Published in final edited form as:
Ann Neurol. 2013 July ; 74(1): 4–10. doi:10.1002/ana.23948.

MANAGEMENT OF PATIENTS WITH STROKE IS IT TIME TO EXPAND TREATMENT OPTIONS?

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Abstract

Approximately 700,000 people in the United States have an ischemic stroke annually. Substantial research has tested therapies for the very early treatment of ischemic stroke but, to date, only intravenous thrombolysis and intra-arterial measures to restore perfusion have shown success. Despite a 15-year effort to increase the use of these therapies, only approximately 5% of patients with stroke are currently being treated. Although most patients with stroke have some neurological recovery, more than half of stroke survivors have residual impairments that lead to disability or long-term institutionalized care. Laboratory research has demonstrated several mechanisms that help the brain to recover after a stroke. New pharmacological and cell-based approaches that are known to promote brain plasticity are emerging from laboratory studies and may soon expand the window for stroke treatment to restore function. It is time to build on this knowledge and to translate the understanding of recovery after stroke into the clinical setting. Measures that might augment recovery should become a major focus of clinical research in stroke in the 21st century.

Keywords

ischemic stroke; stroke recovery; rehabilitation

Ischemic stroke is feared by the public because of the secondary cognitive, motor, and sensory impairments that lead to prolonged human suffering, long-term disability, and institutionalized care. The secondary economic consequences due to lost productivity and increased health care expenses, including rehabilitation and long-term care, are considerable. A major focus of both laboratory and clinical research has been on the ultra-early emergency treatment of stroke (therapy initiated within the first few hours after onset.) During the last 25 years, multiple clinical trials have tested reperfusion or neuroprotective therapies to limit the neurological injury secondary to an arterial occlusion. To date, only intravenous administration of tissue plasminogen activator (rtPA) and the use of some endovascular mechanical interventions have received acceptance by the medical community and governmental regulators. [1, 2] While strong support for efforts to treat more patients with reperfusion therapy must continue, the medical community should recognize that these treatments have major drawbacks. Approximately 95% of patients with stroke are not being treated with either intravenous or intra-arterial reperfusion therapies. [3] As a result, the societal impact of reperfusion therapy is limited. It is not clear if the results of the current research that emphasizes ultra-early treatment of stroke can overcome these problems. In

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addition, a majority of patients treated with reperfusion therapy have residual neurological impairments that mandate additional management. Long-term management options include interventions to prevent delayed complications of the stroke, therapies aimed at preventing recurrent vascular events, and long-term rehabilitation to promote functional recovery.

New strategies to expand the options for treatment of patients with ischemic stroke are needed. With the rapid advances in our basic understanding of regenerative mechanisms after stroke, a promising approach is to accelerate testing of putative restorative medications that are likely to have a much broader intervention window. At present, no intervention that could foster recovery and that could complement current rehabilitation have been established as effective. Funding agencies, industry, and both laboratory and clinical researchers in stroke should broaden their vision and consider testing the utility of other modalities that might improve outcomes.

While some recovery following stroke occurs spontaneously, recovery is reinforced by rehabilitative efforts that involve relearning or the development compensatory strategies.[4–8] Approximately 75% of stroke survivors need some type of rehabilitation.[9] Several measures to augment the recovery process by combining current rehabilitative interventions with other therapies, including robot-assisted therapy, virtual reality training, and other novel therapies, are now under investigation.[10–13] Brain stimulation also has gained popularity as a post-stroke intervention. [13] Approaches include both invasive modalities, such as epidural stimulation and non-invasive modalities, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS.) [14, 15]

One important consideration for future restorative treatments, whether with pharmacological, cell-based, or device-based strategies is to determine if the intervention is administered alone or as an adjunct to standard rehabilitation interventions. For example, one premise behind brain stimulation approaches is that such stimulation alters the excitability of surviving neuronal populations in the injured hemisphere. Thus, behavioral interventions may be most effective when combined with treatments that enhance neuronal excitability. There is also a long history of interactive effects of pharmacological agents, (e.g. d-amphetamine) and behavioral experience.[16] More recently, preclinical studies have demonstrated that growth-promoting agents interact with behavior and are most effective as an adjunct to rehabilitative training. [17]

THE POTENTIAL FOR RESTORATIVE THERAPIES

Restorative therapies may be a complementary way to treat patients with stroke. Rapid advances in our knowledge of central nervous system neuroplasticity are leading to a better understanding regarding the underlying mechanisms involved in post-stroke recovery.[18, 19] Many of these advances are leading to consideration of new potential targets for restorative treatment that are becoming increasingly feasible.

