Review

Stroke rehabilitation: recent advances and future therapies

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Summary

Despite advances in the acute management of stroke, a large proportion of stroke patients are left with significant impairments. Over the coming decades the prevalence of stroke-related disability is expected to increase worldwide and this will impact greatly on families, healthcare systems and economies. Effective neuro-rehabilitation is a key factor in reducing disability after stroke. In this review, we discuss the effects of stroke, principles of stroke rehabilitative care and predictors of recovery. We also discuss novel therapies in stroke rehabilitation, including non-invasive brain stimulation, robotics and pharmacological augmentation. Many trials are currently underway, which, in time, may impact on future rehabilitative practice.

Introduction

The largest single cause of long-term adult disability in Europe is stroke.¹ Approximately 110 000 people have a stroke each year in UK with over 900 000 alive having survived a stroke.² A substantial proportion of these patients are left with significant residual disability, including hemiparesis in almost one-half of patients.³ Consequently, one of the greatest health effects for patients, their families and the economy results from the long-term physical and cognitive consequences of stroke. By 2030, stroke prevalence is expected to increase by 25% in the USA,⁴ largely due to an ageing population. This change in population demographics will result in increased demands on health services as stroke in older people often result in more severe functional loss.⁵

A large proportion of the focus of stroke research still remains on the acute management of stroke. Significant progress has occurred in recent years including the more widespread use of thrombolytic therapy and the reduction in early post-stroke complications due to the development of organized stroke care in stroke units. As a result, stroke mortality rates have fallen by ~40% in developed countries in recent decades.⁶ However, with a high incidence of residual disability among stroke survivors; neuro-rehabilitation remains one of the cornerstones of post-stroke treatment. It plays a central role in successfully reducing the long-term effects of stroke and achieving optimal functional recovery for community re-integration. Although recovery varies among stroke patients, studies have suggested that functional recovery is predictable in the first days after stroke⁷-⁹ and that long-term survival can be predicted by functional outcome at 6 months.¹⁰

In many countries clear standards of care have been set for better delivery of inpatient and outpatient stroke services. These stroke strategies¹¹,¹² aim
to modernize service provision and consequently, reduce stroke-related death and disability in the future. Internationally, the evidence base for stroke rehabilitation continues to grow. This includes studies using neuroimaging to predict motor recovery as well as studies of novel therapies and techniques, which may influence stroke rehabilitation practice and policy in the future.

The effects of stroke

As most patients with stroke survive the initial period, the greatest long-term effect is development of impairment, disability (limitations of activities) and handicap (reduced participation). After stroke, the long-term effect is determined by the site and size of the initial stroke lesion and by the extent of subsequent recovery. Processes involved in cerebral recovery after stroke are outlined in Table 1. Stroke can result in a large variety of symptoms and signs (Table 2) but the most common and widely recognized impairment caused by stroke is motor impairment, which typically affects the control of movement of the face, arm and leg of one side of the body and affects ~80% of patients to varying degrees. The focus of stroke rehabilitation is largely on the recovery of impaired movement and function in an effort to reduce disability and encourage participation in everyday activities. Many non-motor impairments can also result in significant disability post-stroke. These impairments influence, to varying degrees, the rate and extent of stroke recovery. Frequently encountered examples include cognitive decline (including memory, executive functioning, attention, concentration and alertness), low mood and impaired communication abilities, which can impact upon motivation, interaction with rehabilitation staff and carry-over of learned activities. The presence of sensory impairments, as well as visual and perceptual disorders (including agnosia, apraxia and neglect) may also affect participation in rehabilitation. These deficits commonly affect mobility, reading and driving abilities, which may result in poor quality of life, low mood and social isolation. Multiple studies have assessed novel therapeutic interventions that may improve outcomes in patients with such non-motor deficits, some of which will be discussed later in this review.

It is becoming increasingly important to assess the effects of disease on patient function, independence and quality of life. The impact of stroke on the patient can be measured using performance tests (stroke scales), which may be used to monitor and evaluate interventions. Despite some limitations in their sensitivity, specificity and inter-observer reliability, many stroke scales are useful and are widely used in clinical practice and research trials. The sensitivity and specificity of a test (or scale) describes the accuracy with which the test measures a specific characteristic in a given population. They depend upon characteristics of the population (e.g. age or disease severity) and ‘decision thresholds’ (the definition of an abnormal result) and can vary between different study populations. There is no single scale that can measure all aspects of stroke disability and no scale that can accurately predict all dimensions of stroke recovery. Instead, the choice of a performance scale used after stroke depends largely on rater preference and the type of impairment(s) being measured. Many outcome measures are used inconsistently in clinical trials and for optimal interpretation of results, a good knowledge of the scales used is required. Some of the more

