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New evidence for therapies in stroke rehabilitation

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Abstract

Neurologic rehabilitation aims to reduce impairments and disabilities so that persons with serious stroke can return to participation in usual self-care and daily activities as independently as feasible. New strategies to enhance recovery draw from a growing understanding of how types of training, progressive task-related practice of skills, exercise for strengthening and fitness, neurostimulation, and drug and biological manipulations can induce adaptations at multiple levels of the nervous system. Recent clinical trials provide evidence for a range of new interventions to manage walking, reach and grasp, aphasia, visual field loss, and hemi-inattention.

Keywords

stroke rehabilitation; clinical trials; robotics; neuroplasticity; functional outcomes; physical therapy

Introduction

Stroke remains a leading cause of long-term disability in the United States at a cost of $38 billion per year. About 650,000 persons survive a new stroke yearly and 7 million Americans live with the complications of stroke [1]. Despite evidence that participation in formal rehabilitative therapies lessens disability after stroke [2], less than a third receive inpatient or outpatient therapies [3]. Of those who do access therapies, the frequency of use varies by geographic location and socioeconomic status. For these patients, the amount of rehabilitation available has progressively fallen as subacute stroke inpatient stays have dropped to an average of less than 16 days and as Medicare has capped the number of outpatient therapy sessions to 15/year [4]. In effect, these declines in service may limit rehabilitation gains and place greater burdens on caregivers. In contrast to these fiscally driven realities, the science underlying stroke rehabilitation offers new directions to improve outcomes.

Scientific advances based on animal models have sharpened our understanding of the genetic, molecular, physiologic, cellular, and behavioral adaptations that drive and may limit the recovery of function [5]. Novel types of therapies based on manipulating mechanisms of learning and memory, neurogenesis and axonal regeneration, and neurotransmitters and growth factors can facilitate the recovery process in models. In patients, non-invasive modalities including functional and structural magnetic resonance imaging (MRI) and

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neuronal excitatory and inhibitory stimulation tools such as transcranial magnetic stimulation (TMS) are characterizing changes in connectivity between brain regions after stroke [6]. Therapeutic strategies for patients are also being drawn from engineering and computer science. Wireless health and communication technologies have produced wearable sensors to remotely record the quality and quantity of walking practice, smartphone apps to cue practice, and tele-rehabilitation programs to enable treatment in the home or community [7].

Evidence from adequately powered, randomized control trials demonstrating the efficacy of new interventions when compared to existing therapies has been far outpaced by the number of novel strategies being developed. Trials can be confounded by the patho-anatomic and functional heterogeneity of patients, the complexity and cost of delivering an intervention, and uncertainties regarding optimal therapy timing, dose, and duration [8]. Additionally, the outcome measures used in trials are often relative surrogates for patient performance. rather than direct measures of the types, quantity, and quality of physical functioning [9]. When the goal is to assess use of the upper extremity, walking, exercise, and participation in home and community activities [10], existing measures may not fully capture clinically important changes in physical or cognitive impairments, disability, or health-related quality of life and participation [11]. Despite these confounds, recent trials do provide useful evidence about behavioral, pharmacologic, and neurostimulation treatments for stroke, as well as near future hope for biological interventions for the most highly impaired patients.

Overview of care in rehabilitation

Patients are admitted for inpatient stroke rehabilitation usually because they are unable to walk without considerable human assistance and are dependent in other self-care tasks, yet have adequate memory, attention, and home support to be able to be discharged without the need for skilled nursing placement [12]. In the U.S., Medicare requires that patients can tolerate at least three hours of therapist-directed treatment a day, usually begun within 5–10 days after onset of stroke. Internationally, the time from stroke onset to rehab admission is 1–6 weeks and the duration of inpatient care is 3–8 weeks, but longer in Japan where a more comprehensive post stroke care system is available [13].

Goals of inpatient therapy can include increased independence for self-care activities (e.g., feeding, grooming, bowel and bladder care); the ability to perform safe toilet and wheelchair transfers; walking with or without assistive devices such as canes and orthoses that can brace the ankle and help control the knee; improved receptive and expressive language skills; and better executive, visual-perceptual, working memory, and other cognitive skills. In the outpatient setting, patients work with therapists to refine and build upon these skills to increase their functional independence in the home and community [14].

During rehabilitation, physical, occupational, and speech therapists enable the practice of tasks of importance to patients, set and update realistic goals within the limitations of residual reflexive and voluntary neural control, and instill a regimen of daily skills practice of progressive intensity and difficulty. Therapists may utilize neuromuscular facilitation techniques to begin to guide the re-acquisition of motor skills, before building from simple to more complex actions that comprise goal-directed behaviors [15].

Principles underlying rehabilitative therapies

Two basic principles influence approaches to patient treatment. The first is that the adult central nervous system is adaptive, or plastic, and has some capacity to re-organize itself to recover degraded cognitive and motor functions. Animal studies are identifying genetic and biochemical pathways involved in the establishment of new anatomic connections and functional network reorganization (e.g., axonal sprouting, dendrite proliferation, neurogenesis) [16]. In patients, changing patterns of brain activation appreciated by MRI and other non-invasive imaging techniques reflect regional plasticity of the neuronal ensembles that represent actions and thoughts. Such changes are time-dependent and associated with learning and practice, as well as behavioral compensation for the loss of pre-stroke neural control. Thus, the brain of stroke patients, like healthy persons, constantly undergoes anatomic and physiologic changes induced by motor learning.

The second principle is that progressive, skilled motor practice is essential for continued gains *at any time* after stroke onset. Training must engage the attention, motivation, and learning networks of the brain to be effective. Better gains also depend on greater sparing of the neural networks that represent the components of a behavior. Although observational studies suggest that maximal functional gains are made by 3 months after onset, these studies do not account for other changes that can occur with regular practice, such as improved walking speed and distance or greater coordination in the use of an affected hand [17]. Large, randomized controlled trials in neurologic rehabilitation have reported long-lasting functional improvements after 2–12 weeks of skilled motor practice in patients who were weeks to years past onset of hemiparesis [18–20]. Thus, starting at the time of initial rehabilitation, physicians ought to instill in their patients a regimen of daily repetitive skills practice that can be carried over into the outpatient setting and into daily activities.

