4. Hemiplegic Upper Extremity Rehabilitation

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4.1 Recovery for Upper Extremity

4.1.1 Brunnstrom Stages of Motor Recovery

The Seven Brunnstrom Stages of Motor Recovery (see table below for more details)

1. Flaccid paralysis. No reflexes.
2. Some spastic tone. No voluntary movement. Synergies elicited through facilitation.
3. Spasticity is marked. Synergistic movements may be elicited voluntarily.
4. Spasticity decreases. Synergistic movements predominate.
5. Spasticity wanes. Can move out of synergies although synergies still present.
6. Coordination and movement patterns near normal. Trouble with more rapid complex movements.
7. Normal.

Stages of Motor Recovery of the Chedoke McMaster Stroke Impairment Inventory (Gowland et al. 1993)

Stages	Characteristics
1	**Flaccid paralysis is present.** Phasic stretch reflexes are absent or hypoactive. Active movement cannot be elicited reflexively with a facilitatory stimulus or volitionally.
2	**Spasticity is present** and is felt as a resistance to passive movement. **No voluntary movement** is present but a **facilitatory stimulus will elicit the limb synergies reflexively**. These limb synergies consist of stereotypical flexor and extensor movements.
3	**Spasticity is marked**. The **synergistic movements can be elicited voluntarily** but are not obligatory.
4	**Spasticity decreases.** Synergy patterns can be reversed if movement takes place in the weaker synergy first. Movement combining antagonistic synergies can be performed when the prime movers are the strong components of the synergy.
5	**Spasticity wanes** but is evident with rapid movement and at the extremes of range. Synergy patterns can be revised even if the movement takes place in the strongest synergy first. Movements that utilize the weak components of both synergies acting as prime movers can be performed.
6	**Coordination and patterns of movement can be near normal. Spasticity** as demonstrated by resistance to passive movement is **no longer present**. Abnormal patterns of movement with faulty timing emerge when rapid or complex actions are requested.
7	**Normal.** A “normal” variety of rapid, age appropriate complex movement patterns are possible with normal timing, coordination, strength and endurance. There is no evidence of functional impairment compared with the normal side. There is a “normal” sensory-perceptual motor system.

4.1.2 Typical Recovery and Predictors

Nakayama et al. (1994) reported that for stroke patients with severe arm paresis with little or no active movement at the time of hospital admission:

- 14% complete motor recovery.
- 30% partial recovery.

Kwakkel et al. (2003) reported that at 6 months, 11.6% of patients had achieved complete functional recovery, while 38% had some dexterity function.

Potential predictors of upper extremity recovery include active finger extension and shoulder abduction:

1) Active finger extension was found to be a strong predictor of short, medium and long term post-stroke recovery (Smania et al. 2007).
2) Minimal shoulder abduction and upper motor control of the paretic limb upon admission to rehabilitation had a reasonably good chance of regaining some hand capacity whereas patients without proximal arm control had a poor prognosis for regaining hand capacity (Houwink et al. 2013).
3) The EPOS study demonstrated that patients with some finger extension and shoulder abduction on Day 2 after stroke onset had a 98% probability of achieving some degree of dexterity at 6 months; this was in contrast to only 25% in those who did not show similar voluntary motor control.
4) In addition, 60% of patients with finger extension within 72 hours had regained full recovery of upper limb function according to ARAT score at 6 months. (Nijland et al. 2010).

4.1.3 Recovery of Upper Extremity: Fixed Proportion

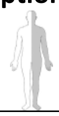
Within 6 months post stroke upper limb impairment recovers by fixed proportion. Fixed proportion notes that 70% of each patient's maximal possible motor improvement occurs regardless of the initial impairment (i.e. Fugl-Meyer score) but only for those with an intact corticospinal (motor) tract function (Prabhakaran et al. 2008). Irreversible structural damage to the corticospinal tract severely limits recovery of the upper limb (Stinear et al. 2007; 2012). This fixed proportion of motor recovery of impairment appears to be unaffected by rehabilitation therapies. 3D kinematics in subacute and chronic stroke survivors have shown **motor recovery associated with rehabilitation is driven more by adaptive or compensatory learning strategies.** Most clinical tests designed to evaluate upper extremity motor recovery (i.e Action Research Arm Test (see below)) only assess function or a patient's ability to accomplish a task.

4.2 Evaluation of Upper Extremity

There is a wide range of upper extremity rehabilitation outcomes measures which have been utilized. They can be categorized into broad categories listed below:

4.2.1 Upper Extremity Asessement and Outcome Measures

Category	Rationale	Individual Assessment Tools
Motor Function	Assess gross motor movements and a series of general impairment measures when using the upper extremities	• Action Research Arm Test (ARAT) • Disabilities of the Arm, Shoulder and Hand (QuickDASH) • Fugl-Meyer Assessment (FMA) • Finger Oscillation Test (FOT) • Jebsen-Taylor Hand Function Test (JTHFT) • Manual Function Test (MFT) • Motor Club Assessment (MCA) • Motor Evaluation Scale for UE in Stroke Patients (MES-UE) • Motor Status Scale (MSS) • Rancho Los Amigos Functional Test for the Hemiparetic UE • Rivermead Mobility Assessment (RMA) • Sodring Motor Evaluation Scale (SMES) • Stroke Impairment Assessment Set (SIAS) • Stroke Rehabilitation Assessment of Movement (STREAM) • Sollerman Hand Function Test (SHFT) • Stroke Upper Limb Capacity Scale (SULCS) • University of Maryland Arm Questionnaire (UMAQ) • Upper Extremity Function Test (UEFT) • Wolf Motor Function Test (WMFT)
Global Stroke Severity	Assess the severity of stroke through global assessment of deficits post stroke.	• Brunnstrom Recovery Stages (BRS) • Modified Rankin Scale (MRS) • National Institutes of Health Stroke Scale (NIHSS) • Neurological Function Deficit Scale (NFDS)
Muscle Strength	Assess muscle power and strength during movement and tasks.	• Hand Grip Strength • Isokinetic Peak Torque (IPT) • Manual Muscle Strength Test (MMST) • Medical Research Council Scale (MRCS)
Dexterity	Assess fine motor and manual skills through a variety of tasks, particularly with the use of the hand.	• Box and Block Test (BBT) • Finger to Nose Test (FNT) • Grating Orientation Task (GOT) • Grooved Pegboard Test (GPT) • Minnesota Manual Dexterity Test (MMDT) • Nine Hole Peg Test (9HPT)

		• Purdue Pegboard Test (PPT)
Range of Motion 	Assess ability to freely move upper extremity at joints both passively and actively	• Active Range of Motion (AROM) • Maximal Elbow Extension Angle During Reach (MEEAR) • Passive Range of Motion (PROM)
Proprio-ception 	Assess bodily sensory awareness and location of limbs.	• Joint Position Sense Test (JPST) • Kinesthetic Visual Imagery Questionnaire (KVIQ) • Revised Nottingham Sensory Assessment (RNSA)
Activities of Daily Living 	Assess performance and level of independence in various everyday tasks.	• Arm Motor Ability Test (AMAT) • Assessment of Motor and Process Skills (AMPS) • Barthel Index (BI) • ABILHAND • Canadian Occupational Performance Measure (COPM) • Chedoke Arm and Hand Activity Inventory (CAHAI) • Duruoz Hand Index (DHI) • Frenchay Arm Test (FAT) • Frenchay Activities Index (FAI) • Functional Activity Scale (FAS) • Functional Independence Measure (FIM) • Goal Attainment Scale (GAS) • Modified Barthel Index (mBI) • Motor Activity Log (MAL) • Motor Assessment Scale (MAS) • Nottingham Extended ADLs (NEADL) • Nottingham Stroke Dressing Assessment (NSDA) • Stroke Impact Scale (SIS) • STAIS Stroke Questionnaire (SSQ) • Upper Limb Self-Efficacy Test (UPSET)
Spasticity 		• Ashworth Scale (AS) • Bhakta Finger Flexion Scale (BFFS) • Disability Assessment Scale (DAS) • Modified Ashworth Scale (mAS) • Resistance to Passive Movement Scale (REPAS) • Spasm Frequency Scale (SFS)

4.2.2 Motor Function

Action Research Arm Test (ARAT)

The ARAT is an arm-specific measure of activity limitation that assesses a patient's ability to handle objects differing in size, weight and shape. The test evaluates 19 tests of arm motor function, both distally and proximally. Each test is given an ordinal score of 0, 1, 2, or 3, with higher values indicating better arm motor status. The total ARAT score is the sum of the 19 tests, and thus the maximum score is 57. This measure has been shown to have good test-retest reliability and internal validity when used to assess motor function in chronic stroke patients (Ward et al. 2019; Nomikos et al. 2018).

Action Research Arm Test (ARAT)

Questions	Answer
What does it measure?	Upper extremity function and dexterity (Hsueh et al. 2002).
What is the scale?	The ARAT consists of 19 items designed to assess four areas of function; grasp, grip, pinch, and gross movement. Each question is scored on an ordinal scale ranging from 0 (no movement) to 3 (normal performance of the task).
What are the key scores?	Scores range from 0 – 57, with lower scores indicating greater levels of impairment.
What are its strengths?	Relatively short and simple measure of upper limb function. No formal training is required. Testing can be completed quickly on higher functioning patients.
What are its limitations?	Good concurrent validity, although other forms of validity have not been evaluated within the stroke population. Significant floor and ceiling effects have been identified (Van der Lee et al. 2002). Unidimensional measure; hence, subset analyses should not be used independently but rather summated to provide a single overall score representing upper extremity function (Koh et al. 2006).

Fugl-Meyer Assessment (FMA)

FMA is an impairment measure used to assess locomotor function and control, including balance, sensation, and joint pain in patients poststroke. It consists of 155 items, with each item rated on a three-point ordinal scale. The maximum motor performance score is 66 points for the upper extremity, 34 points for the lower extremity, 14 points for balance, 24 points for sensation, and 44 points each for passive joint motion and joint pain, for a maximum of 266 points that can be attained. The measure is shown to have good reliability and construct validity (Nilsson et al. 2001; Sanford et al. 1993).

Fugl-Meyer Assessment for Upper Extremity (FMA-UE)

FMA-UE is a measure used to assess motor function of the upper extremity in post-stroke patients. It consists of four categories (Shoulder/Elbow/Forearm, Wrist, Hand/Finger, and Coordination) and includes 23 different movements which evaluate 33 items. The items are scored on a 3-point rating scale: 0 = unable to perform, 1 = partial ability to perform and 2 = near normal ability to perform. The assessment has a maximum score of 66, and its reliability and validity have been well demonstrated (Okuyama et al. 2018; Villán-Villán et al. 2018).

Wolf Motor Function Test (WMFT)

The WMFT is a measure that quantifies upper extremity motor ability in stroke survivors. The measure consists of 17 tasks (e.g. lifting arm up using only shoulder abduction, picking up a pencil, picking up a paperclip). These tasks are then subdivided into 3 areas: functional tasks, measures of strength, and quality of movement. Patients are scored on a 6-point scale (1=cannot complete task, 6=completes task as well as the unaffected side. This measure has been shown to have good reliability and validity (Wolf et al. 2005; Wolf et al. 2001).

4.2.3 Dexterity

Box and Block Test (BBT)
BBT is a measure of gross unilateral manual dexterity in stroke survivors. This measure consists of 1 functional task. This task involves a patient moving as many wooden blocks as possible from one end of a partitioned box to the other, in a span of 60 seconds. Patients are scored based on the number of blocks they transfer (the higher the blocks transferred, the better the outcome). The measure has been shown to have good reliability and validity. (Higgins et al. 2005; Platz et al. 2005).

Box and Block Test

Questions	Answer
What does it measure?	Performance based measure of gross manual dexterity.
What is the scale?	150 small wooden blocks are placed in one of two equal compartments of a partitioned rectangular box. Respondents are seated and instructed to move as many blocks as possible, one at a time, from one compartment to the other in 60 seconds.
What are the key scores?	The BBT is scored by counting the number of blocks that are carried over the partition from one compartment to the other during the one-minute trial period.
What are its strengths?	Quick and easy to administer. The simplicity of the performance task and the seated administration position may make the test more accessible to a wider range of individuals. Established age and gender-stratified norms increase the interpretability to the results. Results may have utility as a prognostic indicator of physical health.
What are its limitations?	Noisy to administer and could be distracting to other patients.

Nine Hole Peg Test (9HPT)
The 9HPT is a measure of overall manual dexterity in stroke survivors. The measure consists of 1 functional task. Patients are asked to take 9 pegs out of a container and insert them into the pegboard. Once all 9 pegs are inserted they are then taken out of the pegs as quickly as possible and placed back in the container. Patients are scored on how quickly they can insert and take out the pins, so the faster the time, the better the outcome. This measure has been shown to have good reliability and concurrent validity (da Silva et al. 2017).

Purdue Pegboard Test (PPT)
The PPT is a measure of precision grip strength and speed in stroke survivors. The measure consists of 1 functional task. Patients are asked to place as many pins as they can onto the pegboard in 30 secs, and then repeat this exercise for their other hand. Patients are scored on the number of pins they can place onto the pegboard in the given amount of time. This measure has been shown to have good reliability and validity (Gonzalez et al. 2017, Wittich & Nadon, 2017).

4.2.4 ADLs

Barthel Index (BI)

The Barthel Index is a measure of how well a stroke survivor can function independently and how well they can perform activities of daily living (ADL). The measure consists of a 10-item scale (e.g. feeding, grooming, dressing, bowel control). Each task is then measured on a 3-point functional ability scale/level of independence scale. This measure has been shown to have good reliability and validity in its full form (Gonzalez et al. 2018; Park et al. 2018).

Bimanual Hand Ability (ABILHAND)
The ABILHAND is a measure of how well a stroke survivor utilizes their hands to complete various manual tasks. The measure consists of 23 common bimanual activities (e.g. hammering a nail, wrapping gifts, cutting meat, buttoning a shirt, opening mail). Each task is then scored on a 3-point scale (0=impossible, 1=difficult, 2=easy) assessing overall ability. This measure has been shown to have good reliability and validity in its full form (Ashford et al. 2008; Penta et al. 2001).

Canadian Occupational Performance Measure (COPM)
The COPM is a measure of how well a stroke survivor engages in self-care, productivity and leisure. The measure consists of 25 functional items/tasks (e.g. bathing, ability to work at least part-time, activities involved in). Each task is then scored on a single 10-point rating scale primarily measuring proficiency in each of the 3 sub-categories (self-care, productivity and leisure). This measure has been shown to have good reliability and validity in its full form. (Yang et al. 2017).

Chedoke Arm and Hand Activity Inventory (CAHAI)
The CAHAI is an upper limb measure that uses a 13-point quantitative scale in order to assess recovery of the arm and hand in performing activities of daily living after a stroke. It is a performance test using 13 bimanually performed real-life items, designed to encourage bilateral upper limb use. Scores represent the patient's relative ability to independently perform stabilisation or manipulation in ADL with the impaired upper limb. The measure is shown to have good test-retest and interrater reliability, as well as good construct and concurrent validity (Ward et al. 2019; Schuster-Amft et al. 2018; Barreca et al. 2004).