Post-stroke plasticity has been demonstrated at multiple levels of analysis ranging from changes in gene expression to alterations in physiology and anatomy of brain networks. [20] Such plasticity is time-dependent and may provide a relatively broad window of opportunity (days to weeks) for promoting neural repair after stroke, especially when compared to the narrow therapeutic window afforded by reperfusion therapies. At the onset of focal ischemia both degenerative and restorative processes are set into motion. For example, in the acute phase after experimental stroke, excitotoxic cascades involving AMPA and NMDA receptor signaling lead to substantial cell death.[14] Considerable research has focused on pharmaceutical agents that block post-stroke excitotoxicity in the first hours after stroke but such agents have not been effective in clinical trials. Restorative therapies should not be confused with these neuroprotective agents. Rather than being aimed at limiting the acute

neurologic injury that occurs during the first few hours after stroke, the goal of restorative therapies would be to facilitate the brain's natural ability to recover after stroke by augmenting those processes used in healing. Modulation of regenerative processes with treatment beginning soon after stroke or up to several weeks following the vascular event now is feasible.

A growing number of preclinical studies have demonstrated mechanisms that are initiated in the peri-infarct cortex rapidly after experimental stroke. For example, thrombospondin 1 and 2, extracellular glycoproteins involved in angiogenesis and synaptogenesis and that are necessary for synaptic plasticity and behavioral recovery, are substantially upregulated within one day of experimental stroke.[21] Several other growth factors that may positively influence post-stroke remodeling also are upregulated in the peri-infarct region including growth-associated protein 43 (GAP 43,) myristoylated alanine-rich C-kinase substrate (MARCKS,) cytoskeleton-associated protein 23 (CAP 23,) and brain-derived neurotrophic factor (BDNF.) [22–29] Negative factors also are expressed in the peri-infarct region including neurite outgrowth inhibitor (Nogo-A,) chondroitin sulfate proteoglycan, ephrin A5 and the ephrin receptors, semaphorin 3A, and neuropilin 1.[15, 17] Each of these factors represents a potential therapeutic target for enhancing the restorative process after stroke. A large and growing literature in rodent stroke models has demonstrated neural plasticity and improved recovery either by enhancing growth-promotion factors or blocking growth-inhibition factors. For example, administration of BDNF or other growth factors enhances recovery in rat stroke models.[30–32] Blocking the Nogo-A receptor enhances dendritic and axonal plasticity and promotes recovery in experimental stroke models.[33–35] NEP 1–40 (Nogo extracellular peptide residues 1 to 40,) a specific antagonist of Nogo actions at the Nogo receptor 1 (NgR1) also enhances behavioral recovery after experimental stroke.[17] This latter finding is interesting in light of the recent finding that NgR1 and NgR3 are receptors for chondroitin sulfate proteoglycans.[36]

In addition to targeting the blockage of Nogo, recent preclinical studies show that recovery can be promoted by blocking Ephrin-A5. Ephrin-A5 is induced in reactive astrocytes in experimental stroke models and is known to inhibit axonal sprouting and behavior recovery. The inhibitory effects of Ephrin-A5 can be blocked by the receptor decoy, Ephrin-A5-Fc. After blocking Ephrin-A5 following stroke, a new pattern of axonal connections from in the cerebral cortex is generated and it is associated with improved motor recovery. [37] Other pharmacological treatments that show promise due to their ability to modulate restorative processes in ischemic brains include erythropoietin, statins, and granulocyte-colony stimulating factor. [38–40] In addition to targeting the blockage of Nogo, recent preclinical studies show that recovery can be promoted by blocking Ephrin-A5. Ephrin-A5 is induced in reactive astrocytes in experimental stroke models and is known to inhibit axonal sprouting and behavior recovery. The inhibitory effects of Ephrin-A5 can be blocked by the receptor decoy, Ephrin-A5-Fc. After blocking Ephrin-A5 following stroke, a new pattern of axonal connections from in the cerebral cortex is generated and it is associated with improved motor recovery. [37] Other pharmacological treatments that show promise due to their ability to modulate restorative processes in ischemic brains include erythropoietin, statins, and granulocyte-colony stimulating factor. [38–40]