Interventions for mobility

Fitness and muscle strength

Clinicians should emphasize ways for persons with stroke to augment their general conditioning and muscle strength in both the affected and unaffected limbs. Pre-morbid deconditioning due to sedentary behavior exacerbates the fall-off in activity resulting from new neurologic disability [21]. Indeed, patients disabled by stroke take half as many steps, use their affected arm much less, and have longer daily sedentary periods compared to healthy age-matched persons [22–24]. It becomes very difficult for the hemiparetic person to achieve an aerobic effect from exercise, due to a combination of central weakness, inactivity, and muscle atrophy [25]. This is of concern because secondary stroke prevention recommendations include at least a half-hour of daily exercise rigorous enough to have at least a mild aerobic effect [26]. Just as important, higher levels of physical activity are associated with greater neurogenesis, better performance on cognitive tasks, less age-related hippocampal atrophy, and a reduced risk for vascular dementia [27–28].

Standard rehabilitative therapies include selective muscle strengthening by isometric and isokinetic exercises to improve the power and endurance of affected and unaffected muscle groups. Sets of moderate resistance exercise with weights or elastic bands are feasible for most patients. Simply standing up and sitting down 5–10 times during commercials on television can improve proximal leg strength. Aerobic exercise training, whether by treadmill, over ground walking, or recumbent cycling, can produce a conditioning effect and increase walking speed and endurance [29]. The most impressive results for aerobic exercise training have been reported in chronic stroke patients who have recovered sufficient motor control to participate in moderate-to-vigorous physical activity [30]. Questions remain about how best to provide and reinforce aerobic exercise, such as through a support group [31], and how to maintain compliance with exercise [32]. Physicians can encourage more frequent daily walks over longer distances and at faster speeds in addition to more formal exercise.

Over-ground walking and balance training

Over-ground gait training is an integral component of standard physical therapies to improve dynamic balance and ensure safe ambulation in the home. Patients first practice trunk and head control, sit-to-stand balance, and then stepping in the controlled environment of the parallel bars. Over-ground training emphasizes clearance of the paretic foot to initiate leg swing, knee stability in stance, and stepping with a more rhythmic, safe gait pattern, using an assistive device or orthotic as needed. A Cochrane review found positive correlations between the amount of over-ground training and small improvements in gait speed with no significant increase in the number of adverse events such as falls [33]. Falls are a common outcome for patients recovering from stroke, with an incidence of over 40 percent for more than one fall in the first year [34]. The addition of a series of balance and truncal exercises, either as a supplement to inpatient therapies [35] or as part of an outpatient tele-rehabilitation intervention, [36] may prove to be a cost-effective means by which to prevent further disability.

Body weight-supported treadmill training

Body weight-supported treadmill training (BWSTT) enables supervised, repetitive, task-related practice of walking. Patients with limited motor control wear a chest harness connected to an overhead lift to reduce the need to fully load a paretic leg. The treadmill induces rhythmic stepping, although the paretic leg and trunk often require physical assistance by therapists. The expectation, based on animal studies, was that BWSTT would increase the amount of practice while enabling more normalized sensory inputs to better drive motor output for stepping. The Locomotor Experience Applied Post Stroke (LEAPS) trial, however, failed to identify an additional clinical benefit of BWSTT as compared to a home exercise program of a similar intensity and duration [20]. Although initially a highly regarded potential intervention for poor walkers, BWSTT may not reflect the task-related environment of over-ground training for motor learning [37]. The cost in equipment and personnel with the expertise to deliver BWSTT make it an intervention to be tried only for patients who have at least modest motor control, but are not making progress with intensive over-ground training.

Robotic gait assist devices

Electromechanical-assistive devices, including robotic steppers and exoskeletons, provide patients with either full or partial guidance of the lower limbs during the phases of the gait cycle [38]. As compared to BWSTT, for example, these devices can provide automated gait training on a treadmill or elliptical-like device and require no hands-on supervision by therapists. To date, the devices have generally not led to greater overall gains in over-ground walking parameters than the same intensity of more conventional physical therapy [39]. Robotic devices are being introduced that may better enable motor learning by letting patients make kinematic errors during practice. Very recently, wearable, lightweight, motorized exoskeletons have become available that assist with hip or knee flexion and weight bearing while stepping over ground. Although rather expensive, they may enable slow ambulation when otherwise not feasible; controlled studies will be needed to determine if their use can augment standard rehabilitation practice.

Functional electrical stimulation

FES is a technique that takes advantage of peripheral nerves and muscles left unaffected by damage to the central nervous system. Electrical stimulation is applied to trigger contraction and relaxation of select muscle groups. In the case of walking, excitation of the common peroneal nerve by an externally placed stimulator results in dorsiflexion at the ankle to aid paretic foot clearance. Small, randomized studies of external [40] and implanted [41] electrodes have reported improvements in gait lasting at least six months after the intervention. Though several commercial devices are available in the United States, efforts have only recently begun to demonstrate their potential cost effectiveness [42].

Interventions for the upper extremity

Constraint-induced movement therapy and bimanual practice

Therapy for the hemiparetic arm might begin with single-joint attempts at movement before proceeding gradually to more complex, multi-joint actions, then task-specific practice such as reaching to grasp a coffee cup, a process known as shaping. Facilitation of skilled motor practice for the upper extremity can take several forms, including shaping plus constraint-induced movement therapy (CIMT). This technique includes 6 hours a day of progressive task-related practice with restraint of the unaffected limb all day for 2 weeks. Increased use and faster skilled movements of the affected limb may result and persist for up to two years [43]. However, the intervention has shown efficacy only in patients who can partially extend the wrist and fingers, meaning they have fair motor control and at least modest corticospinal tract sparing. Extensive restraint may not be as critical to gains as the high intensity of practice with a therapist; gains have been seen with just 2 hours of daily practice and without restraining the unaffected hand all day [44–45]. When the hand is chronically very weak, commercially available forearm-hand orthotic devices with embedded FES electrodes can enable a hand grasp or finger pinch to assist functional use.