Functional Independence Measure (FIM)
The FIM is a measure of burden of care and as such is a reverse marker of functional independence, which is defined as the ability to carry out everyday tasks safely and without assistance. The measure consists of 6 areas of function (sphincter control, self-care, mobility, locomotion, communication, and social cognition). The items in these areas consist of: bladder management, grooming, moving in and out of a bathtub, walking speed, comprehension, and social interaction. Each task is then scored on a 7-point Linkert scale (1=total assistance). This measure has been shown to have excellent reliability and concurrent validity in its full form (Granger et al. 1998, Linacre et al. 1994; Granger et al. 1993).

Modified Barthel Index (MBI)
The MBI is a measure of how well a stroke survivor can function independently and how well they can perform activities of daily living (ADL). The measure consists of a 10 item scale (e.g. feeding, grooming, dressing, bowel control). Each task is then measured on a 5-point functional ability scale/level of independence scale. This measure has been shown to have good reliability and validity in its full form. **Note:** The only difference between the modified Barthel Index and the original Barthel Index is that the modified Barthel Index has a 5-point rating scale while the original Barthel Index (MacIsaac et al. 2017; Ohura et al. 2017).

Motor Activity Log (MAL)

The MAL is a patient-reported measure of the use and quality of movement of the impaired arm. The measure consists of 30 functional tasks (e.g. handling utensils, buttoning a shirt, combing hair). Each task is then measured on a 6-point scale (0=complete inability to use affected arm). This measure has been shown to have good reliability and validity (Chuang et al. 2017).

Motor Assessment Scale (MAS)
The MAS is a performance-based measure that assesses everyday motor function. The measure consists of 8 motor-function based tasks (e.g. supine lying, balanced sitting, walking). Each task is then measured on a 7-point scale (0=suboptimal motor performance, 6=optimal motor performance). This measure has been shown to have good reliability and concurrent validity (Simondson et al. 2003).

Stroke Impact Questionnaire (SIS)
The SIS is a patient-reported measure of multi-dimensional stroke outcomes. The measure consists of 59 functional tasks (e.g. dynamometer, reach and grab, walking, reading out loud, rating emotional regulation, word recall, number of tasks completed, and shoe tying). These tasks are then divided into 8 distinct subscales which include: strength, hand function, mobility, communication, emotion, memory, participation and activities of daily living (ADL). Each task is measured on a 5-point scale (1=an inability to complete the task, 5=not difficult at all). The measure has been shown to have good reliability and validity (Mulder et al. 2016; Richardson et al. 2016).

4.2.5 Spasticity

Ashworth Scale (AS)
The Ashworth Scale is a measure of resistance to passive movement in stroke survivors. The measure contains 15 functional movements which are done with the guidance of a trained clinician. These movements are evenly divided into 2 sections: upper extremity and lower extremity. Each movement is then rated on a 5-point scale (0=no increase in muscle tone, 1=barely discernible increase in muscle tone, 2=moderate increase in muscle tone 3=profound increase in muscle tone (movement of affected limb is difficult) 4=complete limb flexion/rigidity (nearly impossible to move affected limb)). This measure has been shown to have good reliability and validity (Merholz et al. 2005; Watkins et al. 2002).

Modified Ashworth Scale (mAS)
The mAS is a measure of muscle spasticity for stroke survivors. The measure contains 20 functional movements which are done with the guidance of a trained clinician. These movements are evenly divided into 2 sections: upper extremity and lower extremity. Each movement is then rated on a 6-point scale (0=no increase in muscle tone, 1=barely discernible increase in muscle tone 1+=slight increase in muscle tone, 2=moderate increase in muscle tone 3=profound increase in muscle tone (movement of affected limb is difficult) 4=complete limb flexion/rigidity (nearly impossible to move affected limb)). This measure has been shown to have good reliability and validity (Mehrholz et al. 2005; Blackburn et al. 2002).

4.2.6 Stroke Severity

Brunnstrom Recovery Stages (BRS)
BRS is a measure of stroke severity and muscle spasticity in stroke survivors. The measure contains 35 functional movements which are done with the guidance of a clinician (e.g. should abduction, shoulder adduction, leg flexion/extension). These movements are evenly divided into 2 sections: upper extremity and lower extremity. Each movement is then rated on a 6-point scale (1=Flaccidity is present, and no

movements of the limbs can be initiated, 2=Movement occurs haltingly and spasticity begins to develop, 3=Movement is almost impossible and spasticity is severe, 4=Movement starts to be regained and spasticity begins to decline, 5=More difficult movement combinations are possible as spasticity declines further. 6=Spasticity disappears, and individual joint movements become possible). This measure has been shown to have good reliability and concurrent validity (Naghdi et al. 2010; Safaz et al. 2009).

Modified Rankin Scale (mRS)

The Modified Rankin Scale is a measure of functional independence for stroke survivors. The measure contains 1 item. This item is an interview that lasts approximately 30-45 minutes and is done by a trained clinician. The clinician asks the patient questions about their overall health, their ease in carrying out ADLs (cooking, eating, dressing) and other factors about their life. At the end of the interview the patient is assessed on a 6-point scale (0=bedridden, needs assistance with basic ADLs, 5=functioning at the same level as prior to stroke). This measure has been shown to have good reliability and validity (Quinn et al. 2009; Wilson et al. 2002).

National Institutes of Health Stroke Scale (NIHSS)

The NIHSS is a measure of somatosensory function in stroke survivors during the acute phase of stroke. This measure contains 11 items and 2 of the 11 items are passive range of motion (PROM) assessments delivered by a clinician to the upper and lower extremity of the patient. The other 9 items are visual exams conducted by the clinician (e.g. gaze, facial palsy dysarthria, level of consciousness). Each item is then scored on a 3-point scale (0=normal, 2=minimal function/awareness). This measure has been shown to have good reliability and validity (Heldner et al. 2013; Weimar et al. 2004).

4.2.7 Muscle Strength

Hand Grip Strength (HGS)

Hand Grip Strength is a measure of the overall hand grip strength in stroke survivors. The measure consists of 1 functional task. This task involves a patient squeezing the dynamometer and then receiving a hand grip strength measurement. This action is then repeated 1 additional time and the best of the two readings is used as a score. This measure has been shown to have good test/retest reliability and validity (Bertrand et al. 2015).

Chedoke-McMaster Stroke Assessment Scale

Questions	Answer
What does it measure?	The Chedoke-McMaster Stroke Assessment Scale (CMSA) is a 2-part assessment consisting of a physical impairment inventory and a disability inventory. The impairment inventory is intended to classify patients according to stage of motor recovery while the disability inventory assesses change in physical function.
What is the scale?	The **scale's impairment inventory has 6 dimensions**; shoulder pain, postural control, arm movements, hand movements, leg movements, and foot movements. **Each dimension** (with the exception of 'shoulder pain') is rated on a **7- point scale** corresponding to Brunnstrom's 7 stages of motor recovery. The **disability inventory consists of a gross motor index (10 items) and a walking index (5 items)**. With the exception of a 2-minute walking test (which is scored as either 0 or 2), items are scored according to the **same 7-point scale** where 1 represents total assistance and 7 represents total independence.

What are the key scores?	The impairment inventory yields a total score out of 42 while the disability inventory yields a total score out of 100 (with 70 points from the gross motor index and 30 points from the walking index).
What are its strengths?	The use of Brunnstrom staging and FIM scoring increases the interpretability of the CMSA and may facilitate comparisons across groups of stroke patients. The CMSA is relatively comprehensive and has been well studied for reliability and validity.
What are its limitations?	Taking approximately 1 hour to complete, the length and complexity of the CMSA may make the scale less useful in clinical practice. As **primarily a measure of motor impairment**, the CMSA should really be accompanied by a measure of functional disability such as the BI or the FIM.

CMSA is based on the Brunnstrom stages of motor recovery (see above).

4.3 Rehabilitation Management of Upper Extremity

Enhancing Stroke Recovery

There are several ways to enhance motor recovery through rehabilitation:

Stimulating the Ipsilateral Brain Cortex

Activities

- Repetitive Practice
- Task-Specific Activities
- Constraint-Induced Movement Therapy
- Virtual Reality
- Telerehabilitation

Mental Stimulation

- Action Observation
- Mirror Therapy
- Mental Therapy

Brain Stimulation

- Direct Cortical Stimulation
- Repetitive Transcranial Magnetic Stimulation (rTMS) (10 Hz – high frequency)
- Transcranial Direct Current Stimulation (tDCS) (anode)

Pharmacological Stimulation

- Pharmacotherapy

Inhibiting the Contralateral Brain Cortex

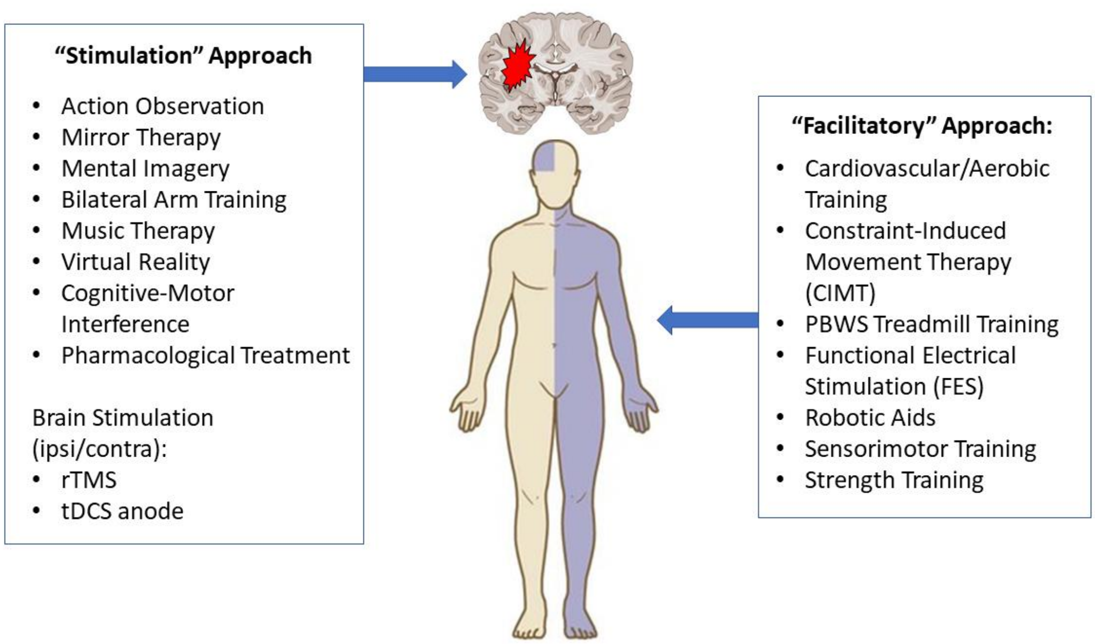
- Repetitive Transcranial Magnetic Stimulation (rTMS) (1 Hz – low frequency)
- Transcranial Direct Current Stimulation (tDCS) (cathode)

Enhancing or Facilitating Recovery of the Hemiplegic Limb

- Repetitive Practice
- Strength Training
- Constraint Induced Movement Therapy
- Functional Electrical Stimulation (FES)
- Robot Assisted
- Sensory Stimulation (EMG/Sensory biofeedback, TENS, Acupuncture)

Encouraging Transfer from Unaffected Limb

- Constraint Induced Movement Therapy
- Bilateral Activity Therapy
- Mirror Therapy



The Basic Principles of Rehabilitation of Upper Extremity

4.3.1 Enhanced or More Intensive Therapy in Upper Extremity

Role of Intensity of Therapy

Post-stroke rehabilitation increases motor reorganization while lack of rehab reduces it; more intensive motor training in animal's further increases reorganization. Clinically greater therapy intensity improves outcomes; reported for PT, OT, aphasia therapy, treadmill training and U/E function in selected patients (i.e. CIMT). One exception is VECTORS trial (Dromerick et al. 2009*);* showed high intensity upper extremity

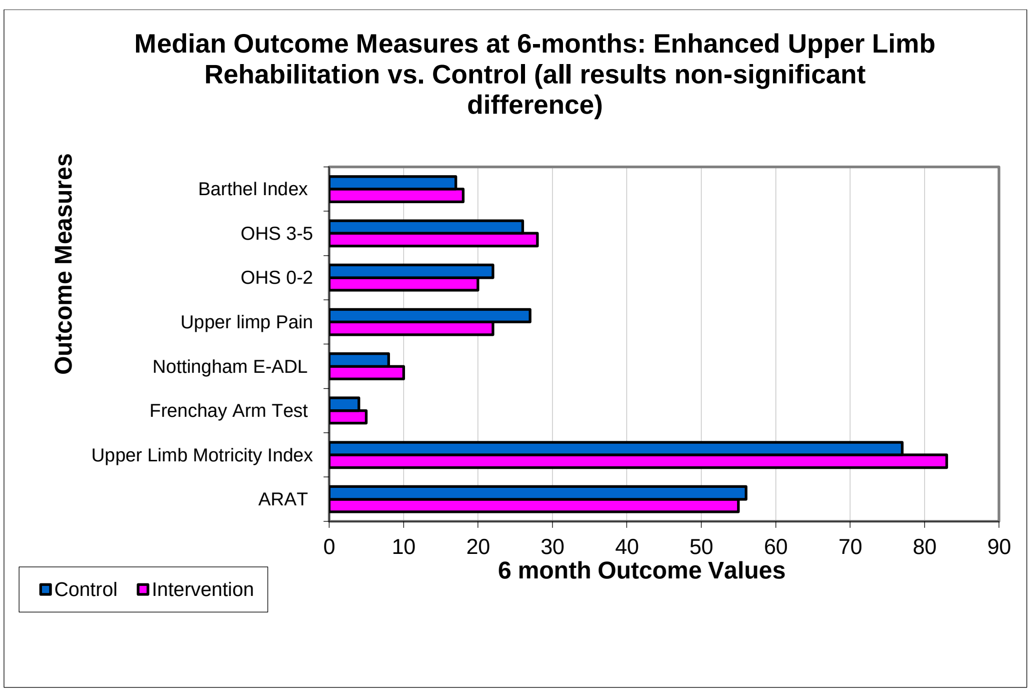
CIMT (6 hrs/day) starting day 10 showed less improvement at 3 months than less intense treatment; Rationale uncertain and it was not a large trial (n=52).

Number of Repetitions in the Upper Extremity

No study has systematically determined a critical threshold of rehab intensity needed to obtain a benefit (MacLellan et al 2011). Animal research involves hundreds of repetitions (250-300 per session). The EXCITE trial involved 196 hours of therapy per patient. If threshold is not reached, there is less recovery of the affected arm; patient develop compensatory movements (Schweighofer et al 2009). Lang et al. (2007) found practice of task-specific, functional upper extremity movements occurred in only 51% of rehab sessions meant to address upper limb rehab. Average number of repetitions per session was only 32. Technology (video gaming, robotics) may be necessary to achieve the maximum number of reps (Saposnik et al. 2010).

Higlighted Study

Rodgers H, Mackintosh J, Price C, Wood R, McNamee P, Fearon T, Marritt A, Curless R. Does an early increased-intensity interdisciplinary upper limb therapy programme following acute stroke improve outcome? Clin Rehabil 2003; 17(6):579-89.		
RCT (PEDro=7) N_{Start}=123 N_{End}=98 TPS = Acute	E: stroke unit care + upper limb therapy C: stroke unit care Duration: 30 min/day, 5 d/wk, for 6 wks.	• Action Research Arm Test (-) • Motricity Index (-) • Frenchay Arm Test (-) • Barthel ADL (-) • Nottingham E-ADL (-) • Cost (-)
This randomized controlled trial of good methodological quality, examined the effectiveness of additional physiotherapy, aimed at the upper extremity, provided acutely following stroke. There was no significant difference between the two groups.		