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Processes involved in cerebral recovery after stroke</th>
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<tbody>
<tr>
<td>Recovery process</td>
<td>Definition</td>
</tr>
<tr>
<td>Restitution</td>
<td>Restoring the functionality of damaged neural tissue</td>
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<td>Substitution</td>
<td>Reorganization of partly spared neural pathways to relearn lost functions</td>
</tr>
<tr>
<td>Compensation</td>
<td>Improvement of the disparity between the impaired skills of a patient and the demands of their environment</td>
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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Common impairments following acute stroke</th>
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<tbody>
<tr>
<td>Altered consciousness/attention/alertness</td>
<td></td>
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<tr>
<td>Reduced energy/motivation</td>
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<tr>
<td>Dysphagia</td>
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<td>Dysphonia/dysarthria/dysphasia</td>
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<tr>
<td>Reduced muscle power/tone</td>
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<tr>
<td>Altered sensation/proprioception</td>
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<td>Reduced co-ordination</td>
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<tr>
<td>Change in temperament/personality</td>
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<tr>
<td>Executive dysfunction/cognitive decline</td>
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<td>Perceptual change</td>
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<td>Loss of visual acuity/field deficit</td>
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<tr>
<td>Reduced joint stability/mobility</td>
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<tr>
<td>Balance impairment</td>
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<td>Altered gait pattern</td>
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### Table 3  Some commonly used stroke scales with their strengths and weaknesses

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS</td>
<td>Stroke deficit scale</td>
<td>Focused and brief scale that can be implemented by many types of health care workers. Reliable and valid tool for clinical research. Good intra-observer reliability (ICC 0.93) and inter-rater reliability (ICC 0.95). Good predictive validity for stroke outcome. Sensitive for serial monitoring of patients after stroke.</td>
<td>Detailed assessment of cranial nerves omitted. Does not identify the cause of the deficit. Does not assess global functioning after stroke.</td>
</tr>
<tr>
<td>Barthel Index (BI)</td>
<td>Assessment of activities of daily living</td>
<td>Excellent validity. High intra-observer and inter-observer reliability (Pearson's r scores ranging from 0.89 to 0.99). Brief score (5 min) and easy to administer. Telephone assessments using BI correlate well with observed scores. Can be reliably rated by proxy. Good predictive validity for stroke outcome. Can be used to monitor response to rehabilitation.</td>
<td>Low sensitivity for high level functioning (cognition language vision and emotion not included). ‘Ceiling effect’ meaning patients can achieve high score despite the presence of significant higher level disability. ‘Floor effect’ in the setting of acute stroke when patients are bed bound.</td>
</tr>
<tr>
<td>mRS</td>
<td>Global disability scale</td>
<td>Good overall disability score. Easy and brief (5 min). Good validity and inter-rater reliability. Very responsive to changes in functional status, especially in mild-to-moderate disability (less ceiling effect). Reflects emotional disability well.</td>
<td>Broad summary measure of impairment and activity. Includes minimal assessment criteria (walking) so may lack specificity. Emotion, language, cognition are not directly measured. Source of disability not measured (e.g. hip pain or stroke). Structured interview needed to improve accuracy and inter-rater agreement. Telephone assessments may not correlate well with direct interview scores. Large category sizes means patients may not move much between categories during their admission. Small stroke (mild neurological deficit) can result in severe disability on mRS and vice versa depending on patient's pre-morbid career and lifestyle. ‘Floor effect’ in early stroke as patients are bed bound.</td>
</tr>
<tr>
<td>Frenchay Aphasia</td>
<td>Assessment of speech and language functions</td>
<td>The sensitivity and specificity as a screening tool for aphasia is 87 and 80%, respectively. Reliable and valid score. Widely used by non-specialists. Easy to use. Good test-retest reliability.</td>
<td>Specificity limited by conditions such as hemianopia, cognitive impairment and spatial neglect.</td>
</tr>
<tr>
<td>Screening Test (FAST)</td>
<td>Balance assessment</td>
<td>Simple to administer and brief (10 min). Well-established score for balance assessment in stroke patients. Excellent internal consistency and inter-rater reliability (ICC 0.95) and intra-rater reliability (ICC 0.97). Scores correlate well with falls risk, functional outcome, length of stay and discharge destination. Score sensitive to small changes in balance. Short form (7-item BBS-3 P) psychometrically similar to the original BBS for stroke patients.</td>
<td>Can have ‘floor’ and ‘ceiling’ effects.</td>
</tr>
<tr>
<td>Berg Balance Score (BBS)</td>
<td>Mobility assessment</td>
<td>Brief (5 min) using combined interview and observation. Reliable score. Easy to administer (no training required) and covers a range of activities. Allows valid comparisons to be made between subgroups of patients undergoing rehabilitation after stroke who differ with respect to age, sex or side of lesion. Excellent intra-test reliability and construct validity in stroke patients.</td>
<td>Sensitivity not tested.</td>
</tr>
<tr>
<td>Rivermead Depression</td>
<td>Depression scale</td>
<td>Brief scale. Easy to use in elderly patients and those with cognitive impairment, low motivation and in those with visual or physical problems. Simple yes/no answers.</td>
<td>High false negative in mild depression. Used to screen not diagnose.</td>
</tr>
<tr>
<td>Geriatric Depression</td>
<td>Anxiety scale</td>
<td>Brief score (10 min) to examine perceived health status. Can be self-administered or administered by phone/interview. Used to measure health status of individual patients, monitor and compare disease burden and establish the cost-effectiveness of a treatment. Assesses many domains including emotions, physical and social functioning and mental health.</td>
<td>Possible ‘floor effect’ in very ill patients with poor physical functioning. Does not assess sleep status.</td>
</tr>
<tr>
<td>Medical Outcomes Study</td>
<td>Quality of life measure</td>
<td>Brief score (10 min) to examine perceived health status. Can be self-administered or administered by phone/interview. Used to measure health status of individual patients, monitor and compare disease burden and establish the cost-effectiveness of a treatment. Assesses many domains including emotions, physical and social functioning and mental health.</td>
<td>Specificity may be limited by hemianopia and spatial neglect.</td>
</tr>
<tr>
<td>(MOS) 36-Item</td>
<td></td>
<td>Brief score (10 min) to examine perceived health status. Can be self-administered or administered by phone/interview. Used to measure health status of individual patients, monitor and compare disease burden and establish the cost-effectiveness of a treatment. Assesses many domains including emotions, physical and social functioning and mental health.</td>
<td>Brief score (10 min).</td>
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<tr>
<td>Short-Form Health</td>
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<td>Survey</td>
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<td>Montreal Cognitive</td>
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<tr>
<td>Assessment</td>
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<tr>
<td>(MoCA)</td>
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ICC: interclass correlation coefficient (ICC > 0.8 represents excellent reliability).
commonly used stroke scales, with their strengths and weaknesses, are outlined in Table 3.