Bimanual practice with simultaneous arm movements aims to activate the bilateral motor cortices and enhance input to the affected upper extremity, thereby leading to increased functional use of the paretic arm and hand. In small trials, bimanual practice has resulted in a similar degree of functional recovery as CIMT [46].

Mechanical devices to assist arm movements

Mechanical devices range from spring-loaded orthotics to assist a specific movement, such as wrist extension, to fully automated, robotic limb prostheses for patient-triggered assistance of shoulder, elbow and wrist movements. Patients practice a series of specific joint movements by guiding an object on a computer screen through a maze. As with the electromechanical-assistive devices designed for gait training, robotic arm devices may enable more practice with more normalized limb kinematics. Used as a supplement to standard care, such devices may provide a benefit, [47–48] but a similar degree of function can usually be achieved using standard therapies at the same intensity [19]. Most are too expensive for home use. These devices may prove more efficacious in combination with other rehabilitative therapies such as non-invasive brain stimulation, [49] but further research is needed.

Pharmacologic therapies to limit spasticity

It is often not medically necessary to treat increased muscle tone, unless spasms or flexor postures of the upper extremity cause pain, skin breakdown or interfere with hygiene. Baclofen and tizanidine are frequently used as first-line agents and dantolene’s effects on calcium action may also reduce hypertonicity. Botulinum toxin injected into selected muscle groups will reduce flexor or extensor postures around a joint for about 3 months, but usually does not improve functional use of a highly paretic hand [50–51]. Shoulder pain is common after hemiplegic stroke, associated with subluxation and joint stresses [52]. Rapid management of pain with light exercise, range of motion, and anti-inflammatory medications can help prevent pain-induced spasticity in the arm and hand. Inversion and plantar flexion of the foot can also be lessened by medications and botulinum toxin to try to improve stepping. When a muscle is partially paralyzed by the toxin, daily stretching and ranging of the affected joint are necessary to maintain the improvement.

Interventions for aphasia

Melodic intonation and constraint-induced therapies

A range of individual speech and language therapy techniques have been developed to address the wide variety of aphasic syndromes that occur after stroke [53]. Most patients need a multi-modal approach to build on their strengths and to limit frustration in word finding and fluency. Melodic intonation therapy was developed for patients who have poor expression but good comprehension. This technique uses simple melodies and rhythmic tapping to engage networks that subserve prosody of language [54]. In a nod to the massed-practice paradigm of CIMT, constraint-induced aphasia therapy was developed as a means to improve verbal output [55]. Where comprehension is poor and output is perseverative, therapies have little effect. Regardless of the treatment modality employed, regular home-based practice with family is imperative for the development of social communication.

Digital technologies

Advances in digital communication technology have led to treatments for aphasia that can be personalized and delivered in the home setting [56]. For example, a recent study of speech entrainment that delivered an audiovisual intervention on an iPod screen reported a significant increase in verbal output for chronic stroke patients with Broca's aphasia [57]. Several helpful computer programs for home practice are also available. Treatment of speech and cognitive disorders is likely to be a growing application of smartphone, tele-rehab, and other Internet-enabled practice and cueing paradigms.

Interventions for visual field deficits and inattention

Visual field loss and visual hemi-inattention degrade long-term functional outcomes in patients with stroke [58]. While it is unlikely that rehabilitation will result in recovery from a hemianopia, computer-based compensatory therapy may assist in directing visual search and attention into the area of loss [59]. The direct dopamine agonist rotigotine modestly lessened hemispatial neglect in sub-acute stroke patients [60]. For spatial hemi-neglect, a prism in eyeglasses will shift the center of vision toward the abnormal field to improve reading and some self-care tasks [61].

Interventions for Locked-In Syndrome

Brain-machine interfaces utilize direct communication between the nervous system and devices outside of the body to enable communication or the performance of goal-directed movements. The devices are most needed for people with locked-in syndrome from brainstem stroke who are without voluntary control of their limbs. Alterations in the amplitude of the mu rhythm by thoughts about an action, are recorded with electroencephalography electrodes and interpreted by a computer algorithm, allowing patients to select letters or words on a computer screen for communication or to search the Web [62]. More advanced systems can record directly from implanted microelectrodes over a variety of cortical regions. An interface then controls directional movements of a prosthetic limb [63]. While some of these technologies are coming into routine use, many challenges about cost and reliability remain.

Non-invasive brain stimulation

In addition to being employed to study brain physiology and neuroplasticity [64], techniques including TMS and transcranial direct current stimulation (tDCS) have been used to modulate cerebral plasticity in combination with physical training. Most trials focus on the recovery of arm function, [65] though the techniques are being exploited to increase verbal output in aphasia [66], improve swallowing [67], and increase walking speed [68] to give but a few examples. Generally modest gains in aspects of motor control have been reported when TMS is combined with other rehabilitative therapies [49, 69–70]. Similar equivocal results have been reported for tDCS protocols [71]. A lack of consensus persists regarding appropriate patient selection, stimulation protocol, location, and duration.[72] The Food and Drug Administration has not approved their use outside of research, except for some types of depression. These techniques seem to work best in patients who have some residual voluntary movement.

Modulation of sensorimotor cortex excitability can also be achieved through the stimulation of peripheral nerves, either in isolation [73] or in conjunction with cortical stimulation [74] [75]. Definitive evidence that peripheral nervous system activation leads to improved functional outcomes is not yet available [76].

Mirror and virtual reality therapies

The connections between parietal cortex and pre-motor and primary motor regions can be modulated by action observation and mirror therapy [77]. These techniques involve patients watching the movements of healthy individuals or, via a mirror, the unaffected limb. The subject attempts to mimic the observed movements. In contrast to other rehabilitative techniques such as CIMT, action observation and mirror therapy can be performed on patients with more severe limb paresis [78]. Clinical benefit has been reported in meta-analysis of small trials, but the magnitude of benefit depends upon the comparator therapy provided [79].