Highlighted Study

Harris JE, Eng JJ, Miller WC, Dawson AS. A self-administered Graded Repetitive Arm Supplementary Program (GRASP) improves arm function during inpatient stroke rehabilitation: a multi-site randomized controlled trial. Stroke 2009; 40:2123-2128.		
RCT (PEDro=8) N_{Start}=103 N_{End}=94 TPS = Acute	E: Upper limb home exercise program (GRASP) (60min/d, 6d/wk, 4wks) C: Education program Duration: 3mo	• Chedoke McMaster Arm and Hand Inventory (+exp) • Action Research Arm Test (+exp) • Grip Strength (+exp) • Motor Activity Log (+exp)
This RCT found stroke patients who received a graded repetitive upper limb supplementary program (GRASP) showed greater improvement in upper extremity function, grip strength and paretic upper extremity use than an education control group.		

Highlighted Study

English C, Bernhardt J, Crotty M, Esterman A, Segal L, Hillier S. Circuit class therapy or seven-day week therapy for increasing rehabilitation intensity of therapy after stroke (CIRCIT): a randomized controlled trial. International Journal of Stroke 2015; 10(4):594-602.		
RCT (PEDro=7) N_{Start}=283 N_{End}=261 TPS = Acute	E1: Physical therapy 7d/wk E2: Circuit class therapy (90min 2x/d) C: Usual care therapy (5d/wk) for 4wk Duration: 4wk	• 6-Minute Walk Test (-) • Gait Speed (-) • Functional Ambulation Classification (-) • Functional Independence Measure (-) • Wolf Motor Function Test (-) • Stroke Impact Scale (-) • Australian Quality of Life (-) • Length of Stay (-)
This RCT found no difference in stroke patients who received 7-day physical therapy, cirucuit training or usual care on upper extremity funciton, ADLs and quality of life.		

The lack of difference found between different therapies reported in English et al. (2015) was inconsistent with the results of a recent meta-analysis conducted by Verbeek et al. (2014) which found that more therapy time leads to better recovery of stroke symptoms. English et al. (2015) suggest that this discrepancy may be due to their broad inclusion and exclusion criteria. However, many RCTs examined found no significant difference between additional therapy and conventional therapy for upper limb motor function (Dickstein et al. 1997; Donaldson et al. 2009; English et al. 2015; Lincoln et al. 1999; Rodgers et al. 2003; Ross et al. 2009). The additional therapies studied included task-specific motor training, enhanced rehabilitation, and functional strength training, among other more broadly defined therapies. In contrast, Kwakkel et al. (1999) found that arm training provided additional improvements in upper limb motor function than conventional therapy, as did Platz et al. (2001), Han et al. (2013), and Repsaite et al. (2015). An RCT by Harris et al. (2009) found that Graded repetitive upper limb supplementary program (GRASP) was superior to education on the Chedoke Arm and Hand Activity Inventory, as well as for grip strength and paretic upper limb use. However, this result should be interpreted with caution because the control group did not receive a conventional active therapy.

Conclusion

Additional upper limb therapy does not appear to be superior to conventional therapy for improving upper limb motor function or functional independence.

4.3.2 Task-Specific Training

Task-specific practice is required for motor learning to occur. The best way to relearn a given task is to retrain for that task. Task-specific training vs. traditional stroke rehab yields long-lasting cortical reorganization of specific area involved. Repetition, in the absence of skilled motor learning, is often not enough for cortical relearning to occur. Page et al. (2003) have noted intensity alone does not account for differences between traditional stroke and task-specific rehab. Task-specific sessions for as short as 15 minutes are also effective in inducing lasting cortical representation changes. Task-specific, low-intensity regimens designed to improve use and function of affected limb have reported significant improvements (Smith et al. 1999; Whitall et al. 2000; Winstein and Rose 2001).

Repetitive Task-Specific Techniques for Upper Extremity

Highlighted Study

Arya KN, Verma R, Garg RK, Sharma VP, Agarwal M, Aggarwal GG. Meaningful task specific training (MTST) for stroke rehabilitation: a randomized controlled trial. Top Stroke Rehabil 2012; 19:193-211.		
MTST Trial RCT (9) N_{Start}=103 N_{End}=102 TPS=Subacute	E: Task-specific training C: Standard training using the Bobath approach Duration: 1h/d, 4-5d/wk for 4wk	• Fugl Meyer Score (+exp) • Action Research Arm Test (+exp)
This RCT found that patients with a highly impaired upper extremity treated with task specific training experienced improved neurorecovery and functional improvements when compared to a Bobath (neurodevelopmental) control group.		

Task-Specific Training Levels of Evidence

Intervention	Motor Function	ADLs	Spasticity	ROM	Global Stroke Severity	Muscle Strength
Task Specific Training	**1a** **11 RCTs**	**1a** **4 RCTs**	**1a** **2 RCTs**	**1b** **1 RCT**	**1b** **1 RCT**	**1b** **2 RCTs**

Conclusions

Task-specific training, alone or in combination with other therapy approaches, may be beneficial for imporving motor function, spasitiy, range of motion and muscle strength, but not stroke severity or ADLs.

4.3.3 Strength Training

Strength training involves progressive active exercises against resistance. Harris and Eng (2010) conducted a systematic review and meta-analysis of strength training on upper limb strength, function and ADL performance following stroke; there was a significant effect associated with training (SMD=0.95, 95% CI 0.05-1.85; p=0.04).

Highlighted Study

Winstein CJ, Rose DK, Tan SM, Lewthwaite R, Chui HC, Azen SP. A randomized controlled comparison of upper-extremity rehabilitation strategies in acute stroke: a pilot study of immediate and long-term outcomes. Archives of Physical Medicine and Rehabilitation 2004; 85(4):620-628.		
RCT (6) N_{start}=64 N_{end}=44 TPS=Acute	E1: Strength training E2: Functional task practice C: Standard care Duration: 1h/d, 5d/wk for 4wk	E1/E2 vs. C • Fugl Meyer Assessment: (+exp & +exp_2) • Functional test of the hemiparetic upper extremity (+exp_1 & +exp_2) • Isometric torque (+exp & +exp_2)

Verbeeek et al. (2014) found nonsignificant summary effect sizes for motor function of the paretic arm (synergy), muscle strength, range of motion and pain.

Strength Training Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	ROM	Muscle Strength
Strength Training	**1a** **6 RCTs**	**1b** **2 RCTs**	**1b** **2 RCTs**	**1b** **2 RCTs**	**1a** **4 RCTs**	**1a** **3 RCTs**

Conclusion
Strength training may improve motor function and range of motion, but not dexterity or spasticity. The literature is mixed regarding strength training and functional strength for imporving ADLs, and muscle strength.

4.3.4 Constraint-Induced Movement Therapy (CIMT)

The two key features of CIMT are restraint of the unaffected hand/arm and increased practice/use of the affected hand/arm (Fritz et al. 2005). Since stroke survivors may experience "learned non-use" of the affected upper extremity within a short period of time (Taub 1980), CIMT is designed to overcome learned non-use by promoting neuroplasticity and use-dependent cortical reorganization (Taub et al., 1999). CIMT is designed to reduce functional deficits in the more affected upper extremity. The key features of CIMT are restraint of the unaffected hand/arm and increased practice/use of the affected hand/arm. CIMT is designed to overcome learned non-use by promoting cortical reorganization (Taub et al. 1999). Suitable candidates for CIMT are patients with **at least 20 degrees active wrist extension and 10 degrees of active finger extension, with minimal sensory or cognitive deficits**.

CIMT can be described as either:

a) Traditional CIMT: 2 week training program, with 6 hours of intensive upper-extremity training with restraint of the unaffected arm for at least 90% of waking hours.
b) Modified CMT: often refers to less intense than traditional CIMT, with variable intensity, time of constraint and duration of program.

The optimal timing of treatment remains uncertain. While there is evidence that patients treated in the acute phase of stroke may benefit preferentially (Taub & Morris 2001), there is also evidence that it may, in fact, be harmful (VECTORS Trial, Dromerick et al. 2009).

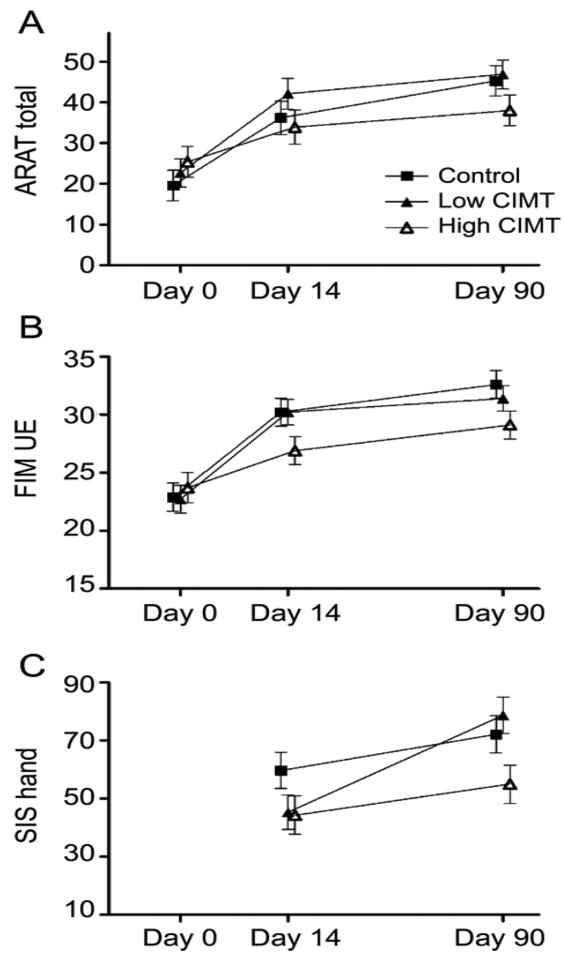
CIMT in Acute/Subacute Phase

A review by Etoom et al. (2016) found that after analyzing 36 trials, CIMT produced a significant effect when compared to a control intervention, although there was a high level of heterogeneity. The authors suggested that the significant effect found may have been skewed by publication bias. However, studies in this review that investigated the effectiveness of CIMT during the first 6 months after stroke overall found a nonsignificant effect (Etoom et al., 2016).

Highlighted Study

Dromerick AW, Lang CE, Birkenmeier RL, Wagner JM, Miller JP, Videen TO, Powers WJ, Wolf SL, Edwards DF. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS) Trial. Neurology 2009; 73:195-201.		
RCT (6) N_{start}=52 N_{end}=52 TPS=Subacute	E1: High-intensity CIMT E2: Standard CIMT C: ADL and UE bilateral training Exercises Duration: 2-3h, 5d/wk for 2wk	<u>E2/C vs E1</u> • Action Research Arm Test: (+exp_2, +con) • Functional Independence Measure (-) • Stroke Impact Scale (-)
See more full discussion below.		

Dromerick AW, Lang CE, Birkenmeier RL, Wagner JM, Miller JP, Videen TO, Powers WJ, Wolf SL, Edwards DF. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS) Trial. Neurology 2009; 73:195-201.



Methods
This was a three arm, single blinded, single center RCT. Patients were stratified for severity, age, NIHSS, pretest ARAT, days from stroke onset. The objective was to examine whether CIMT was superior to an equivalent amount of traditional occupational therapy and whether CIMT treatment effects were dose dependent. 1853 stroke patients were screened (acute stroke admissions) but only 52 patients eventually included in study. Duration of treatment was 2 weeks, 5 days/week. The **control group** received 1 hour ADL retraining and 1 hour U/E bilateral training activities. Equipment, positioning as needed; constraint not allowed. Cueing neither encouraged/discouraged use of affected U/E. **Traditional CIMT group** 2 hours shaping therapy + 6 hours of constraint as well as extensive verbal and written feedback on their progress. **High intensity CIMT group** received 3 hours shaping therapy + constraint 90% of waking hours as well extensive verbal and written feedback on their progress.

Results
Total ARAT score improved from baseline in all groups. There was no significant difference between standard CIMT and control at day 90 for ARAT, FIM UE, SIS Hand. High intensity CIMT had **lower** ARAT and SIS gain at 90 days than control or standard CIMT.

CIMT in Subacute Phase Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	Proprio-ception	Muscle Strength
CIMT in Subacute Phase	1a 8 RCTs	1a 4 RCTs	1a 8 RCTs	2 1 RCT		1b 1 RCT
mCIMT in Subacute Phase	1a 7 RCTs	1b 1 RCT	1a 6 RCTs	1b 1 RCT	1b 2 RCTs	1a 2 RCTs

Conclusions
Constraint induced movement therapy in the acute/subacute phase may be beneficial for improving spasticty and muscle strength, but not motor function. The literature is mixed regarding improvement on ADLs and dexterity.

Modified constraint-induced movement therapy in the acute/subacute phase is beneficial for improving motor function, not be beneficial imporving ADLs, dexterity, spasticity, proprioception or muscle strength.

CIMT in Chronic Phase

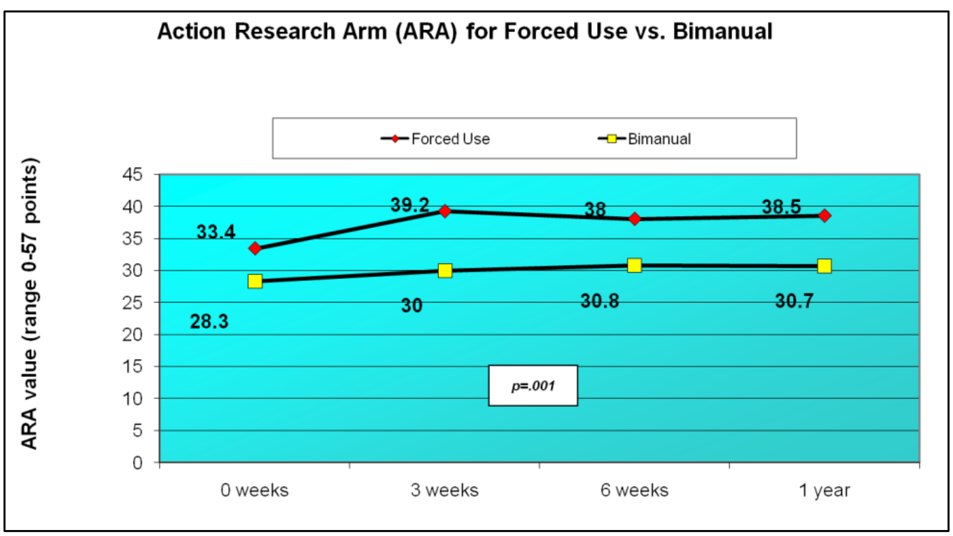
Overall, most studies examined showed a positive effect for CIMT in the chronic phase of stroke for upper limb motor function.