In 2001, the World Health Organization developed and endorsed the International Classification of Functioning, Disability and Health (ICF). The purpose of this framework was to provide a universal language, understood by health professionals, researchers, policymakers and patients, to measure biopsychosocial health outcomes relating to chronic disease. The ICF Core Set for stroke has been defined, following formal international consensus, which includes a comprehensive list of components including body functions (such as attention and memory), activities and participation, environmental factors (such as family and support systems) and body structures. This is the largest of the ICF Core Sets developed for the 12 most burdensome chronic conditions, reflecting the complexity of impairment and disability following stroke. Its use may be employed (internationally or at an individual level, in determining functional outcome, care level and service needs as well as length of hospital stay. Due to the length of this classification system, a Brief ICF Core Set for stroke has been defined and can be more readily used in clinical practice (Table 4). This core set represents a brief selection of ICF domains from the whole classification and includes a total of 18 categories (six on body functions, two on body structures, seven on activities and participation, and three on environmental factors). The relatively larger number of categories relating to restrictions in activities and participation reflects the relevance of these limitations to everyday activities in people with stroke.

### Table 4 ICF categories included in the Brief ICF Core Set for stroke

<table>
<thead>
<tr>
<th>ICF component</th>
<th>ICF category title</th>
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<tbody>
<tr>
<td>Body functions</td>
<td>Consciousness functions</td>
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<td></td>
<td>Orientation functions</td>
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<td>Muscle power functions</td>
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<td>Mental functions of language</td>
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<td>Attention functions</td>
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<td></td>
<td>Memory functions</td>
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<tr>
<td>Body structures</td>
<td>Structure of brain</td>
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<tr>
<td></td>
<td>Structure of upper extremity</td>
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<tr>
<td>Activities and participation</td>
<td>Walking</td>
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<tr>
<td></td>
<td>Speaking</td>
</tr>
<tr>
<td></td>
<td>Toileting</td>
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<tr>
<td></td>
<td>Eating</td>
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<tr>
<td></td>
<td>Washing oneself</td>
</tr>
<tr>
<td></td>
<td>Dressing</td>
</tr>
<tr>
<td></td>
<td>Communicating with—receiving—spoken messages</td>
</tr>
<tr>
<td>Environmental factors</td>
<td>Immediate family</td>
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<tr>
<td></td>
<td>Health professionals</td>
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<tr>
<td></td>
<td>Health services, systems and policies</td>
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</tbody>
</table>

### Principles of stroke rehabilitation

Stroke rehabilitation is a dynamic process with the overall aim of reducing stroke-related disability. There is substantial evidence in support of the multidisciplinary team (MDT) for effective delivery of stroke rehabilitation. They provide an organized package of care through a cyclical process involving assessment, goal setting, intervention and reassessment which is typical of stroke rehabilitation. Stroke recovery is heterogeneous and complex and is likely to occur through a combination of spontaneous and learning-dependent processes. In stroke rehabilitation, involvement of the patient and carer in patient-centred interdisciplinary goal setting has been shown to encourage patient motivation and engagement in therapy and is associated with better rehabilitation outcomes. If possible, therapy should be given in the patient’s own environment and should begin as soon as possible after stroke at an increased level of intensity, as tolerated by the patient. Training should be highly functional and targeted to goals that are relevant for the needs of the patient and there is strong evidence to demonstrate that task-oriented and context-oriented training can assist the natural pattern of functional recovery. This is driven mainly by adaptive strategies that compensate for impaired body functions. By creating specific learning situations (as opposed to simple motor exercises) in stroke recovery, neural plasticity is promoted. Many studies of this relatively novel concept of brain repair (neuroplasticity) are underway. The emerging evidence surrounding the endogenous neurorestorative processes (induced in response to focal brain ischaemia) has generated much interest in the study and development of pharmacological and cell-based therapies (discussed below), which can stimulate neurological recovery after stroke.

### Systems of (post-acute) rehabilitative care

There are many different systems of care that provide rehabilitation to patients after stroke, and ongoing stroke service planning should incorporate best-practice evidence reported in trials and reviews of these care systems. It is clear that early inpatient rehabilitation should be organized and delivered by a dedicated stroke MDT. A Cochrane review from 2007 of 31 trials confirmed the benefits of early organized specialist care for patients with stroke and from a population perspective, it is
stroke unit (SU) care that has had the greatest positive impact on disability levels after stroke. One key component of the success of SU care is the presence of a well co-ordinated MDT. Reported benefits of SU care extend to patients of all ages and with varying stroke severity. As a result, many countries are now moving towards a system involving direct admission of patients with acute stroke to a SU. The most appropriate place and duration of post-acute rehabilitation is less clear and must be individualized for each patient. Many important variables impact upon this decision, including patient cognition and safety awareness, the presence of co-morbidities, the degree of motor (and non-motor) impairment and the presence of a supportive carer.

