful to the patient and measure progress in real-world settings? Do these programs lead to progress in health-related quality of life that is significant enough to warrant the hard, long, and costly therapy sessions? How long will any achieved progress last, beyond those exercise sessions? How will practice on a device interact with better proven and still unproven options for the rehabilitation of motor control?^{79,80} To date, it is unclear how BWSTT and RAST will contribute to a multidimensional strategy⁸¹ for the rehabilitation of mobility.

BWSTT and RAST may yet provide a tool to augment walking skills. The devices could put severely impaired patients in position to be able to practice with much assistance when combined with additional simultaneous interventions such as neural repair^{82,83} and variations of brain,⁸⁴⁻⁸⁶ spinal cord, and functional electrical stimulation of lower extremity muscles⁸⁷ to perhaps promote Hebbian plasticity.^{88,89} Treadmill exercise, with or without a robotic device, that enables aerobic exercise could offer potential advantages for more severely disabled persons.⁹⁰⁻⁹³ To date, however, we have an expensive workhorse that can be further tested, but probably will never grow into the crowned thoroughbred we sought.

Racing Futures

To date, BWSTT and RAST have not answered the need for better than presently available, evidence-based interventions to improve walking capabilities in clinically important ways. Their underlying mechanistic icons, including spinal cord and neural plasticity, repetitive task-specific practice, and optimizing afferent inputs and kinematics, have not come up lame but have not proven powerful enough to place patients in the money. The results of partial and complete SCI in animal models and quasi-experimental pilot studies were promising, but did not hold up when compared with equally progressive OGT and exercise. The accumulated lessons over the past 20 years, however, may lead to ideas for future interventions for walking. Here, we describe a few possible lessons.

Animal models of human disease are informative about a hypothesized, isolated biological process, but translation of results to neurorehabilitation may be no more successful than models of acute stroke and SCI have been for predicting the results of pharmacological trials for neuroprotection. For behavioral interventions, animal models have even greater limitations in going from bench to bedside. For example, the data that underlie the impact of sensory modulation for TM stepping after spinal cord transection do not prove that use of assistive devices or exclusive OGT for patients can interfere with learning-related sensory input or could slow progress toward achieving the goal of energy-efficient walking.

More structured experimental staging of ideas and pilot data need to predate RCTs in neurorehabilitation. These early studies at the least ought to suggest the likely effect size of the intervention when compared with control subjects who receive a relevant parallel treatment.⁶⁶ Before mass production of expensive robotic devices, better strategies to test them for possible efficacy are necessary. Simply designed, randomized trials with as few as 25 homogeneous subjects in the RAST and in another active treatment may be enough to obtain a large enough effect size to suggest whether production ought to proceed. This strategy may also lead to clinically important improvements in the design of the device.

There is no need to deploy *experimental* training methods for most patients who walk at speeds >0.8 m/s, even if normal casual walking speeds are at least 50% higher. Experimental treatments in neurorehabilitation should be reserved for the most impaired and disabled who still have enough voluntary motor control to be trainable.

The environmental context of training may matter, especially given the response to home-based balance and strengthening exercises in LEAPS. Interventions that require equipment may put patients outside of the usual context of real-world demands. Structured, home-based training may have the advantage of practice within personal space, where environmental challenges can be overcome, problem

solving is highly motivated, and patients can most easily incorporate additional practice outside of formal therapy sessions. The therapist can use the client's chairs, stairs, and neighborhood to encourage gains that prevent a sedentary lifestyle. *Practice in the home may represent task-specificity far better than treadmill or robotic step training and care in the unfamiliar environs of a clinic.* This notion needs near-term testing. Indeed, task-specificity seems less well definable than previously considered by experts in neurorehabilitation.

Combinational therapies ought to be promoted, even in RCTs of a novel intervention. For example, the conventional and experimental treatments could include strengthening, conditioning, and balance exercises.⁸⁰

Outcome measurements during pilot studies and RCTs may not be served as well as thought by tools such as the 6-minute walking distance and the walking speed over a short distance.⁹⁴ In the near future, practice will be monitored remotely to track the daily number of bouts of walking and exercise, as well as the speeds and distances walked in the home and community. Indeed, wearable, wireless motion sensors that are interpreted by machine-learning, activity pattern-recognition algorithms will provide clinicians with insight and patients with feedback via connections to smartphones.⁹⁵⁻⁹⁷ They will also provide RCTs with clinically meaningful, ratio scale outcome measurements drawn from real-world settings.