Highlighted Study

Taub E, Miller NE, Novack TA, Cook EW, Fleming WC, Nepomuceno CS, Connell JS, Crago JE. Technique to improve chronic motor deficit after stroke. Arch Phys Med Rehabil 1993; 74:347-354.		
RCT (PEDro=5) N_{start}=9 N_{end}=9 TPS=Chronic	E: CIMT C: Usual Care with focus on affected limb Duration: 7h/d, 14d	• Emory Motor Function Test (+exp) • Arm Motor Acrtivity Test (+exp) • Motor Acitivty Log (+exp)
This study introduced the Constraint-Induced Movement Therapy (CIMT) which involved restraint of the unaffected hand/arm and increased practice/use of the affected hand arm (Fritz et al. 2005). Despite being a median of over 4 years post-stroke, the treatment group showed a marked increase in their upper extremity use.		

Highlighted Study

Suputtitada A, Suwanwela NC, Tumvitee S. Effectiveness of constraint-induced movement therapy in chronic stroke patients. J Med Assoc Thai 2004; 87:1482-1490.		
RCT (PEDro=6) N_{start}=69 N_{end}=69 TPS=Chronic	E: CIMT C: Bimanual-upper-extremity training based on NDT approach Duration: 6h, 5d/wk for 2wk	• Action Research Arm Test (+exp) • Pinch test (+exp)
This RCT found the treatment group which received 6 hours of restrained therapy showed improved functional recovery when compared to control group receiving bilateral NDT treatment.		



Highlighted Study

Van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Deville WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. *Stroke 1999; 30:2369-2375.*		
RCT (7) N_{start}=66 N_{end}=57 TPS=Chronic	E: Bobath concept C: Forced-use therapy Duration: 6h, 5d/wk for 2wk Data analysis: ANCOVA	• Action Research Arm Test (+con)
This RCT examined Constraint Induced Movement Therapy (CIMT) and intensive therapy and compared it to intensive bimanual training based on NDT in chronic stroke patients. CIMT-treated patients showed significantly greater improvement.		

The results from the largest and most rigorously conducted trial-*The Extremity Constraint Induced Therapy Evaluation (EXCITE),* may provide the strongest evidence of a benefit of CIMT treatment, to date. The study recruited 222 subjects with moderate disability 3 to 9 months following stroke, over 3 years from 7 institutions in the US. Treatment was provided for up to 6 hours a day, 5 days a week for 2 weeks. Patients were reassessed up to 24 months following treatment. At 12 months, compared with the control group who received usual care, subjects in the treatment group had significantly higher scores on sections of the WMFT and the Motor Activity Log. At 24 months these gains were maintained. While these results are encouraging, the number of patients for whom this treatment may be suitable, remains uncertain (Cramer, 2007). In the EXCITE trial, only 6.3% of patients screened were eligible. While larger estimates of 20-25% have been suggested, it remains uncertain if subjects with greater disability would benefit from treatment.

Highlighted Study

Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, Giuliani C, Light KE, Nichols-Larsen D. Effect of Constraint-Induced Movement Therapy on Upper Extremity Function 3 to 9 months after stroke. JAMA 2006; 296:2095-2104 (EXCITE Trial).		
RCT (8) N_{start}=222 N_{end}=201 TPS=Chronic	E: CIMT + shaping procedure C: Usual care Duration: 6h, 5d/wk for 2wk	• Wolf Motor Function Test (+exp) • Motor Activity Log (+exp)
The EXCITE trial is the largest RCTs showing a significant benefit in upper extremity motor recovery for CIMT compared to usual care.		

Highlighted Study

Wolf SL, Thompson PA, Winstein CJ, Miller JP, Blanton SR, Nichols-Larsen DS, Morris DM, Uswatte G, Taub E, Light KE, Sawaki L. The EXCITE Stroke Trial. Comparing Early and Delayed Constraint-Induced Movement Therapy. Stroke 2010; 41(10):2309-2315.		
RCT (8) N_{start}=226 N_{end}=192 TPS=Chronic	E1: CIMT early (3-9 months' post stroke) E2: CIMT delayed (15 to 21 months post stroke) Duration: 90% of waking time for 2wk	• Wolf Motor Function Test (+exp1) • Motor Activity Log (+exp1) • Stroke Impact Scale (+exp1)

Verbeek et al (2014) reported high intensity CIMT (mitt worn 90% of day and 3-6 hours of therapy/day) and lower intensity CIMT (mitt worn <90% of day and 0-3 hours of therapy/day) demonstrated significant summary effect sizes for paretic arm (synergies) and arm-hand activities.

CIMT in Chronic Phase Levels of Evidence

Intervention	Motor Function	ADLs	Muscle Strength
CIMT during the chronic phase	**1a** **13 RCTs**	**1a** **11 RCTs**	**1a** **2 RCTs**
mCIMT during the chronic phase	**1a** **10 RCTs**	**1a** **8 RCTs**	

Conclusions

Constraint-induced movement therapy may be beneficial for imporving motor function, ADLs and muscle strength in the chronic phase following stroke.

Modified constraint-induced movement therapy may be beneficial for imporving motor function and ADLs in the chronic phase following stroke.

Priming the Motor System

4.3.5 Action Observation

Action observation is a form of therapy whereby a motor task is performed by an individual while watching a mirror image of another individual perform the same task. The therapy is designed to increase cortical excitability in the primary motor cortex by activating central representations of actions through the mirror neuron system (Kim & Kim, 2015a). Although action observation has been evaluated mainly in healthy volunteers, studies have evaluated its benefit in motor relearning following stroke.

Highlighted Study

Franceschini M, Ceravolo MG, Agosti M, Cavallini P, Bonassi S, Dall'Armi V, Massucci M, Schifini F, Sale P. Clinical relevance of action observation in upper-limb stroke rehabilitation: a possible role in recovery of functional dexterity. A randomized clinical trial. Neurorehabil Neural Repair 2012; 26(5):456-462.

RCT (PEDro=8) N_{start}=102 N_{end}=79 TPS=Subacute	E: Video footage C: Static images Duration: 15min/d, 5d/wk for 4wk	• Box and Block Test (+exp) • Fugl-Meyer Test (-) • Frenchay Arm Test (-) • Modified Ashworth Scale (-) • FIM (-)

Action Observation Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	Muscle Strength
Action Observation	**1a** **6 RCTs**	**1a** **3 RCTs**	**1b** **4 RCTs**	**2** **1 RCT**	**1b** **1 RCT**

Conclusion

Action observation may be beneficial for improving dexterity and spasticity, but not muscle strength. The evidence is mixed regarding improvement for motor function and ADLs.

4.3.6 Mirror Therapy

Mirror therapy is a form of visual imagery in which a mirror is used to convey visual stimuli to the brain through observation of one's unaffected body part as it carries out a set of movements. The mirror is placed in patient's mid-saggital plane, reflecting movements of the non-paretic side as if it was the affected side. The premotor cortex is important to neuroplasticity and is responsive to visual feedback.

Example of Mirror Therapy

Highlighted Study

Yavuzer G, Selles R, Sezer N, Sutbeyaz S, Bussmann JB, Koseoglu F, Atay MB, Stam HJ. Mirror therapy improves hand function in subacute stroke: a randomized controlled trial. Arch Phys Med Rehabil 2008; 89(3):393-398.		
RCT (7) N_{Start}=40 N_{End}=40 TPS=Subacute	E: Mirror Therapy C: Sham Therapy Duration: 2-5h/d, 5d/wk for 4wk	• Brunnstrom Recovery Stages (+exp) • Funtional Indepence Measure (+exp) • Modified Ashworth Scale (-)

Mirror Therapy Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	Proprio-ception	Stroke Severity	Muscle Strength
Mirror therapy	1a 15 RCTs	1b 2 RCTs	1a 11 RCTs	1a 6 RCTs	1b 1 RCT	1a 5 RCTs	1a 2 RCTs

Conclusion

Mirror therapy may improve motor function, dexterity proprioception and stroke severity, but the literature is mixed regarding improvements in ADLs, spasticity and muscle strength.

4.3.7 Mental Practice

Mental imagery was adapted from sports psychology where the technique has been shown to improve athletic performance, when used as an adjunct to standard training methods. Mental practice involves rehearsing a specific task or series of tasks mentally. The most plausible explanation for its benefit is that stored motor plans for executing movements can be accessed and reinforced during mental practice. Page et al. (2001a, b, c, 2005, 2007) patients in mental practice group showed improved upper extremity function. A Cochrane review (Barclay-Goddard et al. 2011) showed that based on results of 6 RCTS (119 participants), mental practice in combination with other treatments appeared to be more effective in improving upper extremity function than did the other treatment alone (SMD=1.37, 95% CI 0.60 to 2.15, $p<0.0001$). It has been recommended as a treatment adjunct to other upper limb interventions and used as a precursor to constraint-induced therapy.

Nilsen et al. (2010) conducted a systematic review on the use of mental practice as a treatment for motor recovery, including the results from 15 studies, 4 of which were classified as Level 1 (i.e., RCTs). Although the authors concluded that there was evidence that mental practice was effective, especially when combined with upper-extremity therapy, they also discussed the problems in summarizing the results of heterogeneous trials. Studies varied with respect to treatment protocols, patient characteristics, eligibility criteria, dosing, methods used to achieve mental practice (audiotapes, written instruction, pictures) the chronicity of stroke, and outcomes assessed. The authors cautioned that additional research must be conducted before specific recommendations regarding treatment can be made.

A meta-analysis (Cha et al. 2012) included the results from 5 RCTs and assessed the additional benefit of mental practice combined with functional task training. The outcomes assessed in the individual studies included the FMA, ARAT and Barthel index. The estimated treatment effect size when the studies were pooled was 0.51 (95% CI 0.27 to 0.750, indicating a moderate effect. However, a meta-analysis by Machado et al. (2015) found that compared to the control, mental practice was not more effective at improving upper limb motor function when used as an adjunct therapy, based on the results of 7 RCTs.

Kho et al. (2014) conducted a recent meta-analysis on the effects of mental imagery on motor recovery of the upper extremity following a stroke. A total of six studies were included in the analysis, of which only five were RCTs and one was a controlled clinical trial. The pooled effects from three studies regarding the FMA showed no significant effect favouring the intervention. Conversely, when evaluating the ARAT measured in four studies, the findings revealed a significant effect in favour of mental imagery (Kho et al., 2014). The authors suggested that a possible explanation for the lack of effect observed on the FMA may be due to a ceiling effect in performance, given that a large proportion of participants had mild motor impairment.

Highlighted Study

Letswaart M, Johnston M, Dijkerman HC et al. Mental practice with motor imagery in stroke recovery: randomized controlled trial of efficacy. Brain 2011; 134(5):1373-1386.		
RCT (7) N_{start}=121 N_{end}=101 TPS=Subacute	E1: Motor imagery E2: Attention placebo C: Usual care Duration: 45min/d, 3d/wk for 4wk	• Action Research Arm Test (-)

Verbeek et al. (2014) found significant summary effect sizes for arm-hand activities but not motor function of the paretic arm (synergy) or muscle strength.

Mental Practice Levels of Evidence

Intervention	**Motor Function** 	**ADLs** 	**Muscle Strength** 
Mental practice	**1a** **15 RCTs**	**1a** **6 RCTs**	**2** **2 RCTs**

Conclusions
Mental practice may produce improvements in motor function and muscle strength, but the evidence is mixed regarding improvements in ADLs.

4.3.8 Bilateral Arm Training

In bilateral arm training patients practice the same activities with both upper limbs simultaneously. Practicing bilateral movements may allow the activation of the intact hemisphere to facilitate the activation of the damaged hemisphere through neural networks linked via the corpus callosum (Morris et al. 2008; Summers et al. 2007).

A Cochrane review by Coupar et al. (2010), which included the results from 18 RCTs, and 549 participants, reported that there was no significant improvement in ADL function (standardized mean difference of 0.25, 95% CI: -0.14 to 0.63), functional movement of the arm (SMD=-0.07, 95% CI -0.42 to 0.28) or hand, (SMD -0.04, 95% CU -0.50 to 0.42) of bilateral arm training compared with usual care following stroke.

Cauraugh et al. (2010) conducted a meta-analysis, including the results from 25 studies, the majority of which were RCTs. The overall treatment effect was a standardized mean difference (SMD) of 0.734, representing a large effect. The effect size was influenced by the type of treatment (pure bilateral, Bilateral Arm Training with Rhythmic Auditory Cueing (BATRAC), coupled bilateral and electromyography (EMG) -triggered neuromuscular stimulation and active/passive movement using robotics). BATRAC and EMG-triggered stimulation studies were associated with the largest SMD.

Van Delden et al. (2012) evaluated the effectiveness of bilateral versus unilateral upper limb therapy and whether or not it was affected by severity of paresis. The review included the results from 9 RCTs. Pooled analyses of 452 patients were conducted for the Fugl-Meyer Assessment (FMA), Action Research Arm test (ARAT), Motor Assessment Scale (MAS) and Motor Activity Log (MAL). Across all severity categories, unilateral training was superior when outcomes were assessed using the ARAT, but there were no differences in the scores of patients who had severe or moderate paresis. There were no significant differences in improvement between groups of either severe or moderate patients on MAS or FMA scores, suggesting both training approaches were effective. Improvements in MAL scores favored patients in the unilateral training group, although only the mild subgroup was represented.

Highlighted Study

Morris JH, van WF, Joice S, Ogston SA, Cole I, MacWalter RS. A comparison of bilateral and unilateral upper-limb task training in early poststroke rehabilitation: a randomized controlled trial. Arch Phys Med Rehabil 2008; 89:1237-1245.		
RCT (7) N_{start}=106 N_{end}=85 TPS=Chronic	E: Bilateral training C: Unilateral training Duration: 20min, 5d/wk for 6wk	• Modified Motor Assessment Scale (+exp)

Highlighted Study

Morris JH, Van WF. Responses of the less affected arm to bilateral upper limb task training in early rehabilitation after stroke: A randomized controlled trial. Arch Phys Med Rehabil 2012; 93(7):1129-37.		
RCT (7) N_{start}=106 N_{end}=85 TPS=Not reported	E: Bilateral training C: Unilateral training Duration: 20min, 5d/wk for 6wk	• 9 Hole Peg Test (+exp) • Action Research Arm Test (-)

Highlighted Study

Whitall J, Waller SM, Sorkin JD, Forrester LW, Macko RF, Hanley DF, Goldberg AP, Luft A. Bilateral and unilateral arm training improve motor function through differing neuroplastic mechanisms: a single-blinded randomized controlled trial. Neurorehabil.Neural Repair 2011; 25(2):118-129.		
RCT (6) N_{Start}=111 N_{End}=92 TPS=Chronic	E: Bilateral arm training with rhythmic auditory cueing C: Dose matched unilateral therapeutic exercises Duration: 20min, 3d/wk for 6wk	• Fugl Meyer Assessment (-) • Wolf Motor Function Test (-) • Stroke Impact Scale (-) • Elbow extension (-) • Shoulder extension (-) • Wrist extension (+exp) • Elbow flexion (-)

Verbeek et al. (2014) found non-significant summary effect sizes for motor functions and motor strength of the paretic arm.

Bilateral Arm Training Levels of Evidence

Intervention	**Motor Function**	**Dexterity**	**ADLs**	**Muscle Strength**

Bilateral Arm Training	**1a** **4 RCTs**	**1a** **2 RCTs**	**1a** **3 RCTs**	**1a** **2 RCTs**

Conclusions

Bilateral arm training may improve motor function, but not muscle strength. The literature is mixed regarding bilateral arm training for improving dexterity and ADLs.

