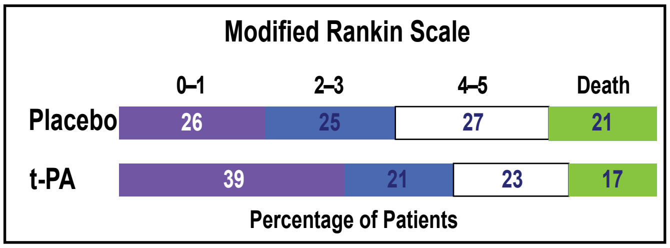
therapy for acute ischemic stroke. In a recent re-analysis of the NINDS rt-PA trial, "none of the bad outcomes was increased by rt-PA," said Dr. Zivin (Figure 1). Demaerschalk (*Stroke* 2007) estimated the likelihood of being helped to being harmed (LHH) by rt-PA to be approximately 10. In other words, rt-PA therapy would be 10 times more likely to help a patient with acute ischemic stroke than to harm them.

**Figure 1. NINDS rt-PA Trial.**




These findings have not always translated into clinical practice. A survey conducted by the American College of Emergency Physicians indicated that 40% of emergency room doctors were unlikely to use rt-PA under ideal conditions (Brown et al. *Ann Emerg Med* 2005). When asked why, 65% cited concerns about intracerebral hemorrhage, 23% said due to lack of efficacy, and 12% replied that both reasons contributed to their decision. Ironically, the decision not to use rt-PA has resulted in more lawsuits than lawsuits that have been filed due to harm caused by using the drug (Bambauer et al. *Ann Neurol* 2006). "Many physicians believe that 'to do no harm' is a good strategy to avoid malpractice suits. What they fail to realize under those circumstances is that to fail to treat, to decide not to do something, is a decision. Failure to treat with rt-PA is more likely to result in adverse legal decisions," said Dr. Zivin.

What can physicians do in this increasingly litigious environment? According to Michael Weintraub, MD, New York Medical College, Valhalla, NY, detailed documentation is absolutely critical. Legibly documenting time of symptom onset, time of diagnosis, time of workup completion, and rationale for using or not using rt-PA is particularly important. "Poor medical records can suggest negligence to the jury," noted Dr. Weintraub. John P. Conomy, MD, JD, Case Western Reserve University, Cleveland, OH, offered additional advice. Because patients often turn to the internet to educate themselves, physicians need to be aware of this and step up their efforts to educate patients. Physicians should also educate themselves about the legal issues they face. "Attorneys know a great deal about a great many things. Physicians as a group know very little about law, because they've been taught very little about law. I think it belongs in the curricula of medical schools, at least in an introductory way," summarized Dr. Conomy.

## Clinical Approaches to Brain Repair After Stroke

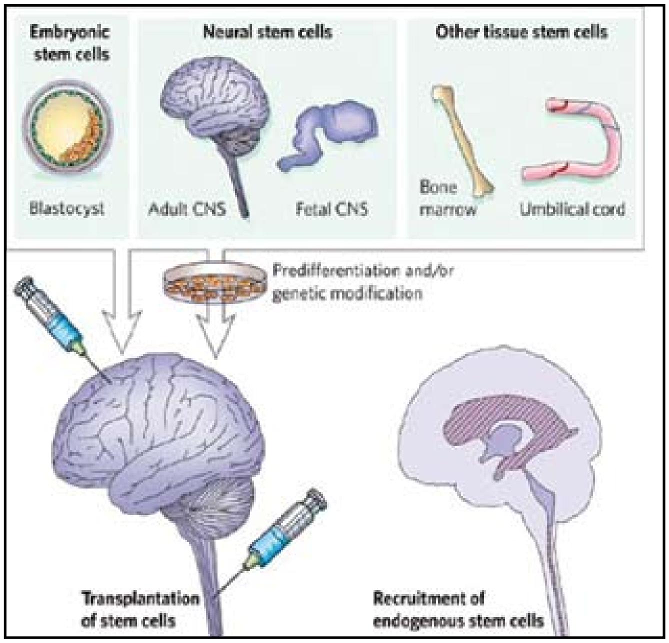
Patients who suffer strokes experience residual symptoms in many areas. Reports in the literature indicate that 38% of patients reported major difficulty in hand function 1-3 months post-stroke (Duncan et al. *Stroke* 2003), and up to 65% of patients could not use their paretic hand in daily activities 6 months post-stroke (Mayo et al. 2002). "The impact of manual function on independent living is significant...this is one of the precursors of losing independent capability," said Carolee Winstein, PhD, PT, University of California, Los Angeles, CA. Different approaches are being explored to help alleviate post-stroke disability, and studies suggest that intensive, task-oriented upper limb training (TOULT) may be effective. The Stroke Arm Recovery (STAR) trial was a phase 2, unblinded, single-center study that compared TOULT, strength training (ST), and standard care (SC) on upper limb recovery. The TOULT group was significantly better than the SC group in measures of impairment ($p=0.04$) and strength ($p=0.02$). Nine months later, the less severe stroke patients outperformed the ST group in strength ($p<0.05$; Winstein et al. *Arch Phys Med Rehabil* 2004). In the phase 3 Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial, 222 stroke patients were randomized to receive either constraint-induced movement therapy (CIMT) or SC 3-9 months post-stroke. Patients who received CIMT had statistically significant, clinically relevant improvements that lasted for at least one year (Wolf et al. *JAMA* 2006). "The critical elements of constraint therapy remain unresolved. Is it the task-oriented training, is it the shaping repetition, is it the forced use?" commented Dr. Winstein. These questions are in need of additional research.