Virtual reality (VR) therapies use technology to combine action observation with repetitive skills practice. The hope is that this strategy will be especially engaging and reinforce practice paradigms. As simple as a commercially available video game that can be played at home or as complex as a system that measures joint angles in the arm and provides visual corrective feedback, VR has generated much excitement in the rehabilitation community as a means to promote and monitor skills practice [80]. Individual trials have reported benefits [81], but given the diversity of interventions and outcomes used, efficacy for a particular type or degree of impairment has not yet been demonstrated [82].

Pharmacologic interventions

Attempts to augment stroke recovery by modulating the neurotransmitter pathways of the central nervous system can also involve medications. Amphetamine showed promise in highly selected patients for motor gains, but no adequately powered trial has been completed after twenty years of small studies [83]. Efforts to boost cerebral dopaminergic action through the use of ropinirole proved ineffective in patients with chronic stroke [84]. The NMDA receptor antagonist memantine was reported to improve spontaneous speech and naming skills in chronic stroke patients with aphasia [85]. While individuals seem to occasionally improve in response to neurotransmitter-related drugs, no specific recommendations can be made.

The FLAME trial [86] tested fluoxetine in combination with standard rehabilitative therapies and reported better Fugl-Meyer motor scores, which tests voluntary movements against gravity, for those patients who received the drug. This work needs to be replicated [87]. The drug may also provide benefits as an anti-depressant, as depression affects at least 30% of patients within one year after stroke.

Cell-based and biologic therapies

Embryonic and mesenchymal stem cells, cultivated precursors of neurons and oligodendrocytes, and other autologous and commercialized cells are actively undergoing investigation as potential treatments for stroke. Cells could replace lost neurons or glial cells, remyelinate damaged axons, or produce substances such as growth factors that could help drive network function and plasticity [88]. Several reported trials have not reported clinical efficacy, but others are being planned [89–90]. To be of value, cellular and biologic interventions will have to be combined with applicable rehabilitation strategies to optimize their incorporation and action in neural networks.

Off-shore stem cell clinics are all too easy to find on the Internet. These high-priced cellular interventions can have a powerful placebo effect for patients with neurologic disease. Organizations that study stem cell research policies recommend that no patient should participate in or pay to receive a cellular intervention outside of a registered trial with a formal safety monitoring committee, in order to enable scientifically valuable information to be derived from the trial [91–92].

Miscellaneous approaches

Acupuncture is frequently offered in Asian countries for stroke rehabilitation. While individual patients may report a benefit, controlled trials have generally found little or no added value for improving specific impairments and disabilities [93–94]. A recent trial reported that hyperbaric oxygen therapy may improve functional outcomes after stroke [95]. The study design was less than optimal, however. The cost of this treatment modality is high, there are risks accompanying its use, and the science underlying its utilization in chronic stroke is difficult to support. Etanercept, approved by the FDA for use in psoriatic and rheumatoid arthritis, has been proffered as a treatment for chronic stroke in various clinics. The manufacturer, Amgen, specifically points to a lack of evidence for its use in stroke and the few published reports by one dermatologist are highly biased and lack proper scientific theory, design, and interpretation of results [96].

Conclusions

Most survivors of a stroke are left with chronic disability. Rehabilitation efforts during the initial three to six months after stroke should aim to maximize patients' physical, communicative, and cognitive functioning. Continued improvement in the chronic phase of stroke can occur with regular, progressive skills practice of goal-directed tasks in the home [12]. Many new rehabilitation strategies, built upon attempts to leverage technological developments to augment the effects of practice, are opening innovative avenues to amplify gains in performance at any time after stroke. The future of stroke rehabilitation remains one of promise and challenge in treating residual disabilities, especially for testing biological interventions for neural repair in the most profoundly affected individuals.

References

Papers of particular interest, published recently, have beenhighlighted as:

• Of importance

•• Of major importance

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, et al. Heart disease and stroke statistics-2013 update: a report from the American Heart Association. Circulation. 2013 Jan 1; 127(1):e6–e245. [PubMed: 23239837]

2. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database of Syst Rev. 2009 Jan 21.(1):CD000197.

3. Centers for Disease Control and Prevention (CDC). Outpatient rehabilitation among stroke survivors-21 states and the District of Columbia, 2005. MMWR Morb Mortal Wkly Rep. 2007; 56:504–507. [PubMed: 17522589]

4. Centers for Medicare and Medicaid Services. Therapy cap. Accessed 4 Mar 2013http://www.cms.gov/research-statistics-data-and-systems/monitoring-programs/medical-review/therapycap.html * It is remarkable how relatviely few people of Medicare age are able to obtain stroke rehabilitation services.

5. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. Nat Rev Neurosci. 2009 Dec; 10(12):861–872. [PubMed: 19888284]

6. Rehme AK, Grefkes C. Cerebral network disorders after stroke: evidence from imaging-based connectivity analyses of active and resting brain states in humans. J Physiol. 2013 Jan 1; 591(Pt 1): 17–31. [PubMed: 23090951]

7. Iosa M, Morone G, Fusco A, Bragoni M, et al. Seven capital devices for the future of stroke rehabilitation. Stroke Res Treat. 2012; 2012:187965. [PubMed: 23304640]

8. Dobkin BH. Progressive staging of pilot studies to improve Phase III trials for motor interventions. Neurorehabil Neural Repair. 2009 Mar-Apr;23(3):197–206. [PubMed: 19240197]

9. Dobkin BH, Dorsch A. The promise of mHealth: daily activity monitoring and outcome assessments by wearable sensors. Neurorehabil Neural Repair. 2011; 25(9):788–798. [PubMed: 21989632]

10. [Accessed 4 Mar 2013] Stroke Engine. Stroke Engine-Assess. http://www.strokengine.ca/assess

11. Hobart JC, Cano SJ, Zajicek JP, Thompson AJ. Rating scales as outcome measures for clinical trials in neurology: problems, solutions, and recommendations. Lancet Neurol. 2007; 6(12):1094–1105. [PubMed: 18031706]

12. Dobkin BH. Clinical practice. Rehabilitation after stroke. N Engl J Med. 2005 Apr 21; 352(16): 1677–1684. [PubMed: 15843670]

13. Koyama T, Sako Y, Konta M, Domen K. Poststroke discharge destination: functional independence and sociodemographic factors in urban Japan. J Stroke Cerebrovasc Dis. 2011 May-Jun;20(3):202–207. [PubMed: 20621511]

14. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet. 2011; 377(9778):1693–1702. [PubMed: 21571152] * This paper reviews the most frequently employed interventions and the scientific basis for them.