A Finish Line

Confirmation bias leads many of us to seize on facts that bolster our preconceptions and to overlook contradictory data. Our nature is to promote what we find, even if further study and reflection might reduce its significance. BWSTT, RAST, and LT have been placed on the racetrack of well-conducted RCTs. They are not big winners or big losers. Rehabilitation research has shown that these seemingly conceptually sound, well-defined interventions are as likely to be no better, incrementally better, or incrementally worse than similar conventional workhorses. These strategies, at best, are better than no intervention but not superior in conception, cost, or outcomes to other forms of goal-directed, progressive, and well-dosed therapy. Yet patients are still being led to spend 50 to 200 hours in BWSTT to try to achieve gains, and early generation robotics are selling well. If truly valuable gains for patients were being made, cost-effectiveness studies and the numbers needed to treat to reach those gains would have to be weighed by society, before it paid to bet. For now, no such data exist. Perhaps these patients ought to be encouraged to spend their time transitioning to home-based and community-based physical therapy and activity programs to improve motor control, balance, strength, endurance, and disability-related problem solving. This approach may empower them for sustained activity and community reintegration.

It may be time to stop promoting LT, BWSTT, and presently available RAST as unbeatable horses for the "right" patient. At most, rehabilitation researchers can include these techniques as part of a team of specialty workhorses running on the racetrack of future scientific trials for highly disabled persons. For hemiplegic and paraplegic persons and their families to commit to lengthy and expensive courses of training that have not met intended goals over the past 20 years is to mislead them with hope. Instead, clinicians should provide them with treatments that have successfully run the race of best clinical evidence. In the face of the challenges of costly, high-technology health care, we wonder whether these step-training devices, as well as spinal cord electrical stimulation, will ever decisively win a race of efficacy or cost-effectiveness.

Scientific studies are self-correcting over time as basic and clinical information accrues. What has been learned from these locomotor trials to date must be reexamined if neurorehabilitationists are going to be able to further improve the odds that their wagers will pay off for disabled persons.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Institute of Neurological Disorders and Stroke (RO1 NS050506) and the National Center for Medical Rehabilitation Research.

References

1. Dobkin B. Overview of treadmill locomotor training with partial body weight support: a neurophysiologically sound approach whose time has come for randomized clinical trials. *Neurorehabil Neural Repair*. 1999;13:157-165.
2. Dobkin B, Apple D, Barbeau H, et al. Methods for a randomized trial of weight-supported treadmill training versus conventional training for walking during inpatient rehabilitation after incomplete traumatic spinal cord injury. *Neurorehabil Neural Repair*. 2003;17:153-167.
3. Duncan PW, Sullivan KJ, Behrman AL, et al. Protocol for the Locomotor Experience Applied Post-stroke (LEAPS) trial: a randomized controlled trial. *BMC Neurol*. 2007;7:39.
4. Dobkin B, Apple D, Barbeau H, et al. Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. *Neurology*. 2006;66:484-493.
5. Duncan P, Sullivan K, Behrman A, et al. Body-weight-supported treadmill rehabilitation program after stroke. *N Engl J Med*. 2011;364:2026-2036.
6. Behrman A, Harkema S. Locomotor training after human spinal cord injury: a series of case studies. *Phys Ther*. 2000;80:688-700.
7. Hesse S, Schmidt H, Werner C, Bardeleben A. Upper and lower extremity robotic devices for rehabilitation and for studying motor control. *Curr Opin Neurol*. 2003;16:705-710.