Electromagnetic brain stimulation methodology and its potential effect on motor stimulation training were reviewed by Leonardo Cohen, MD, National Institutes of Health, Bethesda, MD. "One line of evidence that has been demonstrated so far...is that when different forms of brain stimulation are applied over the primary motor cortex (M1), there is a resultant increase in motor cortical excitability," said Dr. Cohen. This led to the idea that stimulation may provide a synergistic effect on motor training in humans, and emerging technologies are in the proof-of-concept stage

(Hummel FC, Cohen LG. *Lancet Neurology* 2006). The types of issues that need resolution include optimization of the stimulation site, technique optimization, characterization of the patients/injuries/tasks that may be helped, and the safety of the procedures (Tallelli P, Rothwell J. *Curr Opin Neurol* 2006; Fregni F, Pascual-Leone A. *Cogn Behav Neurol* 2006).

Cellular therapies are also being explored as a mechanism for brain repair after stroke, as discussed in an overview given by Sean Savitz, MD, University of Texas, Houston, TX. The concept arose from stem cell transplantation in cancer patients as well as transplantation in those with Parkinson disease. Promotion of lost neuronal connections and conductivity, enhancement of trophic support for neurogenesis, angiogenesis, synaptogenesis, prevention of cell death, and reduction of inflammatory responses and scar formation are some of the possible mechanisms whereby cell therapy could enhance brain recovery. Although it is an exciting idea, it is an area that is full of challenges. "Is it really possible to consider that cellular therapy or cellular transplantation is going to reconstruct the complex tapestry of the infarcted brain?" asked Dr. Savitz. Some of the parameters that researchers must determine are the infarct size and location, the timing of therapy, injection sites, routes of delivery, which cell types (Figure 1), and patient safety monitoring. The search for an effective therapy to promote brain repair after stroke continues to evolve across the domains of physical therapy, brain stimulation, and cell therapy.

**Figure 1. Complexity of Cell Types.**

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In a large group of stroke patients who were admitted within 24 hours of symptom onset, plasma levels of 15dPGJ(2) on admission were significantly higher than in control patients. A linear relationship between increased plasma 15-dPGJ(2) concentration and better neurological outcome at 3 months, less neurological deterioration, and smaller infarct volume was noted, indicating a neuroprotective effect for 15-dPGJ(2) in atherothrombotic ischemic stroke [Blanco M et al. *Stroke* 2005].

In another clinical study, the use of PPARγ was associated with enhanced functional recovery in stroke patients with type 2 diabetes compared with a control group [Lee J, Reding M. *Neurochem Res* 2007].

Dr. Moro feels that experimental evidence together with these early clinical results shows a need for larger clinical studies that use PPARγ agonists as potential therapeutic agents not only for prevention but also for treatment of acute stroke.

**Continued from page 23**

Seven subjects were successfully implanted with 5-7 microstimulators. After a 12-week period of functional exercise using personalized activity programs supported by electrical stimulation, improvement was noted in function (ARAT scores), impairment motor scores (Fugl-Meyer), motor control (Tracking Index), and spasticity (Stretch Index). The largest gains were seen in patients <2 years post-stroke. There were no infections or delayed wound healing. Six of the seven subjects continue to use the system at home. Dr. Burridge looks forward to the next generation of microstimulators and the feasibility of using fewer devices.