15. Dobkin, BH. The clinical science of neurologic rehabilitation. 2nd ed. Oxford University Press; 2004.

16. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? Neurorehabil Neural Repair. 2012 Oct; 26(8):923–931. [PubMed: 22466792] * This reviews the limitations and potential of animal models to enable development of translational neurorehabilitation strategies. Timing, dose, duration and intensity of a rehabilitation therapy must be determined to optimize the strategy.

17. Ferrarello F, Baccini M, Rinaldi LA, Cavallini MC, et al. Efficacy of physiotherapy interventions late after stroke: a meta-analysis. J Neurol Neurosurg Psychiatry. 2011 Feb; 82(2):136–143. [PubMed: 20826872]

18. Wolf SL, Winstein CJ, Miller JP, Taub E, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006; 296(17):2095–2104. [PubMed: 17077374]

19. Lo AC, Guarino PD, Richards LG, Haselkorn JK, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010; 362(19):1772–1783. [PubMed: 20400552] ** This largest randomized clinical trial of upper extremity robotic training versus the same intensity of conventional therapy in highly impaired, hemiparetic participants revealed equivalent primary outcomes, but left open the possibility of some clinical usefulness for future studies.

20. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, et al. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011; 364(21):2026–2036. [PubMed: 21612471] ** This largest randomized clinical trial of BWSTT revealed that the experimental, highly task-oriented

intervention was equivalent to home-based, progressive exercise and balance training at the same intensity in terms of changes in gait speed, distance, and physical functioning, but significantly better than usual care starting 2 months post stroke. No differences were found between the two active interventions when starting BWSTT at 6 months after onset either.

21. Baert I, Daly D, Dejaeger E, Vanroy C, et al. Evolution of cardiorespiratory fitness after stroke: a 1-year follow-up study. Influence of prestroke patients' characteristics and stroke-related factors. Arch Phys Med Rehabil. 2012; 93(4):669–676. [PubMed: 22336102]
22. Rand D, Eng JJ, Tang PF, Jeng JS, Hung C. How active are people with stroke?: use of accelerometers to assess physical activity. Stroke. 2009; 40(1):163–168. [PubMed: 18948606] * Free-living physical activity was very low in 40 subjects and 58% of the participants did not meet recommended physical activity levels. Use of a single commercial accelerometer to count steps is fairly reliable if walking speeds exceed 0.5m/s. Physicians might encourage longer walks at higher speeds within the limits of confidence about safety.
23. Manns PJ, Dunstan DW, Owen N, Healy GN. Addressing the nonexercise part of the activity continuum: a more realistic and achievable approach to activity programming for adults with mobility disability? Phys Ther. 2012 Apr; 92(4):614–625. [PubMed: 22156025]
24. Han CE, Kim S, Chen S, Lai YH, et al. Quantifying arm nonuse in individuals poststroke. Neurorehabil Neural Repair. 2013 Jan 25. [Epub ahead of print].
25. Billinger SA, Coughenour E, Mackay-Lyons MJ, Ivey FM. Reduced cardiorespiratory fitness after stroke: biological consequences and exercise-induced adaptations. Stroke Res Treat. 2012; 2012:959120. [PubMed: 21876848]
26. Furie KL, Kasner SE, Adams RJ, Albers GW, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011; 42(1):227–276. [PubMed: 20966421]
27. Voss MW, Heo S Prakash RS, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: Results of a one-year exercise intervention. Hum Brain Mapp. 2012 Jun. [Epub ahead of print; ** One of a series of small trials from AF Kramer and colleagues that reveals structural and functional connectivity improvements in the brain, as well as in several cognitive domains, with moderate walking exercise.
28. Verdelho A, Madureira S, Ferro JM, Baezner H, et al. Physical activity prevents progression for cognitive impairment and vascular dementia: results from the LADIS (Leukoaraiosis and Disability) study. Stroke. 2012 Dec; 43(12):3331–3335. [PubMed: 23117721]
29. Brazzelli M, Saunders DH, Greig CA, Mead GE. Physical fitness training for stroke patients. Cochrane Database Syst Rev. 2011 Nov 9.(11):CD003316. [PubMed: 22071806]
30. Globas C, Becker C, Cerny J, Lam JM, et al. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial. Neurorehabil Neural Repair. 2012 Jan; 26(1):85–95. [PubMed: 21885867] ** Participants randomized to receive 3 months (3×/week) of progressive graded, high-intensity aerobic treadmill exercise improved significantly more than those who received conventional care physiotherapy in Vo2 peak, walking speed, balance and mental self-reported functioning.
31. Dean CM, Rissel C, Sherrington C, Sharkey M, et al. Exercise to enhance mobility and prevent falls after stroke: the community stroke club randomized trial. Neurorehabil Neural Repair. 2012 Nov-Dec;26(9):1046–1057. [PubMed: 22544817]
32. Touillet A, Guesdon H, Bosser G, Beis JM, Paysant J. Assessment of compliance with prescribed activity by hemiplegic stroke patients after an exercise programme and physical activity education. Arch Phys Rehabil Med. 2010 May; 53(4):250–257. 257–265.
33. States RA, Pappas E, Salem Y. Overground physical therapy gait training for chronic stroke patients with mobility deficits. Cochrane Database Syst Rev. 2009 Jul 8.(3):CD006075. [PubMed: 19588381]
34. Weerdesteyn V, de Niet M, van Duijnhoven HJ, Geurts AC. Falls in individuals with stroke. J Rehabil Res Dev. 2008; 45(8):1195–1213. [PubMed: 19235120]
35. Saeys W, Vereeck L, Truijen S, Lafosse C, et al. Randomized controlled trial of truncal exercises early after stroke to improve balance and mobility. Neurorehabil Neural Repair. 2012 Mar-Apr; 26(3):231–238. [PubMed: 21844283]

36. Chumbler NR, Quigley P, Li X, Morey M, et al. Effects of telerehabilitation on physical function and disability for stroke patients: a randomized, controlled trial. Stroke. 2012 May 24.