8. Mehrholz J, Kugler J, Pohl M. Locomotor training for walking after spinal cord injury. *Cochrane Database Syst Rev.* 2008;(2):CD006676.
9. Mehrholz J, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke. *Cochrane Database Syst Rev.* 2007;(4):CD006185.
10. Moseley AM, Stark A, Cameron ID, Pollock A. Treadmill training and body weight support for walking after stroke. *Cochrane Database Syst Rev.* 2005;(4):CD002840.
11. Wessels M, Lucas C, Eriks I, de Groot S. Body weight-supported gait training for restoration of walking in people with an incomplete spinal cord injury: a systematic review. *J Rehabil Med.* 2010;42:513-519.
12. Tefertiller C, Pharo B, Evans N, Winchester P. Efficacy of rehabilitation robotics for walking training in neurological disorders: a review. *J Rehabil Res Dev.* 2011;48:387-416.
13. Damiano D, DeJong S. A systematic review of the effectiveness of treadmill training and body weight support in pediatric rehabilitation. *J Neurol Phys Ther.* 2009;33:27-44.
14. Swinnen E, Duerinck S, Baeyens J, Meeusen R, Kerckhofs E. Effectiveness of robot-assisted gait training in persons with spinal cord injury: a systematic review. *J Rehabil Med.* 2010;42:520-526.
15. Nooijen C, Ter Hoeve N, Field-Fote E. Gait quality is improved by locomotor training in individuals with SCI regardless of training approach. *J Neuroeng Rehabil.* 2009;6:36.
16. Field-Fote E, Roach K. Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. *Phys Ther.* 2011;91:48-60.
17. Franceschini M, Carda S, Agosti M, Antenucci R, Malgrati D, Cisari C. Walking after stroke: what does treadmill training with body weight support add to overground gait training in patients early after stroke? A single-blind, randomized, controlled trial. *Stroke.* 2009;40:3079-3085.
18. Ada L, Dean C, Morris M, Simpson J, Katrak P. Randomized trial of treadmill walking with body weight support to establish walking in subacute stroke: the MOBILISE trial. *Stroke.* 2010;41:1237-1242.
19. Høyer E, Jahnsen R, Stanghelle J, Strand L. Body weight supported treadmill training versus traditional training in patients dependent on walking assistance after stroke: a randomized controlled trial. *Disabil Rehabil.* 2011;34:210-219.
20. Willoughby K, Dodd K, Shields N, Foley S. Efficacy of partial body weight-supported treadmill training compared with overground walking practice for children with cerebral palsy: a randomized controlled trial. *Arch Phys Med Rehabil.* 2010;91:333-339.
21. Hidler J, Nichols D, Pelliccio M, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. *Neurorehabil Neural Repair.* 2009;23:5-13.
22. Picelli A, Melotti C, Origano F, et al. Robot-assisted gait training in patient with Parkinson disease: a randomized controlled trial [published online ahead of print January 18, 2012]. *Neurorehabil Neural Repair.* doi:10.1177/1545968311424417.