4.3.9 Music Therapy

Music therapy is a promising rehabilitation technique for improving function of the hemiparetic arm following stroke. It involves many components of conventional upper limb rehabilitation interventions including repetitive task practice, finger individualization, as well as tactile and auditory feedback (van Wijck et al. 2012). The rehabilitation program can also be shaped by increasing the tempo of the songs or incorporating more difficult musical pieces based on individual performance. Additionally, music therapy may be more emotionally involving than traditional upper limb interventions which could lead to increased engagement of the patient (Van Vugt et al. 2014).

Highlighted Study

Altenmuller E, Marco-Pallares J, Munte TF, Schneider S. Neural reorganization underlies improvement in stroke-induced motor dysfunction by music-supported therapy. Ann NY Acad Sci 2009; 1169:395-405.		
RCT (5) N_{Start}=62 N_{End}=62 TPS=Acute	E: MIDI piano and electronic drum training + conventional therapy C: Conventional therapy only Duration: 1hr/d, 5d/wk for 3wk	• Box and Block Test (+exp) • Nine Hole Pegboard Test (+exp) • Action Research Arm Test (+exp) • Finger/Hand tapping (+exp)

Music Therapy Levels of Evidence

Intervention	**Motor Function**	**Dexterity**	**ADLs**	**ROM**	**Muscle Strength**
Music therapy	**1b** **4 RCTs**	**2** **3 RCTs**	**2** **1 RCT**	**2** **1 RCT**	**2** **2 RCTs**

Conclusion

Overall, the literature is mixed regarding music therapy for upper limb rehabilitation post stroke. It should be noted that many of the studies in this section differ significantly on the implementation of music therapy.

Sensory Stimulation of the Upper Extremity

Sensorimotor Training in Hemiparetic Upper Extremity

Sensorimotor stimulation treatment included thermal stimulation, intermittent pneumatic compression, splinting, cortical stimulation, and sensory training programs.

4.3.10 Transcutaneous Electrical Nerve Stimulation (TENS)

Laufer & Gabyzon (2011) conducted a systematic review of the effectiveness of TENS for motor recovery, including the findings from 15 studies. Seven of these studies examined treatments focused on the upper extremity, while two included both the upper and lower extremities. The majority of studies recruited participants in the chronic stage of stroke. The outcomes assessed in these studies included movement kinematics during reaching, pinch force, the Jebsen-Talyor Hand Function test, the ARAT, the Barthel Index, and the Modified Motor Assessment Scale. The authors stated while there was much variability in the stimulation protocols and the timing and selection of outcome measures to enable definitive conclusions, there was still evidence that TENS treatment, when combined with rehabilitation therapies, may help to improve motor recovery.

Highlighted Study

Tekeoglu Y, Adak B, Goksoy T. Effect of transcutaneous electrical nerve stimulation (TENS) on Barthel Activities of Daily Living (ADL) index score following stroke. Clinical Rehabilitation 1998; 12(4):277-280.		
RCT (6) N_{start}=60 N_{end}=60 TPS=Subacute	E: Rehabilitation + TENS C: Rehabilitation Duration: 30min/d, 5d/wk for 8wk	• Barthel Index (+exp)

TENS Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Muscle Strength
TENS	**1a 10 RCTs**	**1a 2 RCTs**	**1a 3 RCTs**	**1a 5 RCTs**

Conclusion
TENS may be beneficial for improving motor function, but the evidence is mixed regarding improvement in dexterity, ADLs and muscle strength.

4.3.11 Electroacupuncture

Electroacupuncture was found to be no more effective for improving upper limb motor function than conventional therapy based on the results of three studies with high methological quality and large sample sizes (Li et al 2012; Quian et al 2014; Zhang et al 2017).

Highlighted Study

Quian, Zhao Y, Wang C.-w, Xing D-b, LÜ J-q, Pan H, Yang Y, Li J, Li N. Effects of acupuncture intervention on omalgia incidence rate of ischemic stroke in acute stage. World Journal of Acupuncture - Moxibustion, 2014; 24(1):19-25.		
RCT (7) N_{Start}=300 N_{End}=276 TPS=Acute	E: Electroacupuncture + moxibustion C: Basic therapy Duration: 2 to 15Hz, 5-7d/wk for 4wk	• Fugl-Meyer Assessment (-)

Electroacupuncture Levels of Evidence

Intervention	Motor Function	ADLs	Spasticity	Global Stroke Severity	Muscle Strength
Electro-acupuncture	1a 6 RCTs	1a 3 RCTs	1a 5 RCTs	1a 2 RCTs	1b 1 RCT

Conclusions
Electroacupuncture improves spasticity and may improve motor function, stroke severity and muscle strength, but not ADLs.

4.3.12 Acupuncture

In China, acupuncture is an acceptable, time-efficient, simple, safe and economical form of treatment used to ameliorate motor, sensation, verbal communication and further neurological functions in post-stroke patients," (Wu et al., 2002). According to Rabinstein and Shulman (2003), *"Acupuncture is a therapy that involves stimulation of defined anatomic locations on the skin by a variety of techniques, the most common being stimulation with metallic needles that are manipulated either manually or that serve as electrodes conducting electrical currents*". Acupuncture may stimulate the release of neurotransmitters (Han & Terenius, 1982) and have an effect on the deep structure of the brain (Wu et al., 2002). Lo et al. (2005) established acupuncture, when applied for at least 10 minutes, led to long-lasting changes in cortical excitability and plasticity even after the needle stimulus was removed. A study using positron emission tomography (PET) to observe cerebral function after electroacupuncture treatments showed that glucose metabolism changed significantly immediately after treatment, and after three weeks of daily electroacupuncture treatments in multiple cerebral motor areas (Fang et al., 2012). From these results, Fang et al. (2012) concluded that electroacupuncture participated in modulating motor plasticity.

Highlighted Study

Bai Yl, Li L, Hu YS, Wu Y. Xie PJ, Wang SW, Yang M, Xu YM, Zhu B. Prospective randomized controlled trial of physiotherapy and acupuncture on motor function and daily activities with ischemic stroke. J. Altern. Complement. Med 2013; 19(8):684-689.		
RCT (9) N_{Start}=120 N_{End}=120 TPS=NR	E1: Acupuncture E2: Physical therapy E3: Acupuncture + physical therapy Duration: *Not Specified*	<u>E1 vs E2</u> • Fugl-Meyer Assessment (-) • Modified Barthel Index (-) <u>E1 vs E3</u> • Fugl-Meyer Assessment (-) • Modified Barthel Index (-) <u>E2 vs E3</u> • Fugl-Meyer Assessment (-) • Modified Barthel Index (-)

Highlighted Study

Chen L, Fang J, Ma R, et al. Additional effects of acupuncture on early comprehensive rehabilitation in patients with mild to moderate acute ischemic stroke: a multicenter randomized controlled trial. BMC Complementary Alternative Medicine 2016; 16: 226 (a).		
RCT (8) N_{Start}=250 N_{End}=250 TPS=Chronic	E: Acupuncture C: Conventional therapy Duration: 45min/d, 6d/wk for 3wk	• National Institute of Health Stroke Scale (+exp) • Fugl-Meyer Assessment (+exp)

Highlighted Study

Zhuangl LX, Xu SF, D'Adamo CR, Jia C, He J, Han DX, Lao LX. An effectiveness study comparing acupuncture, physiotherapy, and their combination in poststroke rehabilitation: A multicentered, randomized, controlled clinical trial. Alternative Therapies in Health & Medicine 2012; 18(3).		
RCT (7) N_{start}=295 N_{end}=274 TPS=Chronic	E1: Acupuncture E2: Physiotherapy E3: Acupuncture + physiotherapy Duration: 1hr/d, 6d/wk for 4wk	• Fugl-Meyer Assessment (-) • Barthel Index (-) • Neurologic Defect Scale (-)

A majority of studies investigating the effectiveness of acupuncture for improving upper limb motor function found that there was no significant benefit to acupuncture when compared to a control

Acupuncture Levels of Evidence

Intervention	Motor Function	ADLs	Spasticity	ROM	Global Stroke Severity
Acupuncture	1a 8 RCTs	1a 7 RCTs	1a 3 RCTs	1a 2 RCTs	1a 4 RCTs

Conclusion

Acupuncture likely does not improve upper limb motor function or level of independence. It does appear to improve spasticity.

4.3.13 EMG / Biofeedback in Hemiparetic Upper Extremity

EMG biofeedback uses external electrodes attached to targeted muscles to capture motor unit electrical potentials. This provides audio or visual feedback about how much the patient is activating the targeted muscle. Overall, the evidence suggests that biofeedback through EMG technology, either delivered alone or in combination with other treatments, may not improve upper limb motor function, manual dexterity, or spasticity. More high-powered RCTs are required to determine whether this method of rehabilitation is beneficial for improving other aspects of upper limb function.

There is strong evidence that EMG / Biofeedback therapy is not superior to other forms to treatment and may not improve upper extremity motor function or spasticity.

EMG Biofeedback Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	ROM	Stroke Severity	Muscle Strength

EMG Biofeedback	1a 8 RCTs	1b 1 RCT	1a 3 RCTs	2 2 RCTs	1 4 RCTs	1b 2 RCTs	1b 2 RCTs

Conclusions
The literature is mixed regarding EMG biofeedback alone for improving ADLs, ROM, stroke severity and muscle strength, but does not appear to be beneficial for improving motor function, dexterity or spasticity.

Motor Stimulation

4.3.14 Functional Electrical Stimulation (FES) in Hemiparetic Upper Extremity

Neuromuscular electrical stimulation (NMES) can be used to improve motor recovery, reduce pain and spasticity, strengthen muscles and increase range of motion following stroke. NMES is a technique that uses trains of electrical pulses to generate muscle contraction by stimulating motor axons. Three forms of NMES are available: 1) cyclic NMES, which contracts paretic muscles on a pre-set schedule and does not require participation on the part of the patient; 2) electromyography (EMG) triggered NMES, which may be used for patients who are able to partially activate a paretic muscle and may have a greater therapeutic effect; 3) Functional electrical stimulation (FES), which refers to the application of NMES to help achieve a functional task. FES can be used to improve or restore volitional grasp and manipulation functions required for typical ADLs (Popovic et al., 2002), or can be intended as a permanent assistive device (i.e., neuroprosthesis) for helping patients perform ADL.

Example of Functional Electrical Stimulation treatment

Example of H200 Wireless Hand Rehabilitation System

Highlighted Study

Powell J, Pandyan AD, Granat M, Cameron M, Stott DJ. Electrical stimulation of wrist extensors in post stroke hemiplegia. Stroke 1999; 30(7):1384-1389.		
RCT (7) N_{start}=60 N_{end}=48 TPS=Subacute	E: Cyclic electrical stimulation + standard rehabilitation C: Standard rehabilitation Duration: 30 min (3x per day), 3d/wk for 8 wk	• Action Research Arm test (+exp)

Highlighted Study

Page SJ, Levin L, Hermann V, Dunning K, Levine P. Longer versus shorter daily durations of electrical stimulation during task-specific practice in moderately impaired stroke. Arch Phys Med Rehabil 2012; 93:200-206.		
RCT (7) N_{start}=32 N_{end}=32 TPS=Chronic	E1: 30 minutes of electrical stimulation therapy with repetitive task specific practice E2: 60 minutes of electrical stimulation therapy with repetitive task specific practice E3: 120 minutes of electrical stimulation therapy with repetitive task specific practice Duration: 30 min OR 60 min OR 120 min, 5d/wk for 8 wk.	<u>E3 vs. E2/E1</u> • Fugl-Meyer Assessment (+exp_3) • Arm Motor Ability Test (+exp_3) • Action Research Arm Test (+exp_3)

Among the studies evaluating FES/NMES in the subacute stage of stroke, most assessed the same treatment comparison, electrical stimulation versus physical therapy alone or sham stimulation. The results indicated that FES/NMES was associated with improvements in motor function, range of motion, ADL and dexterity in acute to subacute strokes. In the chronic phase, FES/NMES may be advantageous at recovering impaired manual dexterity, coordination and range of motion however, improvements in motor function in general following FES/NMES are less clear. Despite improvements observed during both phases of stroke recovery, limited evidence indicates that recovery may be more significant when FES was delivered early (<6 months) compared to when it was delivered at a later chronic stage (>6 months) (Popovic et al. 2004). More research is needed to verify this effect. Furthermore, in unfavourable patients, EMG-NMES was found to have no effect when compared to those receiving usual care on measures of upper limb motor function and dexterity (Kwakkel et al. 2016).

Two studies compared a high intensity NMES or FES exercise therapy (60 minutes) against a low intensity exercise program (Hsu et al., 2010; Kowalczewski et al., 2007). Both studies found that there was no significant difference between groups in upper limb motor function in patients during the acute/subacute phase post stroke.

There is strong evidence that FES treatment improves upper extremity function in acute stroke (<6 months post onset) and chronic stroke (>6 months post onset) when offered in combination with conventional therapy or delivered alone.

Verbeek et al. (2014) found a more mixed effect; summary effect sizes for wrist and finger extensor stimulation with NMS but not EMG-NMS while the opposite was true for combined stimulation of wrist and finger extensors and flexors.

Functional Electrical Stimulation and NMES Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	ROM	Stroke Severity	Muscle Strength
Cyclic NMES	**1a 7 RCTs**		**1a 3 RCTs**	**1a 6 RCTs**	**1b 2 RCTs**	**1b 2 RCTs**	
EMG-NMES	**1a 7 RCTs**	**1b 4 RCTs**	**1a 5 RCTs**	**2 1 RCT**	**2 2 RCTs**		**1a 2 RCTs**
FES	**1a 11 RCTs**	**1b 1 RCT**	**1a 5 RCTs**	**1a 8 RCTs**	**1b 4 RCTs**	**1a 2 RCTs**	**1b 1 RCT**

Conclusions
Cyclic NMES may be beneficial for improving motor function but not ADLs and muscle strength. The literature is mixed regarding improvements in spasticity and range of motion.
EMG triggered NMES may be beneficial for improving dexterity, spasticity and range of motion, but not motor function and muscle strength. The literature is mixed regarding improvements in ADLs.
FES may be beneficial for improving dexterity, but not muscle strength. The literature is mixed regarding improvements in motor function, ADLs, spasticity, range of motion and stroke severity.

Brain Stimulation

Brain stimulation is a procedure that uses a neurostimulator to send electrical impulses to the brain. The most common types of brain stimulation in rehabilitation include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS may be delivered in a single pulse, in paired pulses or as repetitive trains of stimulation. It can facilitate or suppress targeted regions of the brain, depending on the stimulation parameters. tDCS involves the application of mild electrical currents (1-2 mA) conducted through 2 saline soaked, surface electrodes applied to the scalp, overlaying the area of interest and the contralateral forehead above the orbit; it does not induce action potentials, but instead modulates the resting membrane potential of the neurons.

4.3.15 Invasive Motor Cortex Stimulation (MCS)

Due to the invasive nature of this technique and the complications associated with the procedure, the evidence for its use in the stroke population is limited.