37. Dobkin BH, Duncan PW. Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? Neurorehabil Neural Repair. 2012 May; 26(4):308–317. [PubMed: 22412172] * A review of the pitfalls of translating animal studies of stepping interventions into pilot studies and then phase III trials of robotic and treadmill-based strategies for stroke and spinal cord injury. The outcomes have generally been equivalent to the same intensity of over-ground practice despite the theoretical basis for a means to better motor control.

38. Mehrholz J, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2010

39. Mehrholz J, Pohl M. Electromechanical-assisted gait training after stroke: a systematic review comparing end-effector and exoskeleton devices. J Rehabil Med. 2012 Mar; 44(3):193–199. [PubMed: 22378603]

40. Stein RB, Everaert DG, Thompson AK, et al. Long-term therapeutic and orthotic effects of a foot drop stimulator on walking performance in progressive and nonprogressive neurological disorders. Neurorehabilitation and Neural Repair. 2010; 24(2):152–167. [PubMed: 19846759]

41. Daly JJ, Zimbelman J, Roenigk KL, McCabe JP, 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 Sep; 25(7):588–596. [PubMed: 21515871]

42. Taylor P, Humphreys L, Swain I. The long-term cost-effectiveness of the use of Functional Electrical Stimulation for the correction of dropped foot due to upper motor neuron lesion. J Rehabil Med. 2013 Jan 25; 45(2):154–160. [PubMed: 23303521]

43. Wolf SL, Winstein CJ, Miller JP, Thompson PA, et al. Retention of upper limb function in stroke survivors who have received constraint-induced movement therapy: the EXCITE randomised trial. Lancet Neurol. 2008 Jan; 7(1):33–40. [PubMed: 18077218] * This clinical trial, first reported in JAMA in 2006, has continued to reveal important information about the recovery of upper extremity functioning, measures of gains, and long-term consequences of the massed practice intervention.

44. Smania N, Gandolfi M, Paolucci S, Iosa M, et al. Reduced-intensity modified constraint-induced movement therapy versus conventional therapy for upper extremity rehabilitation after stroke: a multicenter trial. Neurorehabil Neural Repair. 2012 Nov-Dec;26(9):1035–1045. [PubMed: 22661278] * Using the EXCITE trial's entry criteria, this randomized trial showed that just two hours of CIMT, rather than 6 hours a day for 10 days, may be more effective than conventional rehabilitation in improving motor function and use of the paretic arm in patients with hemiparetic chronic stroke.

45. Kitago T, Liang J, Huang VS, Hayes S, et al. Improvement after constraint-induced movement therapy: recovery of normal motor control or task-specific compensation? Neurorehabil Neural Repair. 2013 Feb; 27(2):99–109. [PubMed: 22798152]

46. Wu CY, Chuang LL, Lin KC, Chen HC, Tsay PK. Randomized trial of distributed constraint-induced therapy versus bilateral arm training for the rehabilitation of upper-limb motor control and function after stroke. Neurorehabil Neural Repair. 2011 Feb; 25(2):130–139. [PubMed: 20947493] * Hemiparetic patients with chronic stroke were randomized to treatment for 2 h/d and 5 d/wk for 3 weeks to either CIMT, bimanual training (BAT) or a neurodevelopmental therapy approach. Outcomes were better for the first two over the latter. BAT led to modestly higher arm forces and CIMT to modestly greater functional ability.

47. Mann G, Taylor P, Lane R. Accelerometer-triggered electrical stimulation for reach and grasp in chronic stroke patients: a pilot study. Neurorehabil Neural Repair. 2011 Oct; 25(8):774–780. [PubMed: 21628605]

48. Mehrholz J, Hädrich A, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev. 2012 Jun 13.6:CD006876. [PubMed: 22696362]

49. Hesse S, Waldner A, Mehrholz J, Tomelleri C, et al. Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: an exploratory, randomized

multicenter trial. Neurorehabil Neural Repair. 2011 Nov-Dec;25(9):838–846. [PubMed: 21825004]