On discharge from the SU, patients with persistent neurological deficits may continue inpatient rehabilitation, either within the acute hospital or in a separate rehabilitation facility, or may receive ongoing rehabilitation as an outpatient, either in a hospital (outpatient or day hospital setting) or in the patient’s home (through community rehabilitation teams). A Cochrane review assessing the effects of MDT-delivered therapy-based rehabilitation services targeted towards stroke patients resident in the community (vs. conventional or no therapy) within 1 year of stroke onset/discharge from hospital reported a reduction in the likelihood of a poor outcome i.e. death or deterioration in ability to perform activities of daily living (both personal and extended) for those patients residing at home. However, this analysis was based on a review of heterogeneous interventions and further research is therefore needed to define the most effective outpatient interventions and the most appropriate level of service delivery.

Early supported discharge (ESD) services, available in the UK and Scandinavian countries for some years, allow early discharge from hospital with a programme of rehabilitation provided by a stroke MDT at home. ESD results in patients with stroke returning home earlier with less need for institutional care and an increased likelihood of regaining independence in daily activities. However, for successful outcomes, these services should be offered to suitable patients only (medically stable with mild-to-moderate disability) and must be delivered by well co-ordinated MDTs who meet regularly. A randomized controlled trial is currently underway to assess the superiority of ESD services over conventional rehabilitative care. This study will also compare outcomes when ESD multi-disciplinary services are delivered through a day unit vs. those delivered in the patient’s own home. The optimal duration and intensity of any rehabilitation programme are difficult to standardize and may be influenced by a number of factors including the level of post-stroke disability, the patient’s pre-morbid medical and functional status, patient motivation and interaction with the MDT and their observed clinical response to therapy. As a result, in clinical practice, the duration and intensity of stroke rehabilitation programmes for patients are largely individualized, regularly reviewed and often updated at regular MDT meetings.

Predicting recovery after stroke

An accurate prognosis of recovery after stroke can help to decide on the type, duration and specific goals of rehabilitation for individual patients. Many factors impact on stroke recovery, including the baseline (pre-stroke) cognitive and functional status of the patient in addition to the non-motor stroke deficits described earlier. Although certain individual impairments (such as dysphagia or incontinence) are associated with severe future disability levels after stroke, the simplest indicator of prognosis is the degree of motor impairment, with worse functional outcome predicted by more severe initial impairment. The most significant predictors of upper limb (UL) recovery have been reported as initial measures of UL impairment (less impairment is associated with better UL recovery; OR = 14.84; CI 9.08–23.25) and upper limb function (greater UL function is associated with better UL recovery; OR = 38.62; CI 8.40–177.53). A strong relationship has been reported between leg motor power and voluntary shoulder and finger movements 7 days after stroke and subsequent recovery of gait and upper limb function, respectively. Nijland’s recent study of 156 stroke patients reported that if finger extension and shoulder abduction could be performed within 72 h of stroke, there was a 98% probability of recovery of some manual dexterity within the subsequent 6 months. If neither movement could be made within 72 h that probability dropped to 25%. Despite some study limitations, these findings, like earlier studies, support the value of early clinical assessment in predicting recovery. However, as both stroke and stroke recovery are largely heterogeneous, accurate prognosis based on clinical examination and motor impairment scores alone may be difficult. Two retrospective studies combining clinical factors with radiographic imaging (computed tomography or magnetic resonance) of ischaemic injury reported good prediction of functional independence, up to 1 year after stroke.

More recently, studies have explored the use of other modalities to predict stroke outcome. Many studies have examined the association between
blood biomarker levels and stroke outcome, but to date reports of group data (including large numbers of potentially useful blood markers) have not established the clinical usefulness of these markers for predicting recovery after ischaemic stroke. Despite the study of many markers of inflammation (such as C-reactive protein, interleukins, tissue necrosis factor, white cell count and adiponectin), thrombosis (including D-dimer, fibrinogen and tissue-type plasminogen activator), neural and glial damage (tau and S100b) and cardiac strain [troponin T and N-terminal pro brain-type natriuretic peptide (BNP)], one recent prospective study found that only interleukin-6 and N-terminal pro BNP were significantly associated with poor outcome.48 However, neither had sufficient predictive power to be of clinical use to predict poor outcome at 3 months after stroke. A further recent prospective study of BNP, including 569 patients, concluded that BNP levels are strongly associated with cardioembolic stroke and functional outcome at 6 months after ischaemic stroke.49 A meta-analysis of studies of blood markers in acute stroke concluded that admission glucose may be a strong marker of poor prognosis following acute thrombolytic therapy,50 but that further studies are warranted before sensitive blood-based tests can be used routinely to predict outcome.