23. Beer S, Aschbacher B, Manoglou D, Gamper E, Kool J, Kesselring J. Robot-assisted gait training in multiple sclerosis: a pilot randomized trial. *Mult Scler.* 2008;14:231-236.
24. Vaney C, Gattlen B, Lugon-Moulin V, et al. Robotic-assisted step training (Lokomat) not superior to equal intensity of overground rehabilitation in patients with multiple sclerosis [published online ahead of print December 2, 2012]. *Neurorehabil Neural Repair.* doi:10.1177/1545968311425923.
25. Lo AC, Triche EW. Improving gait in multiple sclerosis using robot-assisted, body weight supported treadmill training. *Neurorehabil Neural Repair.* 2008;22:661-671.
26. Schwartz I, Sajin A, Moreh E, et al. Robot-assisted gait training in multiple sclerosis patients: a randomized trial [published online ahead of print December 6, 2011]. *Mult Scler.* doi:10.1177/1352458511431075.
27. Wirz M, Bastiaenen C, de Bie R, Dietz V. Effectiveness of automated locomotor training in patients with acute incomplete spinal cord injury: a randomized controlled multicenter trial. *BMC Neurol.* 2011;11:60.
28. Grillner S. Neurobiological bases for rhythmic motor acts in vertebrates. *Science.* 1985;228:143-149.
29. Barbeau H, Rossignol S. Recovery of locomotion after chronic spinalization in the adult cat. *Brain Res.* 1987;412:84-95.
30. Lovely R, Gregor R, Roy R, Edgerton V. Weight-bearing hindlimb stepping in treadmill-exercised adult spinal cats. *Brain Res.* 1990;514:206-218.
31. Ichiyama RM, Courtine G, Gerasimenko YP, et al. Step training reinforces specific spinal locomotor circuitry in adult spinal rats. *J Neurosci.* 2008;28:7370-7375.
32. Lavrov I, Courtine G, Dy C, et al. Facilitation of stepping with epidural stimulation in spinal rats: role of sensory input. *J Neurosci.* 2008;28:7774-7780.
33. Singh A, Balasubramanian S, Murray M, Lemay M, Houle J. Role of spared pathways in locomotor recovery after body-weight-supported treadmill training in contused rats. *J Neurotrauma.* 2011;28:2405-2416.
34. Nadeau S, Jacquemin G, Fournier C, Lamarre Y, Rossignol S. Spontaneous motor rhythms of the back and legs in a patient with complete spinal transection. *Neurorehabil Neural Repair.* 2010;24:377-383.
35. Dobkin B, Harkema S, Requejo P, Edgerton V. Modulation of locomotor-like EMG activity in subjects with complete and incomplete chronic spinal cord injury. *J Neurol Rehabil.* 1995;9:183-190.
36. Harkema S, Hurley S, Patel U, Dobkin B, Edgerton V. Human lumbosacral spinal cord interprets loading during stepping. *J Neurophysiol.* 1997;77:797-811.
37. Harkema S, Gerasimenko Y, Hodes J, et al. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia. *Lancet.* 2011;377:1938-1947.
38. Blicher J, Nielsen J. Cortical and spinal excitability changes after robotic gait training. *Neurorehabil Neural Repair.* 2009;23:143-149.
39. Levin M, Kleim J, Wolf S. What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabil Neural Repair.* 2009;23:313-319.