50. Shaw LC, Price CI, van Wijck FM, et al. Botulinum toxin for the upper limb after stroke (BoTULS) trial: effect on impairment, activity limitation, and pain. Stroke. 2011; 42(5):1371–1379. [PubMed: 21415398]
51. Rosales RL, Kong KH, Goh KJ, Kumthornthip W, et al. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2012 Sep; 26(7):812–821. [PubMed: 22371239]
52. Blennerhassett JM, Gyngell K, Crean R. Reduced active control and passive range at the shoulder increase risk of shoulder pain during inpatient rehabilitation post-stroke: an observational study. J Physiother. 2010; 56(3):195–199. [PubMed: 20795926]
53. Brady MC, Kelly H, Godwin J, Enderby P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev. 2012 May 16.5:CD000425. [PubMed: 22592672]
54. van der Meulen I, van de Sandt-Koenderman ME, Ribbers GM. Melodic Intonation Therapy: present controversies and future opportunities. Arch Phys Med Rehabil. 2012 Jan; 93(1 Suppl):S46–S52. [PubMed: 22202191]
55. Meinzer M, Rodriguez AD, Gonzalez Rothi LJ. First decade of research on constrained-induced treatment approaches for aphasia rehabilitation. Arch Phys Med Rehabil. 2012 Jan; 93(1 Suppl):S35–S45. [PubMed: 22202189]
56. Cherney LR, van Vuuren S. Telerehabilitation, virtual therapists, and acquired neurologic speech and language disorders. Semin Speech Lang. 2012 Aug; 33(3):243–257. [PubMed: 22851346]
57. Fridriksson J, Hubbard HI, Hudspeth SG, Holland AL, et al. Speech entrainment enables patients with Broca's aphasia to produce fluent speech. Brain. 2012 Dec; 135(Pt 12):3815–3829. [PubMed: 23250889]
58. Ali M, Hazelton C, Lyden P, Pollock A, Brady M. Recovery from poststroke visual impairment: evidence from a clinical trials resource. Neurorehabil Neural Repair. 2013 Feb; 27(2):133–141. [PubMed: 22961263]
59. Mödden C, Behrens M, Damke I, Eilers N, et al. A randomized controlled trial comparing 2 interventions for visual field loss with standard occupational therapy during inpatient stroke rehabilitation. Neurorehabil Neural Repair. 2012 Jun; 26(5):463–469. [PubMed: 22140199]
60. Gorgoraptis N, Mah YH, Machner B, et al. The effects of the dopamine agonist rotigotine on hemispatial neglect following stroke. Brain. 2012; 135(Pt 8):2478–2491. [PubMed: 22761293] * Few trials of pharmacologic agents have led to better outcomes after stroke.
61. Mizuno K, Tsuji T, Takebayashi T, Fujiwara T, et al. Prism adaptation therapy enhances rehabilitation of stroke patients with unilateral spatial neglect: a randomized, controlled trial. Neurorehabil Neural Repair. 2011 Oct; 25(8):711–720. [PubMed: 21700922]
62. Nicolas-Alonso LF, Gomez-Gil J. Brain computer interfaces, a review. Sensors (Basel). 2012; 12(2):1211–1279. [PubMed: 22438708]
63. Hochberg LR, Bacher D, Jarosiewicz B, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature. 2012; 485(7398):372–375. [PubMed: 22596161] * Two subjects with long-standing tetraplegia learned to use a neural interface system-based control of a robotic arm to perform three-dimensional reach and grasp movements. Participants controlled the arm and hand over a broad space without explicit training, using signals decoded from a small, local population of motor cortex (MI) neurons recorded from an implanted 96-channel microelectrode array.
64. Dimyan MA, Cohen LG. Contribution of transcranial magnetic stimulation to the understanding of functional recovery mechanisms after stroke. Neurorehabil Neural Repair. 2010 Feb; 24(2):125–135. [PubMed: 19767591]
65. Adeyemo BO, Simis M, Macea DD, Fregni F. Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in non-invasive brain stimulation in stroke. Front Psychiatry. 2012; 3:88. [PubMed: 23162477]
66. Naeser MA, Martin PI, Ho M, Treglia E, et al. Transcranial magnetic stimulation and aphasia rehabilitation. Arch Phys Med Rehabil. 2012 Jan; 93(1 Suppl):S26–S34. [PubMed: 22202188]

67. Michou E, Mistry S, Jefferson S, Singh S, et al. Targeting unlesioned pharyngeal motor cortex improves swallowing in healthy individuals and after dysphagic stroke. Gastroenterology. 2012 Jan; 142(1):29–38. [PubMed: 21963761]
68. Wang RY, Tseng HY, Liao KK, Wang CJ, et al. rTMS combined with task-oriented training to improve symmetry of interhemispheric corticomotor excitability and gait performance after stroke: a randomized trial. Neurorehabil Neural Repair. 2012 Mar-Apr;26(3):222–230. [PubMed: 21974983]
69. Seniów J, Bilik M, Le niak M, Waldowski K, et al. Transcranial magnetic stimulation combined with physiotherapy in rehabilitation of poststroke hemiparesis: a randomized, double-blind, placebo-controlled study. Neurorehabil Neural Repair. 2012 Nov-Dec;26(9):1072–1079. [PubMed: 22588639] * Repetitive TMS at 1Hz to contralesional primary motor cortex to suppress its activity and disinhibit the lesioned side did not result in greater upper extremity gains compared to sham stimulation. Other smaller studies suggested modest improvements, but these may depend on the level of spared motor control and lesion location.
70. Talelli P, Wallace A, Dileone M, Hoad D, et al. Theta burst stimulation in the rehabilitation of the upper limb: a semirandomized, placebo-controlled trial in chronic stroke patients. Neurorehabil Neural Repair. 2012 Oct; 26(8):976–987. [PubMed: 22412171]
71. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology. 2010 Dec 14; 75(24):2176–2184. [PubMed: 21068427] * Twenty Participants were randomly assigned to 5 consecutive sessions of either bihemispheric transcranial direct current stimulation to upregulate excitability of ipsilesional motor cortex and downregulate excitability of contralesional motor cortex with simultaneous rehabilitation or to sham stimulation with therapy. Motor function improved significantly more in the real stimulation group (20.7% in Fugl-Meyer; 19.1% in Wolf Motor Function Test scores) compared to sham (3.2% in Fugl-Meyer; 6.0% in Wolf scores). The effects outlasted stimulation by 1 week.
72. Hummel FC, Celnik P, Pascual-Leone A, Fregni F, et al. Controversy: Noninvasive and invasive cortical stimulation show efficacy in treating stroke patients. Brain Stimul. 2008 Oct; 1(4):370–382. [PubMed: 20633395]
73. Conforto AB, Ferreiro KN, Tomasi C, dos Santos RL, et al. Effects of somatosensory stimulation on motor function after subacute stroke. Neurorehabil Neural Repair. 2010 Mar-Apr;24(3):263–272. [PubMed: 19884642]
74. Castel-Lacanal E, Marque P, Tardy J, de Boissezon X, et al. Induction of cortical plastic changes in wrist muscles by paired associative stimulation in the recovery phase of stroke patients. Neurorehabil Neural Repair. 2009 May; 23(4):366–372. [PubMed: 19060132]
75. Celnik P, Paik NJ, Vandermeeren Y, et al. Effects of combined peripheral nerve stimulation and brain polarization on performance of a motor sequence task after chronic stroke. Stroke. 2009 May; 40(5):1764–1771. [PubMed: 19286579]
76. Laufer Y, Elboim-Gabyzon M. Does sensory transcutaneous electrical stimulation enhance motor recovery following a stroke? A systematic review. Neurorehabil Neural Repair. 2011 Nov-Dec; 25(9):799–809. [PubMed: 21746874]
77. Garrison KA, Winstein CJ, Aziz-Zadeh L. The mirror neuron system: a neural substrate for methods in stroke rehabilitation. Neurorehabil Neural Repair. 2010 Jun; 24(5):404–412. [PubMed: 20207851]
78. Michielsen ME, Selles RW, van der Geest JN, Eckhardt M, et al. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. Neurorehabil Neural Repair. 2011 Mar-Apr;25(3):223–233. [PubMed: 21051765]
79. Thieme H, Mehrholz J, Pohl M, Behrens J, Dohle C. Mirror therapy for improving motor function after stroke. Cochrane Database Syst Rev. 2012 Mar 14.3:CD008449. [PubMed: 22419334]
80. Winstein CJ, Requejo PS, Zelinski EM, Mulroy SJ, Crimmins EM. A transformative subfield in rehabilitation science at the nexus of new technologies, aging, and disability. Front Psychol. 2012; 3:340. [PubMed: 23049517]
81. Subramanian SK, Lourenço CB, Chilingaryan G, Sveistrup H, Levin MF. Arm motor recovery using a virtual reality intervention in chronic stroke: randomized control trial. Neurorehabil Neural Repair. 2013 Jan; 27(1):13–23. [PubMed: 22785001]