An additional, clinically useful, and predictive measurement after stroke is aortic stiffness,51 the presence of which has been shown to independently predict functional outcome after ischaemic stroke, at 3 and 6 months, respectively. Further studies have employed the use of functional magnetic resonance imaging (fMRI) or non-invasive brain stimulation using transcranial magnetic stimulation (TMS) to predict recovery after stroke. In one small retrospective study, signal intensity along the corticospinal tract was calculated from diffusion-weighted MRI scans taken at multiple early time points after stroke.52 These values were correlated with National Institutes of Health Stroke Scale (NIHSS) motor scores 3 months after stroke and poor recovery was strongly predicted by a decrease in apparent diffusion coefficient signal in the ipsilesional cerebral peduncle at 7 days after stroke. Another study using fMRI assessed cortical activity within days after stroke and reported a correlation between patterns of brain activation and subsequent motor recovery at 3 months.53 fMRI may also be useful in predicting language outcome after stroke.54

Neurophysiological assessments using non-invasive brain stimulation have also been studied for their prognostic accuracy. A small study using repetitive TMS (rTMS) [given as intermittent theta-burst stimulation (iTBS)] in acute ischaemic stroke measured the correlation of its effects with stroke outcome at 6 months.55 Recovery was measured using the modified Rankin Scale (mRS) and was found to be strongly predicted by the effects of iTBS on corticomotor excitability. This correlation is likely related to adaptive cortical plasticity. These findings further support the use of such neuromodulatory techniques in the promotion of recovery after stroke.

### National Institute for Health and Clinical Excellence clinical guideline

The recently published draft guideline on ‘The rehabilitation and support of stroke patients’, developed by the UK National Clinical Guideline Centre and commissioned by the National Institute for Health and Clinical Excellence (NICE), contains a comprehensive list of recommendations on interventions used in stroke rehabilitation.56 The remit for this report, due for final publication in 2012, is to produce a joint clinical and social care guideline on the long-term rehabilitation and support of stroke patients in UK and Northern Ireland. It covers many clinical areas including therapies to improve physical, cognitive and speech functions as well as activities of daily living and vocational rehabilitation. Interventions to address dysphagia and visual field loss are also discussed. It reviews the advised intensity of rehabilitation therapy, support services for patients and carers and ESD services for stroke patients. The guideline development group (GDG) has identified 10 key priorities for implementation (Table 5) which aim to improve patient outcomes and reduce variation in patient care, in addition to promoting patient choice and more efficient use of National Health Service (NHS) resources.

This guideline has received much attention and some criticism from various interested stakeholders. Although it refers to many acute stroke complications, long-term sequelae and social care issues, there are areas where clear guidance is lacking. There is no reference made to driving post-stroke or to the promotion of exercise programmes on discharge after stroke. There is also a lack of guidance on the management of stroke-related pain and spasticity. The report outlines clear future research recommendations regarding the clinical effectiveness and cost-effectiveness of high-intensity therapy [speech and language therapy (SLT) and physical therapy] vs. standard low-intensity therapy. It recommends further research to guide psychosocial interventions which would promote better psychological outcomes for patients, help patients return to work after stroke and allow more effective...
inter-agency communication between governmental and non-governmental bodies in the future. For now, some questions remain unanswered with regard to best (clinical and economic) practice in the rehabilitation of stroke patients. As stroke outcomes are heterogeneous and patients often require focused and individualized care, the strict application of generic guidance to the rehabilitative management of these patients may remain challenging.

Recent developments in motor rehabilitation after stroke

In recent years, there is a greater understanding of the huge potential of the brain for clinically meaningful recovery and adaptation following injury. This can even occur in the chronic phase after stroke, when intensive motor practice can result in functional gains in patients with a perceived plateau in recovery. Biofeedback has been used in rehabilitation for many years and recent reviews have explored the evidence for this therapy in the recovery of motor function after stroke. Electromyogram biofeedback (EMG-BFB) delivers an auditory or visual stimulus to the patient (generated from muscle activation) via electrodes placed on the skin, which can positively influence the patients use of their affected limb. A small number of studies (of EMG-BFB combined with standard physiotherapy) have described some benefits in motor power, functional recovery and gait quality but this effect was diminished when a combination of all available trial evidence was combined. Benefit has also been reported for biofeedback in older patients for balance, gait and transfers although long-term benefits are unclear.

Up to one-third of patients develop spasticity after stroke, more commonly in the upper than the lower limb. Many treatments have been studied, including splinting (volar and dorsal) electrical stimulation, therapeutic ultrasound and botulinum toxin A. While the efficacy of most of these therapies is yet to be determined, botulinum toxin has demonstrated effectiveness in reducing tone in upper and lower limbs post-stroke in multiple studies, but to date this has not resulted in measurable improvements in patient function. However, botulinum toxin is well tolerated and easily administered following suitable training and does remain a very useful therapy for selected stroke patients.

Despite concerns regarding its potential adverse effect on tone and pain, strength training has shown beneficial outcomes on motor recovery after stroke.

Table 5 NICE draft guideline on stroke rehabilitation: key priorities for implementation