40. Lang C, Macdonald J, Reisman D. Observation of amounts of movement practice provided during stroke rehabilitation. *Arch Phys Med Rehabil*. 2009;90:1692-1696.
41. van Wijk R, Cumming T, Churilov L, Donnan G, Bernhardt J. An early mobilization protocol successfully delivers more and earlier therapy to acute stroke patients: further results from phase II of AVERT. *Neurorehabil Neural Repair*. 2012;26:20-26.
42. Birkenmeier R, Prager E, Lang C. Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study. *Neurorehabil Neural Repair*. 2010;24:620-635.
43. Rose D, Paris T, Crews E, et al. Feasibility and effectiveness of circuit training in acute stroke rehabilitation. *Neurorehabil Neural Repair*. 2011;25:140-148.
44. Veerbeek J, Koolstra M, Ket J, van Wegen E, Kwakkel G. Effects of augmented exercise therapy on outcome of gait and gait-related activities in the first 6 months after stroke: a meta-analysis. *Stroke*. 2011;42:3311-3315.
45. Dobkin BH. Confounders in rehabilitation trials of task-oriented training: lessons from the designs of the EXCITE and SCILT multicenter trials. *Neurorehabil Neural Repair*. 2007;21:3-13.
46. Conklyn D, Stough D, Novak E, Paczak S, Chemali K, Bethoux F. A home-based walking program using rhythmic auditory stimulation improves gait performance in patients with multiple sclerosis. *Neurorehabil Neural Repair*. 2010;24:835-842.
47. Pelton T, Johannsen L, Chen H, Wing A. Hemiparetic stepping to the beat: asymmetric response to metronome phase shift during treadmill gait. *Neurorehabil Neural Repair*. 2010;24:428-434.
48. Dobkin B, Plummer-D'Amato P, Elashoff R, Lee J, Group S. International randomized clinical trial, Stroke Inpatient Rehabilitation With Reinforcement of Walking Speed (SIRROWS) improves outcomes. *Neurorehabil Neural Repair*. 2010;24:235-242.
49. Timmermans A, Spooren A, Kingma H, Seelen H. Influence of task-oriented training content on skilled arm-hand performance in stroke: a systematic review. *Neurorehabil Neural Repair*. 2010;24:858-870.
50. Kautz S, Bowden M, Clark D, Neptune R. Comparison of motor control deficits during treadmill and overground walking poststroke. *Neurorehabil Neural Repair*. 2011;25:756-765.
51. Regnaud JP, Saremi K, Marehbian J, Bussel B, Dobkin BH. An accelerometry-based comparison of 2 robotic assistive devices for treadmill training of gait. *Neurorehabil Neural Repair*. 2008;22:348-354.
52. Lamontagne A, Fung J, McFadyen B, Faubert J, Paquette C. Stroke affects locomotor steering responses to changing optic flow directions. *Neurorehabil Neural Repair*. 2010;24:457-468.
53. Krasovskiy T, Levin M. Toward a better understanding of coordination in healthy and poststroke gait. *Neurorehabil Neural Repair*. 2010;24:213-224.
54. Cramer S, Sur M, Dobkin B, et al. Harnessing neuroplasticity for clinical applications. *Brain*. 2011;134:1591-1609.
55. Buma F, Lindeman E, Ramsey N, Kwakkel G. Functional neuroimaging studies of early upper limb recovery after stroke: a systematic review. *Neurorehabil Neural Repair*. 2010;24:589-608.
56. Askim T, Indredavik B, Vangberg T, Haberg A. Motor network changes associated with successful motor skill relearning after acute ischemic stroke: a longitudinal fMRI study. *Neurorehabil Neural Repair*. 2009;23:295-304.
57. de Bode S, Mathern GW, Bookheimer S, Dobkin B. Locomotor training remodels fMRI sensorimotor cortical activations in children after cerebral hemispherectomy. *Neurorehabil Neural Repair*. 2007;21:497-508.
58. Dobkin B, Firestone A, West M, Saremi K, Woods R. Ankle dorsiflexion as an fMRI paradigm to assay motor control for walking during rehabilitation. *NeuroImage*. 2004;23:370-381.
59. Winchester P, McColl R, Querry R, et al. Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury. *Neurorehabil Neural Repair*. 2005;19:313-324.
60. Luft AR, Macko RF, Forrester LW, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke. A randomized controlled trial. *Stroke*. 2008;39:3341-3350.
61. Enzinger C, Dawes H, Johansen-Berg H, et al. Brain activity changes associated with treadmill training after stroke. *Stroke*. 2009;40:2460-2467.
62. Visintin M, Barbeau H. The effects of body weight support on the locomotor pattern of spastic paretic patients. *Can J Neurol Sci*. 1989;16:315-325.
63. Wernig A, Muller S, Nanassy A, Cagol E. Laufband therapy based on "Rules of Spinal Locomotion" is effective in spinal cord injured persons. *Eur J Neurosci*. 1995;7:823-829.
64. Dietz V, Wirz M, Curt A, Colombo G. Locomotor patterns in paraplegic patients: training effects and recovery of spinal cord function. *Spinal Cord*. 1998;36:380-390.
65. Sullivan KJ, Knowlton BJ, Dobkin BH. Step training with body weight support: effect of treadmill speed and practice paradigms on poststroke locomotor recovery. *Arch Phys Med Rehabil*. 2002;83:683-691.
66. Dobkin BH. Progressive staging of pilot studies to improve phase III trials for motor interventions. *Neurorehabil Neural Repair*. 2009;23:197-206.
67. Bowden MG, Balasubramanian CK, Behrman AL, Kautz SA. Validation of a speed-based classification system using quantitative measures of walking performance poststroke. *Neurorehabil Neural Repair*. 2008;22:672-675.
68. Prasad V, Cifu A, Ioannidis J. Reversals of established medical practices: evidence to abandon ship. *JAMA*. 2012;307:37-38.
69. Pohl M, Werner C, Holzgraefe M, et al. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GANtrainerStudie, DEGAS). *Clin Rehabil*. 2007;21:17-27.