82. Saposnik G, Levin M. Outcome research Canada Working Group. Virtual reality in stroke rehabilitation: a meta-analysis and implications for clinicians. Stroke. 2011 May; 42(5):1380–1386. [PubMed: 21474804] * A pooled analysis of 5 randomized trials, motor impairment was decreased by VR interventions, but no differences were found for functional use of the arm and hand.
83. Schuster C, Maunz G, Lutz K, Kischka U, et al. Dexamphetamine improves upper extremity outcome during rehabilitation after stroke: a pilot randomized controlled trial. Neurorehabil Neural Repair. 2011 Oct; 25(8):749–755. [PubMed: 21712481]
84. Cramer SC, Dobkin BH, Noser EA, et al. Randomized, placebo-controlled, double-blind study of ropinirole in chronic stroke. Stroke. 2009; 40(9):3034–3038. [PubMed: 19520987]
85. Berthier ML, Green C, Lara JP, et al. Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia. Annals of Neurology. 2009; 65(5):577–585. [PubMed: 19475666]
86. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurology. 2011; 10(2):123–130. [PubMed: 21216670] ** Selective movements (Fugl-Meyer scores) significantly improved in participants with moderate motor impairment who received 20 mg of fluoxetine starting 3–5 days after onset of stroke. Augmentation of gains was hypothesized to be from modulation of mechanisms of cerebral plasticity.
87. Mead GE, Hsieh CF, Lee R, Kutlubaev M, et al. Selective Serotonin Reuptake Inhibitors for Stroke Recovery: A Systematic Review and Meta-analysis. Stroke. 2013 Jan 29.44:844–850. [PubMed: 23362083]
88. Dihné M, Hartung HP, Seitz RJ. Restoring neuronal function after stroke by cell replacement: anatomic and functional considerations. Stroke. 2011 Aug; 42(8):2342–2350. [PubMed: 21737804]
89. Lee JS, Hong JM, Moon GJ, et al. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. Stem Cells. 2010; 28(6): 1099–1106. [PubMed: 20506226]
90. Lindvall O, Kokaia Z. Stem cell research in stroke: how far from the clinic? Stroke. 2011 Aug; 42(8):2369–2375. [PubMed: 21757669]
91. Hyun I, Lindvall O, Ahrlund-Richter L, Cattaneo E, et al. New ISSCR guidelines underscore major principles for responsible translational stem cell research. Cell Stem Cell. 2008 Dec 4; 3(6):607–609. [PubMed: 19041777] ** This working group reviews the ethical uses of cellular interventions; other societies subsequently echoed their recommendations.
92. Wechsler L, Steindler D, Borlongan C, Chopp M, et al. Stem Cell Therapies as an Emerging Paradigm in Stroke (STEPS): bridging basic and clinical science for cellular and neurogenic factor therapy in treating stroke. Stroke. 2009 Feb; 40(2):510–515. [PubMed: 19095993]
93. Kong JC, Lee MS, Shin BC, Song YS, Ernst E. Acupuncture for functional recovery after stroke: a systematic review of sham-controlled randomized clinical trials. CMAJ. 2010 Nov 9; 182(16): 1723–1729. [PubMed: 20876268]
94. Zhuangl LX, Xu SF, D'Adamo CR, Jia C, et al. An effectiveness study comparing acupuncture, physiotherapy, and their combination in poststroke rehabilitation: a multicentered, randomized, controlled clinical trial. Altern Ther Health Med. 2012 May-Jun;18(3):8–14. [PubMed: 22875557]
95. Efrati S, Fishlev G, Bechor Y, Volkov O, et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients - randomized, prospective trial. PLoS One. 2013; 8(1):e53716. [PubMed: 23335971]
96. Tobinick E, Kim NM, Reyzin G, Rodriguez-Romanacce H, DePuy V. Selective TNF inhibition for chronic stroke and traumatic brain injury: an observational study involving 629 consecutive patients treated with perispinal etanercept. CNS Drugs. 2012 Dec; 26(12):1051–1070. [PubMed: 23100196] * The Internet has enabled desperate patients to locate the claims made by clinicians that sell cells and pharmacologic interventions. Physicians should be prepared to discuss such highly biased claims with their patients. This paper leaves open the possibility of hope for improvement, despite the obvious biases that even the authors point out.