Levy RM, Harvey RL, Kissela BM, Winstein CJ, Lutsep HL, Parrish TB, Cramer SC, Venkatesan L. Epidural Electrical Stimulation for Stroke Rehabilitation: Results of the Prospective, Multicenter, Randomized, Single-Blinded Everest Trial. Neurorehabil Neural Repair 2016: 30(2):107-119.		
RCT (6) N_{Start}=164 N_{End}=128 TPS=Chronic	E: Cortical implant with epidural 6-contact lead perpendicular to the primary motor cortex and a pulse generator C: Conventional rehabilitation Duration: *Not Specified*	• Arm Motor Ability Test (-) • Fugl-Meyer Assessment (-)
A large study by Levy et al. (2016) found no significant difference on upper limb motor function outcomes between patients receiving a cortical implant providing primary motor cortex stimulation with a pulse generator when compared to those not receiving an implant.		

Invasive Motor Cortex Stimulation Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Muscle Strength
Motor Cortex Stimulation	**1a** **4 RCTs**	**2** **1 RCT**	**1a** **3 RCTs**	**2** **1 RCT**

Conclusions
The literature is mixed concerning invasive motor cortex stimulation for improving upper limb rehabilitation post stroke.

4.3.16 Repetitive Transcranial Magnetic Stimulation (rTMS)

TMS is a novel approach to neurorehabilitation following stroke. TMS may be delivered in a single pulse, in paired pulses or as repetitive trains of stimulation. Repetitive TMS (rTMS) produces effects which last longer than the period of stimulation. When TMS is applied in the form of trains of stimuli (rTMS) to the motor cortex, it can facilitate or suppress targeted regions of the brain, depending on the stimulation parameters. Low stimulation frequencies (1 Hz or lower) decrease cortical excitability and inhibit the targeted cortex, while high frequency (10 to 20Hz) stimulation increases excitability and has a facilitatory effect.

The stimulation process is both painless and non-invasive and involves the use of a coil that produces a magnetic field which passes through the skull to the cerebral cortex. Repetitive TMS induces sustained increases in cortical excitability through mechanisms that are still not well defined; however, inhibition of the unaffected hemisphere theoretically results in decreased inhibitory projections to the affected hemisphere, increasing intracortical excitability within the ipsilesional cortical tissue that ultimately would translate into an improvement in motor function (Fregni et al. 2006).

Highlighted Study

Long H, Wang H, Zhao C et al. Effects of combining high-and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke. Restor Neurol Neurosci 2018; 36(1): 21-30.		
RCT (7) N_{Start} =62 N_{End} =62 TPS=Acute	E1: Low Frequency (1Hz) combined with High Frequency (10Hz) Repetitive Transcranial Magnetic Stimulation E2: Low Frequency (1Hz) Repetitive Transcranial Magnetic Stimulation C: Sham Repetitive Transcranial Magnetic Stimulation Duration: *Not specified*	E2 vs C • Fugl-Meyer Assessment (+exp_2) • Wolf Motor Function Test (-)

Highlighted Study

Du JL, Tian W, Liu, J et al. Effects of repetitive transcranial magnetic stimulation on motor recovery and motor cortex excitability in patients with stroke: a randomized controlled trial." Eur J Neurol 2016; 23(16):1666-1672.		
RCT (7) N_{Start} =69 N_{End} =59 TPS=Acute	E1: High frequency (3Hz) rTMS E2: Low frequency (1Hz) rTMS C: Sham rTMS Duration: 30min/d, 5d/wk for 1wk	E1 vs C • Fugl-Meyer Assessment (-) • Medical Research Council Score (-) • National Institute of Health Stroke Scale (+exp) • Modified Rankin Scale (+exp) • Barthel Index (+exp) E2 vs C • Fugl-Meyer Assessment (+exp_2) • Medical Research Council Score (+exp_2) • National Institute of Health Stroke Scale:(+exp_2) • Modified Rankin Scale (+exp_2) • Barthel Index (+exp_2)

Highlighted Study

Li J, Meng XM, Li RY, Zhang R, Zhang Z, Du YF. Effects of different frequencies of repetitive transcranial magnetic stimulation on the recovery of upper limb motor dysfunction in patients with subacute cerebral infarction. Neural regeneration research 2016; 11(10):1584.		
RCT (7) N_{Start} =127 N_{End} =127 TPS=Subacute	E1: Low frequency (1Hz) rTMS E2: High frequency (10Hz) rTMS C: Sham Duration: 40min/d, 5d/wk for 2wk	E1 vs C • Fugl-Meyer Assessment (+exp) • Wolf Motor Function Test (-) E2 vs C • Fugl-Meyer Assessment (+exp_2) • Wolf Motor Function Test (-)

A recent meta-analysis (Hsu et al. 2012) including the results of 18 RCTs and representing data from 392 patients, examined the effectiveness of rTMS for improving motor function following stroke. The authors reported a clinically significant treatment effect. The outcomes evaluated included finger tapping tasks, the Nine Hole Peg Test, hand grip strength and the Wolf Motor Function test. The treatment effects associated with treatment in the acute, subacute and chronic stages of stroke were 0.79, 0.63 and 0.66, respectively. Low-frequency rTMS (1 Hz) over the unaffected hemisphere appeared to be more effective than high-frequency rTMS (10 Hz) over the unaffected hemisphere (treatment effect =0.69 vs. 0.41).

A systematic review with meta-analysis by Graef et al. (2016) investigated whether there is a significant difference between rTMS with upper limb training in comparison to sham rTMS with upper limb training. The review included 11 studies, and overall found no significant difference between groups for upper limb motor function or spasticity.

rTMS Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	ROM	Proprio-Caption	Stroke Severity	Muscle Strength
Low frequency rTMS	1a 20 RCTs	1a 10 RCTs	1a 9 RCTs	1a 7 RCTs	1a 2 RCTs	1b 1 RCT	1a 5 RCTs	1a 10 RCTs
High frequency rTMS	1a 7 RCTs	1a 4 RCTs	1a 6 RCTs				1a 6 RCTs	1a 6 RCTs
Bilateral rTMS	1b 1 RCT							

Conclusions
Low frequency rTMS may be beneficial for improving motor function, dexterity, ADLs, proprioception, stroke severity, but not spastcity or range of motion.
High frequency rTMS may be beneficial for improving dexterity, ADLs, stroke severity and muscle strength, but not motor function.

4.3.17 Transcranial Direct Current Stimulation (tDCS)

Another form of noninvasive electrical stimulation is transcranial direct-current stimulation (tDCS). This procedure involves the application of mild electrical currents (1-2 mA) conducted through 2 saline soaked, surface electrodes applied to the scalp, overlaying the area of interest and the contralateral forehead above the orbit. Anodal stimulation increases cortical excitability while cathode stimulation decreases it (Alonso-Alonso et al., 2007). In contrast to TMS, tDCS does not induce action potentials, but instead modulates the resting membrane potential of the neurons (Alonso-Alonso et al. 2007).

A systematic review conducted by Elsner et al. (2016) revealed evidence favouring the use of tDCS over sham tDCS or a differing control condition, but there was no evidence of lasting effects at follow-up. It was also reported that ADLs were found to improve after tDCS treatment, but this effect was not maintained after excluding studies that were at a high risk for bias (Elsner et al. 2016). Another meta-analysis, authored by Butler et al. (2013), was restricted to the examination of anodal tDCS and included the results from eight RCTs, all of which examined motor function in the upper extremity following stroke. Outcomes assessed included the Jebsen-Taylor Hand Function test, BBT, pinch and grip strength, and reaction time. Butler et al. (2013) reported a significant increase in pooled scores favouring tDCS from baseline to post-treatment, although only a small to moderate effect size (0.40) was obtained.

tDCS Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	Stroke Severity	Muscle Strength

Anodal tDCS	**1a 11 RCTs**	**1a 5 RCTs**	**1a 4 RCTs**	**1b 1 RCT**	**1b 1 RCT**	**1a 9 RCTs**
Cathodal tDCS	**1a 9 RCTs**	**1a 3 RCTs**	**1a 3 RCTs**	**1b 1 RCT**	**1a 2 RCTs**	**1a 6 RCTs**
Dual tDCS	**1a 4 RCTs**	**1a 5 RCTs**	**1b 1 RCT**	**1a 2 RCTs**	**1b 1 RCT**	**1a 4 RCTs**

Conclusions:
The literature is mixed for anodal, cathodal or dual (bilateral) transcranial direct current stimulation (tDCS), alone or in combination with other therapy approaches, for upper limb rehabilitation post stroke.

Technology

4.3.18 Telerehabilitation

It is known that distance to a rehabilitation centre can impede patients from receiving the care they need once they are discharged from the hospital. Therefore, providing rehabilitation services remotely via a kiosk or by telephone can limit the challenge of location and transportation especially for patients isolated from these services. This form of service provision has been termed “telerehabilitation”. It is an intervention that can be delivered for a longer duration and at a reduced cost when compared to therapies provided in the inpatient rehabilitation setting (Benvenuti et al. 2014).

Highlighted Study

Emmerson KB, Harding KE, Taylor NF. Home exercise programmes supported by video and automated reminders compared with standard paper-based home exercise programmes in patients with stroke: a randomized controlled trial. Clin Rehabil 2017; 31(8):1068-1077.		
RCT (7) N_{Start}=62 N_{End}=58 TPS=Chronic	E: Home exercise program using an electronic tablet with automated reminders C: Paper-based home exercise program Duration: 45min/d, 5d/wk for 4wk	• Wolf Motor Function Test (-) • Grip Strength (-)

Highlighted Study

Wolf SL., Sahu K, Bay RC et al. The HAAPI (Home Arm Assistance Progression Initiative) trial: a novel robotics delivery approach in stroke rehabilitation. Neurorehabil and Neural Repair 2015; 29(10):958-968.		
RCT (7) N_{Start}=99 N_{End}=92 TPS=Subacute	E: Telerehabilitation through an upper extremity hand robot with home exercise program C: Home exercise program only Duration: 3h/d, 5d/wk for 8-12wk	• Fugl Meyer Assessment (-) • Action Research Arm Test (-) • Wolf Motor Function Test (+exp)

Highlighted Study

Benvenuti F, Stuart M, Cappena V, Gabella S, Corsi S, Taviani A, Albino A, Marchese S, Weinrich M. Community-Based Exercise for Upper Limb Paresis: A Controlled Trial with Telerehabilitation. Neurorehabilitation and Neural Repair, 2014; 28(7):611-620.		
Cohort Study N_{Start}=99 N_{End}=92 TPS=Subacute	E: community based telerehabilitation monitoring for upper limb home exercise program C: Usual Care Duration: 3mo	• Wolf Motor Function Test (+exp) • 9-hole Peg Test (+exp) • Motricity Index (+exp) • Nottinham Extended ADLs (+exp) • Barthel Index (+exp) • Short Physical Performance Battery (+exp)

Telerehabilitation Levels of Evidence

Intervention	Motor Function
Telerehabilitation	1a 2 RCTs

Conclusions

Home-based telerehabilitation interventions were not effective for improving upper limb motor function when compared to an active control.

4.3.19 Orthosis in Hemiparetic Upper Extremity

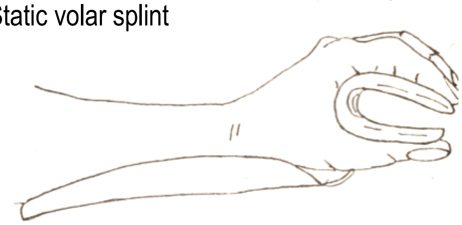
Upper Extremity Orthosis

The common orthosis used in hemiplegic upper extremity is the wrist-hand-orthosis/splints. These orhoses an be static/passive (volar, dorsal splints) or dynamic/active (eg. Saebo-Flex®).

Aims in Applying Orthosis

- Reduction in spasticity
- Reduction in pain
- Improvement in functional outcome
- Prevention of contracture
- Prevention of edema

Static volar splint



Tyson and Kent (2011) conducted a systematic review on the effect of upper limb orthotics following stroke, which included the results from 4 RCTs representing 126 subjects. The treatment effects associated with measures of disability, impairment, range of motion, pain, and spasticity were small and not statistically significant.

Basaran A, Emre U, Karadavut KI, Balbaloglu O, Bulmus N. Hand splinting for poststroke spasticity: a randomized controlled trial. Top Stroke Rehabil 2012 Jul-Aug; 19(4):329-37.		
RCT (6) N_{start}=39 N_{end}=39 TPS=Chronic	E1: Volar splint E2: Dorsal splint C: No splint Duration: up to 10h/d for 5wk	<u>E1 vs E2 vs C</u> • Modified Ashworth Scale (-) • Passive range of motion (-)

Orthotics Level of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	ROM	Muscle Strength
Orthotics	1a 5 RCTs	1b 2 RCTs	1a 4 RCTs	1b 7 RCTs	1a 5 RCTs	1b 2 RCTs

Conclusions

Splinting, taping, and orthoses likely do not improve upper limb motor function, dexterity, ADLs, spasticty or muscle strength but may improve range of motion.

4.3.20 Robotics in Rehabilitation of Upper Extremity Post-Stroke

Robotic devices can be used to assist the patient in a number of circumstances. First of all, the robot can aid with passive range of motion to help maintain range and flexibility, to temporarily reduce hypertonia or resistance to passive movement. The robot can also assist when the patient has active movements, but cannot complete a movement independently. Robotics may be most appropriate for patients with dense hemiplegia, although robotics can be used with higher-level patients who wish to increase strength by providing resistance during the movement. According to Lum et al. (2002) *"even though unassisted movement may be the most effective technique in patients with mild to moderate impairments, active-assisted movement (with robotic devices) may be beneficial in more severely impaired patients…especially during the acute and subacute phases when patients are experiencing spontaneous recovery,"*. Krebs et al. 2003 noted that robotic devices rely on the repetition of specific movements to improve functional outcomes.

Robotic Devices Used for Upper Limb Rehabilitation Post Stroke

Robotic Devices	Description
InMotion robot (Massacheusetts Insitute of Technology/MIT-Manus)	MIT-Manus was one of the first robotic devices to be developed. It features a 2-degree-of-freedom robot manipulator that assists in shoulder and elbow movement by guiding the patient's hand in a horizontal plane, while visual, auditory and tactile feedback is provided during goal-directed movements. A commercially available unit (InMotion2) of this device is also available.
Mirror-Image Motion Enabler Robots (MIME)	MIME is a 6 degree of freedom robotic device developed "to provide therapy that combines bimanual movements with unilateral passive, active-assisted and resisted movements of the hemiparetic upper extremity," (Burgar et al. 2011). The unit applies force to the more affected forearm during goal-directed movements.

ARMin	This exoskeleton robot has 7 degrees of freedom and also provides intensive and task-specific training to target improvements in motor function.
Assisted Rehabilitation and Measurement (ARM) Guide	This unit uses a motor and chain drive to move the user's hand along a linear rail, which assists reaching in a straight-line trajectory.
Bi-Manu-Track	This arm-training device enables bilateral and passive and active practice of forearm and wrist movement.
Neuro-Rehabilitation-Robot (NeReBot)	The NeReBot device was developed in Italy designed to produce sensorimotor stimulation. The 3 degrees of freedom device can perform spatial movements of the shoulder and elbow, is portable and can be used when the patient is either prone or sitting.
Robot-mediated therapy system (GENTLE/s)	This device is a three-degree of freedom haptic interface arm with a wrist attachment mechanism, two embedded computers, a monitor and speakers and an overhead arm support system. The affected arm is de-weighted through a free moving elbow splint attached to the overhead frame. The subject is connected to the device by a wrist splint. Exercises such as hand-to-mouth and reaching movements can then be practised, while feedback is provided.
Amadeo	This device assists in hand rehabilitation, having an end-effecter design. It helps with finger movements to allow for synchronization.
MusicGlove	The glove is used with a game that promotes specific pinching movements to match musical notes displayed on a screen.