<table>
<thead>
<tr>
<th>Function/service</th>
<th>Key recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive functions: visuo-spatial perceptions</td>
<td>Assess the effect of neglect on functional tasks such as mobility dressing, eating and using an electrically powered wheelchair using standardized assessments and behavioural observation.</td>
</tr>
<tr>
<td>Sensory functions: visual field functions</td>
<td>Offer eye movement therapy to people with hemianopia.</td>
</tr>
<tr>
<td>Digestive system functions: swallowing</td>
<td>Offer swallowing therapy to people with dysphagia at least three times per week. Swallowing therapy could include compensatory strategies, exercises and postural advice.</td>
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<tr>
<td>Communication: conversation</td>
<td>Consider providing training in communication skills (slowing down, not interrupting, using communication props, gestures, drawing) to the conversation partners of people with aphasia.</td>
</tr>
<tr>
<td>Mobility: hand and arm: functional electrical stimulation</td>
<td>Do not routinely offer functional electrical stimulation for the hand and arm.</td>
</tr>
<tr>
<td>Mobility: walking: ankle–foot orthosis</td>
<td>Consider offering ankle–foot orthosis to people who have difficulties with swing-phase foot clearance and/or stance-phase control that affect walking.</td>
</tr>
<tr>
<td>Employment</td>
<td>Return to work issues should be identified at onset of stroke, and reviewed regularly and managed actively.</td>
</tr>
<tr>
<td>Service delivery: ESD</td>
<td>Offer ESD to patients who are able to transfer independently or with the assistance of one person. ESD should be considered a specialist stroke service and consist of the same intensity and skill mix available in-hospital without delay in delivery.</td>
</tr>
<tr>
<td>Service delivery: intensity of rehabilitation</td>
<td>Offer at least 45 min of each active rehabilitation therapy for a minimum of 5 days per week to people who have the capacity to participate, and where the individual and the rehabilitation team can identify functional goals that can be achieved.</td>
</tr>
<tr>
<td>Service delivery: intensity of SLT</td>
<td>Provide SLT for people with aphasia both individually and in groups to meet identified needs.</td>
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A recent meta-analysis of 13 trials concluded a positive outcome for grip strength and upper limb function, but not for measures of activities of daily living. Benefits for balance training and mobility are less clear and a phase II randomized trial is currently underway to assess the efficacy of functional strength training on walking and upper limb function after stroke. There is also evidence from multiple studies that increased time spent on exercise (augmented exercise therapy) in the first 6 months post-stroke results in significant improvements in walking ability and speed as well as extended activities of daily living; however, high-quality dose-response trials are needed to quantify optimal intensities. The benefit of augmented exercise therapy for severe arm paresis after stroke has been demonstrated, when combined with impairment-oriented training. Improvements were seen in selective motor control and were related to therapy type rather than time spent in therapy. Meaningful task-specific training (MTST) has also proven effectiveness (statistically and clinically) in motor recovery in the upper and lower limbs and gait-related activities after stroke. With MTST, tasks are practised using a functional approach and can be combined effectively with other strategies, including circuit training and motor imagery, with beneficial outcomes.

Although there is uncertainty around the optimal timing at which to commence mobilization after stroke, there is growing evidence in support of comprehensive gait training in stroke rehabilitation programmes. A review of conventional gait training (without high-technology aids) involving almost 500 participants concluded that there was limited evidence suggesting small benefits for gait speed and 6-min walking time. However, intensive gait training in some studies has demonstrated significant improvements in gait, when commenced early after stroke. Significant improvements in life-role participation have recently been reported when comprehensive gait training was commenced >6 months after stroke. More recently, the use of robotics in gait rehabilitation has gained much interest and is discussed further below.

Constraint-induced movement therapy (CIMT, forced use of the affected limb by restraining the unaffected side) in acute or sub-acute stroke has resulted in an improvement in upper limb mobility and function in small studies, but this benefit did not persist months after stroke. Although this intervention is commonly used in some centres, with most reviews of its use after stroke reporting trends towards positive results, future larger trials are needed to explore the optimal timing and dosing (treatment protocols) of CIMT in stroke rehabilitation.

**Novel therapies for motor rehabilitation after stroke**

**Robotic therapy**

Since the development of the first robotic system for rehabilitation almost 20 years ago, its role in stroke rehabilitation has received much interest. Many joint-specific robotic devices have been developed and some are already in use in centres in the UK and US. They have the potential to deliver functional, reproducible, high-intensity therapy and if shown to be clinically (and cost) effective in large scale studies, they may be more widely used to assist therapists in rehabilitation programmes in future clinical practice. A multi-centre randomized controlled trial of 127 patients with moderate-to-severe upper-limb impairment 6 months or more after stroke compared intensive robot-assisted therapy with intensive comparison therapy and usual care. After 12 weeks of therapy there was no significant improvement in motor function with robot-assisted therapy when compared with intensive comparison therapy or with usual care. However, at 36-weeks further secondary analysis showed an improvement in outcomes with robot-assisted therapy (2.88 points on the Fugl-Meyer score) but only when compared to usual care. A 2012 Cochrane review reported that patients who receive electromechanical and robot-assisted arm training after stroke are more likely to improve their arm motor function and generic activities of daily living. Robot-assisted gait training (RAGT) after stroke has also been studied in a randomized study of 48 patients comparing RAGT in conjunction with conventional gait training vs. conventional gait training alone over 3 months. Only those with greater motor impairment (Motricity Index <29) assigned to RAGT showed significant improvements in the Rivermead Mobility Index (RMI) and walking distance at hospital discharge, when compared with conventional therapy alone. The higher efficacy of the combination therapy on function (Barthel Index) and mobility (RMI) was sustained after 2 years. Similar positive findings have been reported in a recent observational study of intensive robotic and manual gait therapy in sub-acute stroke.