Neurogenesis and proliferation of cells occur spontaneously following experimental stroke, primarily in the subventricular zone of the lateral ventricle and the subgranular layer of the dentate gyrus. [34] These cells may migrate into the area of the infarction and assume the features of mature neurons.[41–44] In the progenitor cells from the subventricular zone, gene expression is strikingly similar to that seen during embryonic development.[45] It is possible that progenitor cells serve as a reservoir of growth promoting factors during a sensitive period after injury. Further, the introduction of a variety of human cells into

experimental stroke models in rodents has demonstrated enhanced neurological recovery. These have included neural precursor cells, bone marrow cells, umbilical cord cells, fetal and embryonic cells, peripheral blood cells and adipose tissue cells.[46] It has been proposed that both cell-based and pharmacologically based therapies may exert their effects by at least partially increasing neurogenesis after stroke.

Experimental models clearly show that many of the processes that lead to recovery are time-dependent. A limited period of robust upregulation of factors that promote, as well as inhibit, growth and plasticity occurs in experimental stroke along a predictable trajectory. [46] Further, neuronal plasticity potential is not limited to the peri-infarct cortex, since remote cortical areas connected to the ischemic core undergo similar time-dependent processes.[33, 47] The precise time window of robust plasticity potential is not yet known with certainty but based on studies of gene and protein expression, it would appear that this process lasts at least several weeks. Though treatment usually is initiated within hours to days after stroke in experimental models, therapeutic benefits have been demonstrated even when treatment is delayed by one month.[48] This extended period of plasticity may offer a relatively broad window for restorative therapies. Though there are significant challenges in translating these findings to clinical populations (e.g. delivery of compounds to brain tissue in sufficient quantities,) these recent basic science advances point to a new direction in stroke treatment.

TRANSITIONING ADVANCES IN THE UNDERSTANDING OF STROKE RECOVERY TO PATIENTS

The translation of advances in the laboratory to the clinical situation has been difficult but experience is greatest when evaluating the potential utility of medical interventions. New interventions, such as genetic or cell-based therapies, will require substantial preclinical work in multiple model systems to understand safety margins, robustness in different stroke models, and the ability of the intervention to penetrate a large brain. Thus, the first clinical trials in testing neurorestorative therapies probably should look at the impact of pharmacological therapies. Those medications that have already been used to treat humans may be the best choices to test first because issues such as human toxicity and side effects already have been largely addressed. Antidepressants are an example of such medications. The pharmacological therapies have the advantage of potentially having a global impact on brain function, which may be translated into the improvements in overall clinical outcome that are of importance to patients, clinicians, and governmental regulatory bodies. Already, a number of medications that may positively influence plasticity mechanisms and that could be given as adjuncts to rehabilitation have been evaluated in both experimental and clinical studies. [49–53] Results are mixed. Stimulants, in particular amphetamines, have received attention and have shown promise in pre-clinical studies but small clinical studies generally are negative.[16, 54–56] Researchers that are translating the advances in the basic science knowledge of stroke recovery can learn from the experiences of these preliminary studies.

There is considerable interest in the potential utility of the antidepressant medications, which may at least indirectly influence recovery through restorative mechanisms.[53, 57, 58] In particular, the selective serotonin reuptake inhibitors (SSRIs) have been the focus of clinical and preclinical research. These medications already are used, with safety, to treat patients who are depressed after stroke. Clinical observations report improved activities of daily living and executive function, augmented motor recovery, and increased survival with the use of the antidepressant medications. [53, 57, 59–61] These effects may be partially independent of the medications' actions on depression. These features make them excellent candidates for use as agents that could augment recovery in the subacute phase of stroke and

other forms of brain injury. They could be administered to non-depressed patients following stroke. [62]

Laboratory studies demonstrate that antidepressant medications may enhance recovery after stroke through several mechanisms. These agents stimulate neurogenesis in the subventricular zone, the dentate gyrus, and the hippocampus.[63–68] The medications increase axonal sprouting and the development of new synapses. They also may activate the supplementary motor area, cingulate cortex, basal ganglia, and cerebellum. Antidepressants alter release of the monoaminergic neurotransmitters including serotonin, dopamine, and norepinephrine. These agents also may increase levels of nitric oxide, improve endothelial function, block voltage-dependent calcium and sodium channels, and counteract the effects of inflammatory cytokines.[69] The medications also appear to activate BDNF and BDNF-medicated cortical plasticity [70].