A Cochrane review (Mehrholz et al., 2012) included the results from 19 trials (328 subjects) evaluating electromechanical and robot-assisted arm training devices. Compared with routine therapy, usually conventional physical therapy, the authors reported significantly greater improvement in activities of daily living (SMD=0.43; 95% CI 0.11 to 0.75, p <0.009) and arm function (SMD=0.45; 95% CI 0.20 to 0.69, p<0.001), but not arm strength (SMD=0.48; 95% CI -0.04 to 0.04, p=0.82).

Highlighted Study

Lo A, Guarino PD, Richards LG, Haselkorn JK, Witterberg GI, Federman DG, Ringer RJ, Wagner TH, Krebs HJ, Volpe BT, Bever CT, Bravata DM, Duncan PW, Corn BH, Maffucci AD, Nadeau SE, Conroy SS, Powell JM, Huang GD. Robot-assisted therapy for long term upper limb impairment after stroke. N Eng Med J, 2010; 362:1777-1783.		
RCT (7) N_{start}=127 N_{end}=127 TPS=Chronic	E1: Intensive robot assisted therapy (MIT-Manus) E2: Intensive comparison therapy C: Usual care Duration: 1hr/d, 3d/wk for 12wk (36 sessions)	<u>E1 vs C</u> • Fugl-Meyer Assessment (-) (+exp at p=.08) • Wolf Motor Function Test (-) • Stroke Impact Scale (+exp) • Modified Ashworth Scale (-) <u>E1 vs E2</u> • Fugl-Meyer Assessment (-) • Wolf Motor Function Test (-) • Stroke Impact Scale (-) • Modified Ashworth Scale (-)
Important study which showed that arm robotic treatment was better than usual care control for some of the outcomes but was not superior to an intensive active control of comparison therapy.		

Highlighted Study

Prange GB, Kottink AI, Buurke et al. The effect of arm support combined with rehabilitation games on upper-extremity function in subacute stroke: a randomized controlled trial. Neurorehabil and Neural Repair 2015; 29(2):174-182.		
RCT (7) N_{Start}=70 N_{End}=68 TPS=Acute	E: Arm training with robot (ArmeoBoom) C : Conventional training Duration : 30min/d, 4d/wk for 6wk	• Stroke Upper Limb Capacity Scale (-) • Reaching Distance (-) • Fugl-Meyer Assessment (-)

Highlighted Review

Mehrholz J, Hädrich A, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database of Systematic Reviews 2012, Issue 6.Art. No.: CD006876. DOI: 10.1002/14651858.CD006876.pub3.

A systematic Cochrane review examined 16 trials involving 666 participants and found patients receiving electromechanical and robot-assisted arm training after stroke showed improvement in arm motor function (SMD 0.45, 95% CI: 0.20 to 0.69) and activities of daily living (SMD 0.43, 95% CI 0.11 to 0.75), but without significant improvement in arm muscle strength. The authors concluded that electro-mechanical and robot assisted arm training improved generic activities of daily living in people after stroke and may have improved arm function but did not improve muscle strength of the partial paralysed (paretic) arm.

A more recent systematic review identified 34 RCTs of low to very low quality which evaluated nineteen different electromechanical assisted devices for their efficacy at improving upper limb motor function (Mehrholz et al. 2015). Results demonstrate that robotic devices targeting arm and hand movement allowed for improvements in activities of daily living and recovery of impaired function and muscle strength (Mehrholz et al. 2015). Verbeek et al. (2014) found significant summary effect sizes for proximal but not distal motor function.

Robotics in Upper Extremity Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Spasticity	ROM	Proprio-ception	Muscle Strength
Various arm/shoulder end-effectors	1a 17 RCTs	1b 6 RCTs	1a 16 RCTs	1b 6 RCTs			1a 9 RCTs
Bi-Manu Track	1b 2 RCTs	1b 1 RCT	1b 1 RCT				1b 1 RCT
Arm/shoulder Exoskeletons	1a 4 RCTs	1b 2 RCTs	1b 2 RCTs			1b 1 RCT	1b 2 RCTs
Hand end-effectors	1a 2 RCTs	1a 2 RCTs		1b 1 RCT			
Hand Exoskeletons	1a 6 RCTs	1a 4 RCTs	1a 4 RCTs	1b 1 RCT	2 1 RCT		1b1 RCT

Conclusions

Arm/shoulder end-effector or exoskeleton, alone or in combination with other therapy approaches, may not be beneficial for for upper limb rehabilitation following stroke.
Hand end-effectors may not be beneficial for improving upper limb rehabilitation, but hand exoskeletons may be beneficial for improving ADLs, spasticity, range of motion and muscle strength. The evidence is mixed for hand exoskeleton's ability to improve motor function and dexterity.

4.3.21 Virtual Reality

Virtual reality allows individuals to to experience and interact with three-dimensional environments. The most common forms of virtual environmental simulators are head-mounted displays (immersion) or with conventional computer models or projector screens. A Cochrane review, which included results from 19 RCTs (565 subjects) and of which 8 examined upper-limb training, reported a moderate treatment effect for arm function (SMD=0.53, 95% CI 0.25 to 0.81) (Laver et al., 2011). Only two of the studies used readily available commercial devices (Playstation EyeToy and Nintendo Wii), while the remainder used customised VR programs.

In a recent systematic review, Laver et al. (2015) sought to determine the efficacy of virtual reality on upper limb motor function. In total, 37 trials were included in the analysis, consisting of 1019 participants. The results revealed that there were no significant effects of virtual reality on grip strength or global motor function. The authors also noted that the participants were relatively young and in the chronic phase of stroke (>1 year), therefore the effect of virtual reality during the acute phase of stroke could not be determined.

Two studies of high methodological quality and with large sample sizes detected no effect when comparing Nintendo Wii virtual reality training to conventional training on measures of upper limb motor function (Kong et al., 2016; Saposnik et al., 2016).

Highlighted Study

Kong KH, Loh YJ, Thia E, Chai A, Ng CY, Soh YM, Toh S, Tjan SY. Efficacy of a virtual reality commercial gaming device in upper limb recovery after stroke: A randomized, controlled study. Topics in Stroke Rehabilitation 2016; 23(5):333-340.		
RCT (7) N_{Start}=105 N_{End}=97 TPS=Acute	E: Nintendo Wii virtual reality training C: Conventional therapy	• Fugl-Meyer Assessment (-) • Action Research Arm Test (-) • Stroke Impact Scale (-) • Functional Independence Measure (-)

Highlighted Study

Saposnik G et al. Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial. Lancet Neurology 2016; 15(10): 1019-1027.		
RCT (6) N_{Start}=141 N_{End}=121 TPS=Acute	E: Virtual reality training using Nintendo Wii C: Recreational activities	• Wolf Motor Function Test (-) • Box and Block Test (+con) • Stroke Impact Scale (-) • Barthel Index (-) • Functional Independence Measure (-) • Grip Strength (-)

This multi-centred RCT showed that patients using virtual reality training with the Nintendo Wii improved upper extremity function but no more than a control group engaging in a similar amount of recreational activities involving the upper extremity, i.e. Jenga.

Highlighted Study

Kiper P, Szczudlik A, Agostini M et al. Virtual reality for upper limb rehabilitation in subacute and chronic stroke: a randomized controlled trial. Arch Phys Med Rehabil 2018;99(5):834-842.		
RCT (7) N_{Start} =139 N_{End} =136 TPS=Subacute	E: Reinforced feedback in virtual environment + conventional rehabilitation C: Conventional rehabilitation	• Fugl-Meyer Assessment (+exp) • Functional Independence Measure (+exp) • National Institute of Health Stroke Scale (+exp)

Highlighted Study

Adie K, Schofield C, Berrow M, Wingham J, Humfryes J, Pritchard C, James M, Allison R. Does the use of Nintendo Wii SportsTM improve arm function? Trial of WiiTM in Stroke: a randomized controlled trial and economics analysis. Clinical rehabilitation. 2017; 31(2):173-85.		
RCT (7) N_{Start} =235 N_{End} =209 TPS=Chronic	E: Wii arm exercises C: Home-based arm exercises	• Action Research Arm Test (-) • Stroke Impact Questionnaire (-) • Canadian Occupational Performance Measure (- • Motor Activity Log (-)

Virtual reality can be a useful as an adjunct to other interventions enabling additional opportunities for increasing repetition, intensity and provide task-oriented training.

Virtual Reality Levels of Evidence

Intervention	Motor Function	ADLs	Dexterity	Spasticity	ROM	Stroke Severity	Muscle Strength
Virtual reality	**1a** **30 RCTs**	**1a** **7 RCTs**	**1a** **10 RCTs**	**1a** **4 RCTs**	**2** **2 RCTs**	**1b** **1 RCTs**	**1a** **12 RCTs**

Conclusions

Virtual reality therapy may not be more beneficial than conventional therapy for improving motor function and stroke severity, but not ADLs, dexterity, spasticity or muscle strength.

Medications

4.3.22 Antidepressants and Upper Extremity Function

Beyond their ability to improve depression following stroke, antidepressants can be used to enhance upper extremity motor recovery through changes in neurotransmission. There is evidence suggesting that serotoninergic modulation may be involved in motor recovery post stroke. Previous research has suggested that patients who have reacted well to antidepressant treatment may also demonstrate improvements in upper limb motor functioning (Chemerinski et al. 2001).

Highlighted Study

Chollet F, Tardy J, Albucher JF, Thalamus C, Berard E, Lamy C, Bejot Y, Deltour S, Jaillard A, Niclot P, Guillon B. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomized placebo-controlled trial. The Lancet Neurology 2011; 10(2):123-130		
RCT (PEDro=9) N_{start}=118 N_{end}=113 TPS=Chronic	E: Fluoxetine (20mg) C: Placebo Duration: Ingested daily (orally) for 3mo	• Fugl Meyer Assessment (+exp) • National Institutes of Health Stroke Scale (-) • Modified Rankin Scale (+exp)

In a multicentre RCT assessing the effect of Fluoxetine on motor recovery compared to a placebo, Chollet et al. (2011) reported significantly greater improvement on the Fugl-Meyer Motor Scale (FMMS) and Modified Rankin Scale (mRS) among patients receiving Fluoxetine. A potential explanation for these results could be that the main function of the serotonergic system is to facilitate motor output which would allow for greater efficiency, especially when combined with physical training (Chollet et al. 2011).

Highlighted Study

Kim JS, Lee EJ, Chang DI, Park JH, Ahn SH, Cha JK, Heo JH, Sohn SI, Lee BC, Kim DE, Kim HY. Efficacy of early administration of escitalopram on depressive and emotional symptoms and neurological dysfunction after stroke: a multicentre, double-blind, randomised, placebo-controlled study. The Lancet Psychiatry. 2017; 4(1):33-41.		
RCT (PEDro= 9) N_{start}=478 N_{end}=338 TPS=Acute	E: Escitalopram (10mg, 14wks) C: Placebo Duration: 3mo	• Montgomery Asberg Depression Rating Scale (-) • Modified Rankin Scale (-) • Barthel Index (-) • Hemispheric Stroke Scale – Motor Function (-)

Highlighted Study

Dennis M, Mead G, Forbes J, Graham C, Hackett M, Hankey GJ, House A, Lewis S, Lundström E, Sandercock P, Innes K. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. The Lancet. 2019 Jan 19;393(10168):265-74.		
RCT (PEDro= 10) N_{start}=3127 N_{end}=2703 TPS=Acute	E: Fluoxetine (20mg/d) C: Placebo Duration: 6mo	• Modified Rankin Scale (-) • Mental Health Inventory – 5 (+exp) • Stroke Impact Scale (-) • EuroQOL5d (-)

Antidepressants Levels of Evidence

Intervention	Motor Function	Dexterity	ADLs	Stroke Severity	Muscle Strength
Antidepressants	1a 3 RCTs	1a 2 RCTs	1b 1 RCT	1a 3 RCTs	1a 2 RCTs

Conclusions

Antidepressants may help improve impaired upper extremity motor function following a stroke, although more recent data is calling this into question.

4.3.23 Peptides

Cerebrolysin contains low molecular weight neuropeptides and free amino acids which are believed to have neuroprotective properties and to reduce excitotoxicity, inhibit free radical formation, reduce neuroinflammation, and activate calpain apoptosis (Muresanu et al. 2016).

Muresanu DF, Heiss WD, Hoemberg V, Bajenaru O, Popescu CD, Vester JC, Rahlfs VW, Doppler E, Meier D, Moessler H, Guekht A. Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial. Stroke 2016: 47(1):151-159.		
RCT (9) N_{start}=208 N_{end}=196 TPS=Acute	E: Cerebrolysin (30mL diluted with 70mL saline) + physical/occupational therapy C: Placebo + physical/occupational therapy Duration: 1x/d for 3wk	• Fugl-Meyer Assessment (+exp)

Chang WH, Park CH, Kim DY, Shin YI, Ko MH, Lee A, Jang SY, Kim YH. Cerebrolysin combined with rehabilitation promotes motor recovery in patients with severe motor impairment after stroke. BMC Neurol 2016; 16:31.		
RCT (6) N_{start}=70 N_{end}=66 TPS=Acute	E: Cerebrolysin (30mL diluted with 70mL saline) + conventional therapy C: Placebo + conventional therapy Duration: 1x/d for 6wk	• Action Research Arm Test (+exp) • National Institute of Health Stroke Scale (+exp) • Barthel Index (+exp) • Modified Rankin Scale (+exp)

Cerebrolysin Levels of Evidence

Intervention	Motor Function	ADLs	Stroke Severity
Cerebrolysin	**1a 2 RCTs**	**1b 1 RCT**	**1b 1 RCT**

Conclusions
Cerebrolysin may improve upper limb motor function, dexterity, and measures of independence/daily living.

4.4 Management of Spasticity

Treatment of Spasticity in the Upper Extremity Post Stroke

Spasticity is classically defined as a velocity dependent increase of tonic stretch reflexes (muscle tone) with exaggerated tendon jerks. Spasticity can be painful, interfere with functional recovery in the upper extremity and hinder rehabilitation efforts. However, Gallichio (2004) cautioned that a reduction in spasticity does not necessarily lead to improvements in function. Van Kuijk et al. (2002) noted that for most stroke patients, *"…spasticity is a variable phenomenon in time and apparent in only certain muscle groups, and therefore, low threshold and "reversible" focal treatment techniques seem to be the preferable first option"*.