Robot-assisted therapy after stroke has also been studied in combination with other modalities, such as virtual reality or interactive video gaming, with mixed results. By creating an interactive, motivating environment, virtual reality can enhance the effect of repetitive task training. A small study of 18 patients with chronic hemiparesis reported that using a robotic device coupled with virtual reality over 4-weeks improved walking ability in the laboratory.
and the community better than robot training alone. However, a recent Cochrane review looking at the use of virtual reality and interactive video gaming in stroke rehabilitation (without robotic therapy) reported that there was limited evidence of any benefit in improving arm function and activities of daily living function when compared with the same dose of conventional therapy. The authors concluded that there was insufficient evidence to reach conclusions about the effect of virtual reality and interactive video gaming on grip strength or gait speed.

In conclusion, although there is evidence to suggest a potential future role for robotic-assisted therapy (with or without virtual reality) in stroke rehabilitation, there is much left to explore in this area. A recent economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke reported uncertainty about the cost-effectiveness of robotic-assisted rehabilitation compared with traditional rehabilitation. Future large studies should determine the overall cost-benefit ratio and clinical effectiveness of robotic therapies in stroke rehabilitation.

Non-invasive brain stimulation techniques

Several trials have explored the use of non-invasive cortical stimulation techniques in the promotion of neuroplasticity and recovery after stroke. The main techniques employed are rTMS and transcranial direct current stimulation (tDCS). In rTMS, an electric current is induced in the underlying cortex by a magnetic field and is used to increase (using high frequencies) ipsilesional cortical excitability and/or decrease (using low frequencies) excitability of the contralesional side. In tDCS, skin electrodes deliver weak currents that can have either an excitatory or an inhibitory effect on the underlying cortex. A small non-randomized study of rTMS in conjunction with intensive occupational therapy for upper limb hemiparesis reported an improvement in upper limb function many months after stroke with no adverse effects. The same investigators reported positive results with high frequency (vs. low frequency) rTMS when used in the early phase after stroke. The use of tDCS with simultaneous occupational therapy was studied in a sham-controlled randomized trial of 20 chronic stroke patients and results showed a significant improvement in motor function that outlasted the study period. However, when combined with RAGT, tDCS was found to have no additional benefit in patients with chronic stroke. These techniques appear to be safe, well tolerated and are potentially useful future therapeutic options in the rehabilitation of stroke patients. However, pending further large randomized studies, they are not yet recommended for use in clinical practice.

Stem cell therapy

Stem cell therapy represents a new therapeutic approach for the promotion of recovery after stroke and plans to advance research in this area are underway. With cell therapy, there is enormous potential for repair of the infarcted area of brain through enhancing neuroprotective and repair mechanisms. Cell therapy promotes re-vascularization and reduces cerebral inflammation after stroke and phase II clinical trials of intravenous transplantation of autologous bone-marrow stem cells have reported safety and tolerability in stroke patients. Pending the results of future larger trials (demonstrating efficacy on clinical endpoints), including the PISCES study currently underway in Glasgow, we may see the application of this therapy to future clinical practice in selected patients.

Other novel therapies

Several brain neurotransmitter systems have been linked to the process of motor learning and this has led to the study of pharmacological augmentation in stroke recovery. A small double-blind placebo-controlled study of noradrenergic enhancement using reboxetine resulted in significantly increased motor performance in stroke patients with hand paresis. A randomized placebo-controlled study of 118 hemiparetic or hemiplegic stroke patients reported enhanced motor recovery and independence after 3 months with the early prescription of fluoxetine (5–10 days after stroke) in conjunction with standard physiotherapy. The short-term use of amphetamine paired with focused activity in rat models has been shown to induce long-term improvement in forelimb motor function after stroke, as a result of axonal sprouting from contralesional neurons. Studies of dopamine in stroke recovery have also demonstrated positive results, including those assessing language outcome. Other studies looking at glutamate and acetylcholine have reported promising results, suggesting that the modulation of brain plasticity using pharmacological interventions is a potential future modality in assisting recovery after stroke.

Until recent years the role of mirror therapy (MT) in stroke rehabilitation programmes has been assessed in very small studies with unclear outcomes. In MT, the patient is instructed to watch the unaffected limb in the mirror (placed at 90° to the midline of the patient) while performing exercises. The patient receives the visual impression that the affected limb is fully functioning. A recent
randomized controlled trial \((n = 40)\) of sub-acute stroke patients in the Netherlands reported the benefit of 1 h of MT daily in addition to standard rehabilitation.\(^{101}\) Benefits of MT are seen in relation to upper extremity motor recovery and hand-related functioning and are found to persist at 6-month follow-up.\(^{101,102}\) Future research is needed to determine the optimum practice intensity and duration.

Studies of electrical stimulation delivered to the peripheral neuromuscular system have not delivered positive results. A Cochrane review\(^{103}\) (2006) concluded that there was insufficient robust data to inform its clinical use for neuromuscular re-training after stroke. Questions remain unanswered regarding the type, dose and timing of these peripheral stimulation techniques.

**Recent advances in the management of non-motor impairments after stroke**

**Cognitive rehabilitation**

Various therapeutic interventions to target non-motor impairments after stroke have been studied in recent years. New dementia is seen in 10% of patients after a first stroke and in more than one-third of patients after recurrent stroke.\(^{104}\) Reviews of a limited number of studies report lack of evidence to support the effectiveness of memory rehabilitation (including mnemonic strategies with or without imagery) on functional outcomes,\(^{105}\) but there is some indication that cognitive training can improve alertness and sustained attention.\(^{106}\) However, this did not translate into improved functional outcome for patients. Further reviews of cognitive interventions\(^{107}\) and of the effectiveness of occupational therapy\(^{108}\) in improving cognitive impairment and function post-stroke were inconclusive, owing to an inadequate number of high-quality trials. More recently the effect of stimulant medications, including levodopa and methylphenidate, on cognition (and mood) post-stroke has been studied\(^{109}\) and early cognitive enhancement (at 2 weeks) was reported, but this effect was not sustained. Escitalopram\(^{110}\) has also shown beneficial effects in global cognitive functioning (specifically in verbal and visual memory functions), independent of its effect on depression.