Small clinical studies have tested the utility of the antidepressant medications to improve recovery of patients with recent stroke.[50, 59, 60, 71–82] While data are not definitive, the results generally are positive. The most important data are from the FLAME study, which was a randomized, double-blind, placebo-controlled trial of fluoxetine (20 mg daily) initiated within 5 – 10 days after stroke and continued for 3 months.[82] The 118 non-depressed subjects had severe hemiparesis and were receiving rehabilitation; the mean National Institutes of Health Stroke Scale (NIHSS) scores in both groups were approximately 13. Outcomes were measured at 3 months using the modified Rankin Scale (mRS) and the Fugl-Meyer Scale (FMS,) which measures motor recovery. A significantly greater improvement in FMS scores (mean improvement 36.4 points vs. 21.9 points) was seen with fluoxetine. NIHSS scores of 0 – 5 were achieved in 55% of the subjects assigned fluoxetine and 43% of those treated with placebo. A mRS score of 0 – 2 was achieved in 26.3% of subjects treated with fluoxetine and 9% administered placebo; the results were statistically significant. The currently available data demonstrate the potential utility of antidepressants; in particular, the SSRI agents may be particularly helpful.[83]. Because antidepressant medications are inexpensive, the cost-effectiveness of the agents could be great even if the relative differences in improvement in outcomes are smaller than with reperfusion therapies. If the time window for initiating therapy is several days, the medications could be given to a wide range of patients, including those that currently are not eligible for reperfusion therapy, and could complement traditional rehabilitation.

PRACTICAL RECOMMENDATIONS FOR FUTURE RESTORATIVE THERAPIES

For a future therapy to be truly useful in augmenting recovery after stroke it must have strong evidence of both safety and efficacy and the potential to be administered to a broad spectrum of patients with stroke, possibly including those with hemorrhagic events. Ideally, the presumed cause of stroke, affected vascular territory, and the severity of the baseline neurological deficit would not greatly alter plans for treatment. The intervention could be given without the strict time constraints that exist for reperfusion therapies. The therapy could be administered following acute interventions, including reperfusion therapies, and given in conjunction to treatments to prevent recurrent stroke or other vascular events. The therapy could be started within the first days after stroke and continued through the first weeks, the time period when the restorative mechanisms are most robust and the rate of recovery is the greatest. The therapy could be administered by a broad spectrum of physicians. The therapy would be easy to administer, should have a limited need for monitoring or ancillary tests, and should not require frequent adjustments in the treatment regimen. In addition, the treatment should be relatively inexpensive and should not require the creation of a new and costly infrastructure. In addition, the therapy would reduce health

care system expenditures. Of the current option to augment recovery, medications, such as the antidepressants, are currently the most likely to meet these attributes.

While research in strategies to limit the acute brain injury should continue, funding agencies, industry, neuroscientists and clinical researchers should be cognizant of the potential limited impact of these advances. It is time to broaden the horizon in stroke care to increase the focus on mechanisms and therapies that speed or improve recovery after stroke. Trials testing treatments in stroke recovery could initially focus on the potential utility of a variety of existing medications. It is time to organize trials that test the usefulness of medications that may facilitate recovery after stroke; the goal would be to determine whether these agents do improve neurological outcomes. The issues related to stroke recovery trials likely will differ in some ways from the acute stroke treatment trials. For example, the time window for enrollment, the duration of treatment, and the period of follow-up likely will be longer than for the emergency stroke treatment trials. Besides testing the potential utility of the medications, these trials could address several issues related to design and conduct of clinical research in this field. Among the issues that could to be clarified by such research are: 1) the timing of initiation of treatment and, if appropriate, the duration and intensity of therapy, 2) the definition of the clinical and other criteria in the selection of patients to treat, 3) the use of global or modality/impairment specific measures to assess responses to treatment, 4) the use of surrogate markers including imaging or biomarkers as secondary measures of outcomes and 5) the standardization of conventional rehabilitation and other treatments following stroke. Still, the standard for success of any intervention to maximize recovery after stroke will be evidence of safety and efficacy in improving outcomes of patients. Even if medications, such as antidepressants, are not found to be effective, the strategies used to address the issues related to design and conduct of clinical trials in stroke recovery would be invaluable for future research. These initial trials would help accelerate drug discovery efforts to establish new and more effective medications that specifically target recovery mechanisms. In effect, the initial clinical trials in stroke recovery potentially are as important at those preliminary studies in emergency management of acute ischemic stroke that resulted in the success of reperfusion therapy. Hopefully, in time, research into therapies to augment recovery will lead to a new strategy to the treatment of the large numbers of patients with recent stroke who are not being treated with reperfusion therapy.

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