70. Morone G, Bragoni M, Iosa M, et al. Who may benefit from robotic-assisted gait training? A randomized clinical trial in patients with subacute stroke. *Neurorehabil Neural Repair*. 2011;25:636-644.
71. Veerbeek J, Van Wegen E, Harmeling-Van der Wel B, Kwakkel G, Investigators E. Is accurate prediction of gait in nonambulatory stroke patients possible within 72 hours poststroke? The EPOS study. *Neurorehabil Neural Repair*. 2011;25:268-274.
72. Dobkin B, Barbeau H, Deforge D, et al. The evolution of walking-related outcomes over the first 12 weeks of rehabilitation for incomplete traumatic spinal cord injury: the multicenter randomized Spinal Cord Injury Locomotor Trial. *Neurorehabil Neural Repair*. 2007;21:25-35.
73. Sterr A, Shen S, Szameitat A, Herron K. The role of corticospinal tract damage in chronic motor recovery and neurorehabilitation: a pilot study. *Neurorehabil Neural Repair*. 2010;24:413-419.
74. Qiu M, Darling W, Morecraft R, Ni C, Rajendra J, Butler A. White matter integrity is a stronger predictor of motor function than BOLD response in patients with stroke. *Neurorehabil Neural Repair*. 2011;25:275-284.
75. Harkema S, Schmidt-Read M, Lorenz D, Edgerton V, Behrman A. Balance and ambulation improvements in individuals with chronic incomplete spinal cord injury using locomotor training-based rehabilitation [published online ahead of print July 19, 2011]. *Arch Phys Med Rehabil*. doi:10.1016/j.apmr.2011.01.024.
76. Harkema S, Behrman A, Barbeau H. *Locomotor Training: Principles and Practice*. New York, NY: Oxford University Press; 2011.
77. Benito-Penalva J, Edwards D, Opisso E, et al. Gait training in human spinal cord injury using electromechanical systems: effect of device type and patient characteristics [published online ahead of print December 29, 2011]. *Arch Phys Med Rehabil*. doi:10.1016/j.apmr.2011.08.028.
78. Koenig A, Omlin X, Bergmann J, et al. Controlling patient participation during robot-assisted gait training. *J Neuroeng Rehabil*. 2011;8:14.
79. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet*. 2011;377:1693-1702.
80. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol*. 2009;8:741-754.
81. Bowden M, Embry A, Gregory C. Physical therapy adjuvants to promote optimization of walking recovery after stroke. *Stroke Res Treat*. 2011;2011:601416.
82. Lima C, Escada P, Pratas-Vital J, et al. Olfactory mucosal autografts and rehabilitation for chronic traumatic spinal cord injury. *Neurorehabil Neural Repair*. 2010;24:10-22.
83. Dobrossy M, Busse M, Piroth T, Rosser A, Dunnett S, Nikkha G. Neurorehabilitation with neurotransplantation. *Neurorehabil Neural Repair*. 2010;24:692-701.
84. Dimyan M, Cohen L. Contribution of transcranial magnetic stimulation to the understanding of functional recovery mechanisms after stroke. *Neurorehabil Neural Repair*. 2010;24:125-135.
85. Tanaka S, Takeda K, Otaka Y, et al. Single session of transcranial direct current stimulation transiently increases knee extensor force in patients with hemiparetic stroke. *Neurorehabil Neural Repair*. 2011;25:565-569.
86. Tseng H, Liao K, Wang C, Lai K, Yang Y. rTMS combined with task-oriented training to improve symmetry of interhemispheric corticomotor excitability and gait performance after stroke: a randomized trial [published online ahead of print October 5, 2011]. *Neurorehabil Neural Repair*. doi:10.1177/1545968311423265.
87. Daly J, Zimelman J, Roenigk K, et al. Recovery of coordinated gait: randomized controlled stroke trial of functional electrical stimulation (FES) versus no FES, with weight-supported treadmill and over-ground training. *Neurorehabil Neural Repair*. 2011;25:588-596.
88. Buetefisch C, Heger R, Schicks W, Seitz R, Netz J. Hebbian-type stimulation during robot-assisted training in patients with stroke. *Neurorehabil Neural Repair*. 2011;25:645-655.
89. Laufer Y, Elboin-Gabyzon M. Does sensory transcutaneous electrical stimulation enhance motor recovery following a stroke? A systematic review. *Neurorehabil Neural Repair*. 2011;25:799-809.
90. Lam J, Globas C, Cerny J, et al. Predictors of response to treadmill exercise in stroke survivors. *Neurorehabil Neural Repair*. 2010;24:567-574.
91. Globas C, Becker C, Cerny J, et al. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized controlled trial. *Neurorehabil Neural Repair*. 2012;26:85-95.
92. Quaney B, Boyd L, McDowd J, et al. Aerobic exercise improves cognition and motor function poststroke. *Neurorehabil Neural Repair*. 2009;23:879-885.
93. Chang W, Kim M, Huh J, Lee P, Kim Y. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study [published online ahead of print November 15, 2011]. *Neurorehabil Neural Repair*. doi:10.1177/1545968311408916.
94. Dickstein R. Rehabilitation of gait speed after stroke: a critical review of intervention approaches. *Neurorehabil Neural Repair*. 2008;22:649-660.
95. Prajapati S, Gage W, Brooks D, Black SE, McLroy W. A novel approach to ambulatory monitoring: investigation into the quantity and control of everyday walking in patients with subacute stroke. *Neurorehabil Neural Repair*. 2011;25:6-14.
96. Dobkin B, Dorsch A. The promise of mHealth: daily activity monitoring and outcome assessments by wearable sensors. *Neurorehabil Neural Repair*. 2011;25:788-798.
97. Weiss A, Sharifi S, Plotnik M, van Vugt J, Giladi N, Hausdorff J. Towards automated, at-home assessment of mobility among patients with Parkinson's disease using a body-worn accelerometer. *Neurorehabil Neural Repair*. 2011;25:810-818.