Much of the attention in the field of stroke is focused on prevention, emergency response, and management of the acute inpatient stay. Despite these efforts, many patients are left with substantial disability. Patients survive their stroke for a mean of 8 years, making poststroke disability a highly prevalent condition; most of the days during which stroke affects the life of the patient occur in this chronic disability phase.

Increased attention is being paid to an emerging set of therapeutic targets that are related to repair and restoration. Such restorative therapies focus on improving function in surviving brain areas rather than salvaging acutely threatened tissue and therefore might be available to a high proportion of patients with stroke. Animal studies have suggested a wide range of potential restorative therapies, including interventions based on physical, cellular, pharmacological, and electromagnetic approaches. However, to date, there has been limited translation of these preclinical findings into late-phase human clinical trials. In this regard, the Extremity Constraint Induced Therapy Evaluation (EXCITE) trial is a major step forward. It is unique among trials of restorative interventions for its size, meticulous multisite organization, preparation, duration of follow up, derivation from biological principle, and application of clinical trial methodology. In many ways, the EXCITE trial represents a paradigmatic shift in restorative stroke trials.

The EXCITE trial was a prospective, single-blind, randomized, multisite clinical study conducted at 7 US academic institutions between 2001 and 2003. The study randomized a total of 222 patients with a first ischemic or hemorrhagic stroke. The index event had to be in the previous 3 to 9 months, a time period during which spontaneous recovery has generally reached a plateau and before many chronic poststroke changes such as atrophy or spasticity are maximally severe. Participants had moderate, but not severe, deficits. For example, each needed to be able to actively move the wrist through at least 10° range of motion, demonstrate good balance, and have no advanced cognitive impairment. Those already showing substantial use of the affected arm were excluded.

Enrollees were randomized to either customary care or constraint-induced therapy. Constraint-induced therapy consisted of 2 main components applied in parallel over a 2-week period: subjects performed intense practice of functional tasks using the affected hand for 6 hours per day plus subjects reduced use of the unaffected hand by covering it with a mitt for at least 90% of waking hours. This therapy is based on Taub's observations in deafferented monkeys that disability can arise in part from learned nonuse of an impaired arm.

The trial found significantly positive results for both of the prespecified primary end points, which were measured 1 year after study enrollment and thus 50 weeks after completion of therapy. The Wolf Motor Function Test, an objective, valid, reliable measure of distal and proximal arm motor function, showed a 52% reduction in time to complete its tasks, significantly \( P<0.001 \) better than the 26% reduction found in those in the customary care group. The Motor Activity Log, a subjective, valid, reliable scale that records estimates of affected arm use, showed a 76% increase in quantity and a 77% increase in quality of arm use, each significantly \( P<0.001 \) better than the 43% and 41% respective increases found in the customary care group. Of note, treatment effects did not differ according to a 2-level stratification of baseline arm motor function.

The authors of the EXCITE study are to be congratulated on many levels. The clinical follow-up period of 1 year is remarkable for any stroke trial as was the retention rate of 76% out to this time point. Behavioral data were collected from the good arm as an internal control; indeed, this showed no differences between treatment groups over time and further increased confidence in results reported for the affected arm. The use of adaptive randomization helped achieve good balance between treatment groups in baseline measures, an issue that has plagued some prior restorative clinical trials. The authors carefully and thoroughly tackled thorny issues that are central to trials that intervene in the chronic phase and...
likely of some relevance to stroke trials that intervene in the acute phase but have assessments in the chronic phase. Such issues include assessment of behavioral compliance and measurement of rehabilitation therapies not prescribed as part of the study protocol.

The study also raises a number of important questions. The fraction of patients with stroke for whom these results hold promise remains to be determined. The requirement that a patient demonstrate 10° of active wrist extension is used to increase the likelihood that the affected arm will improve after therapy, but this also excludes a large fraction of the stroke population. Estimates vary, but only 6.3% of patients screened in this trial and 18% of those screened in a separate study were ultimately found to be eligible to receive constraint-induced therapy. A more theoretical estimate is that 20% to 25% of patients with stroke might be eligible.\(^5\)

The exact component(s) of constraint-induced therapy critical to the observed clinical gains requires further clarification as noted by the authors. Thus, the contribution of intense practice by the affected limb needs to be disentangled from the contribution of constraining the good limb. Note that historically, however, such uncertainty has not prevented implementation of therapy in the setting of vascular disease. For example, the extent to which aspirin’s preventative effects are attributable to antiplatelet versus antiinflammatory activities remains to be fully clarified, yet this therapy is widely prescribed to patients with stroke.\(^6\) Interpretation of the EXCITE trial is also complicated by the fact that the active and the control groups varied by both the amount and the nature of therapy. This leaves open the question as to how much of the observed benefit in the constraint-induced therapy group was attributable to simply receiving more hours of intervention than that provided to subjects in the customary care group. Also, the neurobiological mechanism of treatment effect remains unclear. For example, studies suggest a key role by the contralesional hemisphere among weaker patients\(^7\) and by the ipsilesional hemisphere among stronger patients.\(^8\) Further studies of treatment mechanism might provide insights useful to broader clinical application of this therapy.

A minor feature of the EXCITE study design is noteworthy and could be important to future restorative trials; those randomized to the usual care arm were offered constraint-induced therapy after the 12-month assessments were completed. These were patients who had measurable disability after stroke, eagerly signed up to be part of a research study, and were then given no active intervention. My experience in restorative trials initiated in the chronic phase of stroke is that recruiting subjects represents a major challenge. This feature of the study design is therefore likely important to addressing the challenging issue of subject recruitment in this setting.

One potential future direction for constraint-induced therapy is to identify subjects most likely to derive benefit by using entry criteria that go beyond the clinical examination methods used in the EXCITE trial. The biological target of this therapy is nervous system function. Several studies suggest that a more direct assessment of brain injury and brain function can improve prediction of response to post-stroke therapy.\(^9\)–\(^14\) When the goal is to improve behavioral outcome by boosting brain function, a baseline measure of brain function might provide useful insights not available from the bedside examination.

The EXCITE trial suggests that multicenter, randomized, controlled phase III studies of restorative therapies can be successfully completed in the chronic phase after stroke. The last decade has seen major advances in the science of human brain repair.\(^15\) The EXCITE trial represents a major step forward in translating these advances to evidence-based medicine.

Disclosures

None.

References


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