**Interventions for sensory, visuospatial and perceptual deficits**

Somatosensory impairment (of various modalities) is common following stroke and is associated with stroke severity.\(^{111}\) Studies have focused on sensory interventions for the upper limb post-stroke, including thermal intervention\(^{112}\) and electrical stimulation,\(^{113}\) but overall there is limited evidence in support of the effectiveness of most of these therapies in improving upper limb sensation and function.\(^{114}\) Visual field defects are estimated to affect 20–57% of people who have a stroke\(^{115}\) and despite many studies assessing the effectiveness of various potentially useful interventions, to date there is limited evidence in support of the use of compensatory scanning, visual restitution training (restitutive intervention) or prisms (substitutive intervention) for patients after stroke.\(^{115}\) Rehabilitation for many perceptual deficits post-stroke includes functional training, sensory stimulation, strategy training and task repetition.\(^{116}\) A review of randomized controlled trials assessing these non-pharmacological interventions for perceptual disorders related to stroke (and other brain injury) reported uncertain benefit although patients with neglect, inattention and apraxia were excluded.\(^{116}\) Several neglect-specific therapeutic approaches have also been studied, including structured therapy sessions, computerized therapy and prescription of aids, but their use has not been shown to impact long term on disability or independence.\(^{117}\) Further high-quality randomized controlled trials are needed to investigate the usefulness of cognitive rehabilitation for perceptual deficits, including spatial neglect, on short- and long-term outcomes after stroke. More recently, pharmacological therapies, such as rivastigmine,\(^{118}\) have been explored for their effectiveness in promoting functional recovery when added to conventional treatment in patients with stroke-related spatial neglect. Add-on rivastigmine therapy may improve and accelerate recovery of some specific impairment tests although this beneficial effect may becomes less statistically significant over time.

**Fatigue and mood disorders**

Fatigue after stroke is a common and distressing symptom\(^{119}\) and may impact negatively on rehabilitation potential. As fatigue after stroke may have several causative factors, there are a number of potential interventions, including pharmacological (stimulants, antidepressants), psychological (counselling, cognitive behaviour therapy) or physical treatment (graded exercise) which can be used.\(^{120}\) Despite the high prevalence of this condition, to date there are no large studies providing strong evidence to guide the management of these patients.\(^{119,120}\) Mood disorders including anxiety\(^{121}\) and depression\(^{122}\) are also commonly experienced...
by patients after stroke and reviews of studies assessing interventions for these conditions have found that robust evidence is lacking. Pharmacological therapy has shown benefit in patients with post-stroke anxiety symptoms, but only if there is co-morbid depression. Small effects of psychotherapy on improving mood and preventing depression, and pharmacotherapy (without psychotherapy) on treating depressive symptoms after stroke have been identified. However before the routine use of these treatments can be recommended, more evidence is required.

**Aphasia rehabilitation**

Aphasia is a devastating consequence of stroke and affects approximately one-third of patients, where language reception, expression or both may be affected to varying degrees. Significant improvements can be achieved with SLT, particularly with intensive delivery. These improvements in language may continue years after stroke onset. In recent years, newer approaches to therapy have been explored with positive results. Constraint-induced aphasia therapy (CIAT) is an intensive form of SLT where patients are not permitted to use compensatory strategies (e.g. drawing or writing) to communicate. A number of small studies have shown improvements in functional communication following CIAT in the acute and chronic stages of stroke, with positive feedback from patients. CIAT has also been explored in conjunction with pharmacological therapy using memantine (an NMDA receptor antagonist which may counteract glutamate-induced neurotoxicity seen in animal models of ischaemic stroke). A placebo-controlled randomized trial showed that language improvements were most pronounced in the memantine (combined with CIAT) group and this improvement persisted on long-term follow-up.

With improved knowledge of the intra- and inter-hemispheric interactions involved in language recovery after stroke, non-invasive brain stimulation has been employed to stimulate lesional or contralateral regions of the brain. Studies of both tDCS and rTMS have resulted in language improvements, including receptive and expressive modalities, and may offer future supplementary approaches to conventional therapy. As well as its use in the prediction of language recovery, fMRI can also be used to assess recovery in patients with post-stroke aphasia. The more widespread use of neuroimaging in future research studies will help to build on our understanding of language recovery in stroke patients.

**Conclusion**

Stroke-related disability can impact greatly on a patient’s quality of life and ability to live independently and effective neuro-rehabilitation is central in the recovery of these patients. The recently published draft guideline on rehabilitation by NICE has allowed focus on this often neglected area of stroke care. Although the MDT is a key factor in implementing effective patient-centred therapy, there is a constant need to explore new therapies to complement or enhance current practice. Several trials of novel therapies are underway which offer great promise for future rehabilitative practice. However, questions remain regarding the long-term safety, clinical effect and cost–benefit of many of these interventions on functional recovery. With further research their potential usefulness in the real world will emerge over time. These new techniques offer great hope for the future of stroke rehabilitation.

**Conflict of interest:** None declared.

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