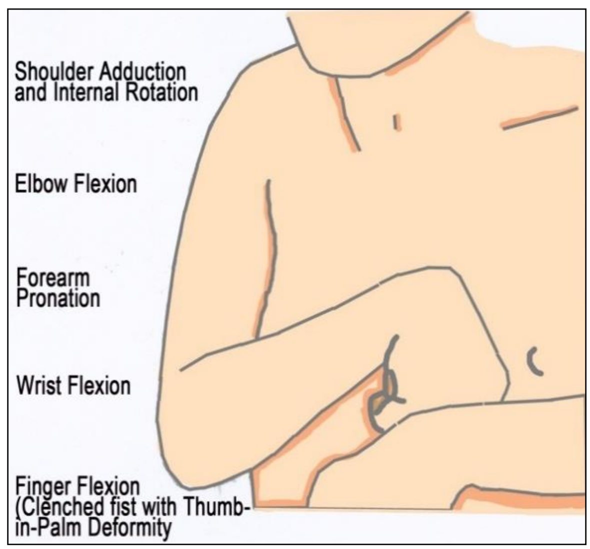
4.4.1 Botulinum Toxin in the Hemiplegic Upper Extremity

Botulinum toxin works by weakening spastic muscles through blocking the release of acetylcholine at the neuromuscular junction. The benefits of botulinum toxin injections are generally dose-dependent and last approximately 2 to 4 months (Brashear et al. 2002; Francisco et al. 2002; Simpson et al. 1996; Smith et al. 2000). One of the advantages of botulinum toxin is that it is safe to use on small, localized areas or muscles, such as those in the upper extremity.

- Botulinum toxin- has been shown to reduce spasticity in the upper extremity.
- However, botulinum toxin has not been shown to necessarily improve function likely because underlying weakness more than spasticity results in the limitation of function.
- Modest improvements in the dressing, grooming and eating on the Barthel Index score have been reported following botulinum toxin injections.

Common Indications for Use of Botulinum Toxin in the Spastic Upper Extremity

- **Adducted/internally rotated shoulder** (subscapularis/pectoralis major) to improve on adduction and internally rotated shoulder tightness/contracture and pain.
- **Flexed elbow** (brachioradialis/biceps/brachialis) to make ADLs and hygiene easier as well as improve cosmesis.
- **Pronated forearm** (pronator quadratus/pronator teres) to improve hand orientation.
- **Flexed wrist** (flexor carpi radialis/brevis/ulnaris/extrinsic finger flexors) to improve ADLs and reduce pain.
- **Clenched fist** (flexor digitorum profundus/sublimis) to improve hygiene.
- **Thumb in palm deformity** (adductor pollicis/flexor pollicis longus/thenar group) to improve thumb for key grasp.



Cardoso et al. (2005) conducted a meta-analysis investigating BTX-A as a treatment for upper limb spasticity following stroke. They included five RCTs (Bakheit et al. 2001; Bakheit et al. 2000; Brashear et al. 2002; Simpson et al. 1996; Smith et al. 2000) and reported that there was a significantly greater reduction in spasticity for patients who underwent BTX-A treatment compared to patients receiving the placebo treatment, as measured by the modified Ashworth Scale and the Global Assessment Scale. The authors concluded that BTX-A reduces spasticity and that the treatment was tolerated well, although the effects of long-term use of BTX-A are unknown.

Highlighted Study

Kaji R, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M. Botulinum toxin type A in post-stroke upper limb spasticity. Curr Med Res Opin 2010; 26(8):1983-1992.		
RCT (9) N_{start}=109 N_{end}=109 TPS=Chronic	E1: 120 U Botox (BoNTA) C1: Placebo E2: 200 U Botox (BoNTA) C2: Placebo	E2 vs C2 • Modified Ashworth Scale (+exp_2) • Disability Assessment Scale (+exp_2) E1 vs C1 • Modified Ashworth Scale (-) • Disability Assessment Scale (+exp_1)

Highlighted Study

Shaw L, Price C, van Wijck, F, Shackley P, Steen N, Barnes M, Ford G, Graham L, Rodgers H. Botulinum Toxin for the Upper Limb after Stroke (BoTULS) Trial: effect on impairment, activity limitation, and pain. Stroke 2011; 42(5):1371-1379.		
RCT (8) N_{start}=333 N_{end}=329	E: 100-200 U Dysport + 4 weeks therapy C: Therapy only	• Action Research Arm Test (-) • Modified Ashworth Scale (+exp) • 9-Hole Peg Test (-) • Barthel Index (-)

Highlighted Study

Elovic E, Munin M, Kanovsky P, Hanschmann A, Hiersemenzel R, Marciniak C. Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke spasticity. Muscle Nerve 2016;53(3):415-421.		
RCT (6) N_{Start}=317 N_{End}=299 TPS=Chronic	E: 400U incobotulinumtoxinA C: Placebo	• Ashworth Scale (+exp) • Disability Assessment Scale (+exp)

Highlighted Study

Brashear A, Gordon MF, Elovic E et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. N Engl J Med 2002; 347(6):395-400.		
RCT (7) N_{start}=126 N_{end}=122 TPS=Chronic	E: Botulinum toxin A (50 U) C: Placebo	• Disability Assessment Scale (+exp) • Ashworth Scale (+exp)

Highlighted Study

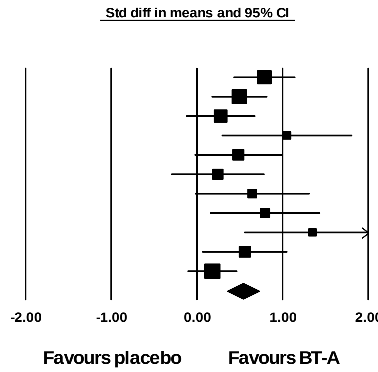
Brashear A, McAfee AL, Kuhn ER, Fyffe J. Botulinum toxin type B in upper-limb post-stroke spasticity: a double-blind, placebo-controlled study. Arch Phys Med Rehabil 2004; 85:705-709.		
RCT (7) N_{start}=15 N_{end}=15 TPS=Chronic	E: 10000 U of BTX-B C: Placebo	• Modified Ashworth Scale (-)

Highlighted Review

Foley N, Pereira S, Salter K, Murie-Fernandez M, Speechley M, Meyer M, Sequeira K, Miller T, Teasell R. Treatment with botulinum toxin improves upper extremity function post stroke? A systematic review and meta-analysis. Archives of Physical Medicine and Rehabilitation 2013; 94(5):977-989.

Methods
Four databases (MEDLINE, EMBASE, Scopus, and ISI Web of Science) were searched to find studies that met the following criteria: (1) the study design was a randomized controlled trial comparing injection of BTX-A with placebo or a nonpharmacologic treatment condition; (2) at least 60% of the sample was composed of adult subjects recovering from either first or subsequent stroke; (3) subjects presented with moderate to severe upper-extremity spasticity of the wrist, finger, or shoulder; and (4) activity was assessed as an outcome. Data pertaining to participant characteristics, treatment contrasts, and outcomes assessing activity limitations were extracted from each trial.
Results
16 RCTs were identified, 10 of which reported sufficient data for inclusion in the pooled analysis (n=1000). Overall BTX-A was associated with a moderate treatment effect (standardized mean difference =.564±.094, 95% confidence interval = .352-.721, P<.0001).

Study name	Outcome	Time point	Statistics for each study				
			Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Brashear 2002	DAS	6 weeks	0.788	0.185	0.426	1.151	0.000
Kanovsky 2009	DAS	2 weeks	0.496	0.167	0.169	0.823	0.003
McCrory 2009	MMAS	8 weeks	0.278	0.207	-0.127	0.683	0.179
Suputtitada 2005	ARAT	8 weeks	1.051	0.390	0.288	1.814	0.007
Guo 2006	BI	4 weeks	0.485	0.262	-0.029	0.998	0.064
Jahangir 2007	BI	4 weeks	0.245	0.279	-0.301	0.791	0.380
Meythaler 2009	MAL	12 weeks	0.647	0.342	-0.023	1.317	0.058
Bhakta 2000	Disability Scale	6 weeks	0.797	0.329	0.153	1.441	0.015
Kahi 2010 (low)	DAS	8 weeks	1.350	0.409	0.549	2.151	0.001
Kaji 2010 (high)	DAS	8 weeks	0.560	0.254	0.061	1.058	0.028
Shaw 2011	ARAT	6 weeks	0.181	0.149	-0.111	0.473	0.225
			0.536	0.094	0.352	0.721	0.000



This meta-analysis showed a moderate treatment effect for botulinum toxin A for function.

Botulinum Toxin Levels of Evidence

Intervention	Motor Function	Dexterity	Activities of Daily Living	Spasticity	ROM	Muscle Strength
Botulinum Toxin A	1a 8 RCTs	1a 2 RCTs	1a 10 RCTs	1a 18 RCTs	1a 4 RCTs	1b 1 RCT
Botulinum Toxin B			1b 1 RCT	1a 2 RCTs		

Conclusions
Botulinum A likely improves spasticity in the upper limb following stroke, but not range of motion or activities of daily living. The effect on general upper limb motor function is conflicting and less clear.
Botulinum toxin A in combination with other types of therapeutic approaches may be beneficial for certain aspects of upper limb function.
Botulinum toxin B has been less well studied to date in comparison to botulinum toxin A.

4.5 Hemiplegic Shoulder Pain

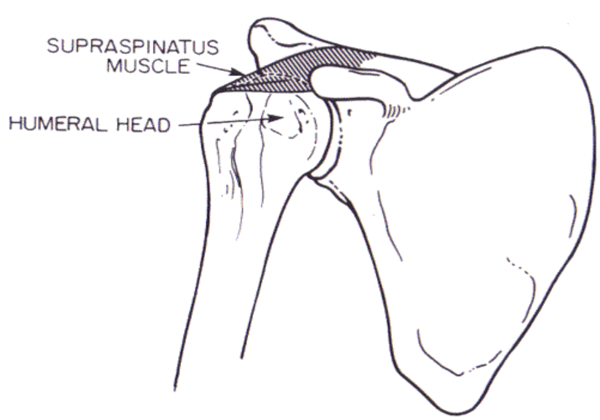
Shoulder pain resulting from hemiplegia is a common clinical consequence of stroke and can result in significant disability (Najenson et al., 1971; Poduri, 1993). The pathogenesis of hemiplegic shoulder pain (HSP) is multifactorial and includes neurologic and mechanical factors, often in combination, which vary among individuals post stroke.

4.5.1 Glenohumural Subluxation

Factors most frequently associated with HSP are glenohumeral subluxation (Grossens-Sills & Schenkman, 1985; Moskowitz et al., 1969; Savage & Robertson, 1982; Shai et al., 1984), adhesive capsulitis, (Bloch & Bayer, 1978; Braun et al., 1971; Fugl-Meyer et al., 1974; Grossens-Sills & Schenkman, 1985; Hakuno et al., 1984; Rizk et al., 1984) and spasticity, particularly of the subscapularis and pectoralis muscles (Caldwell et al., 1969; Moskowitz, 1969; Moskowitz et al., 1969). Suggested causes of HSP include complex regional pain syndrome (CRPS) (Chu et al., 1981; Davis et al., 1977; Perrigot et al., 1975), or injury to the rotator cuff musculotendinous unit (Najenson et al., 1971; Nepomuceno & Miller, 1974). The role of central post-stroke pain in the etiology of shoulder pain is unclear (Walsh, 2001).

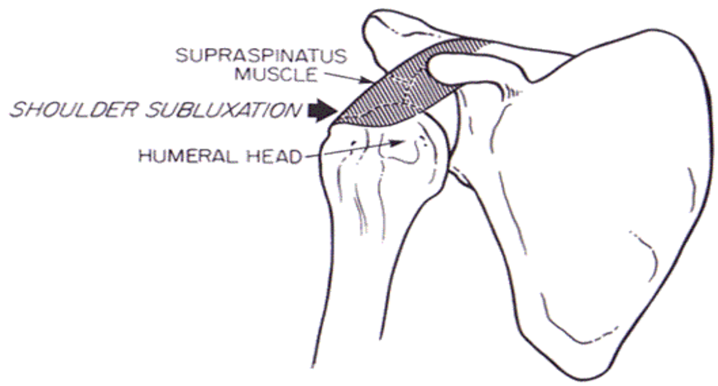
Pathophysiology

Shoulder subluxation is best defined as changes in the mechanical integrity of the glenohumeral joint that results in an incomplete dislocation, where articulating surfaces of the glenoid fossa and humeral head remain in contact. To achieve this mobility, the glenohumeral joint must sacrifice stability. Stability is achieved through the rotator cuff, a musculotendinous sleeve that maintains the humeral head in the glenoid fossa, while at the same time allowing shoulder mobility. During the initial period following a stroke the hemiplegic arm is flaccid or hypotonic. Therefore, the shoulder musculature, in particular the rotator cuff musculotendinous sleeve, cannot perform its function of maintaining the humeral head in the glenoid fossa and there is a high risk of shoulder subluxation.



Normal Shoulder

The humeral head is maintained in the glenoid fossa by the supraspinatus muscle.



Shoulder Subluxation

The supraspinatus muscle is flaccid during the initial phase of hemiplegia. The weight of the unsupported arm can cause the humeral head to sublux downward in the glenoid fossa.

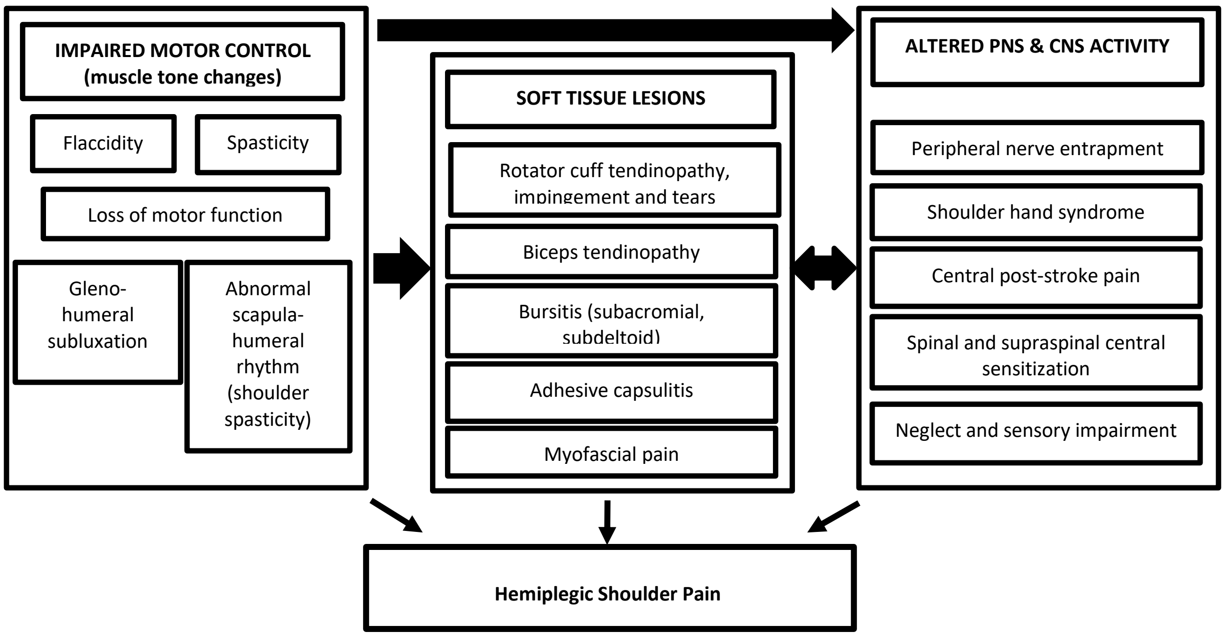
Shoulder subluxation is a common problem in individuals with hemiplegia post stroke. During the initial flaccid stage of hemiplegia, the involved extremity must be adequately supported or the weight of the arm will result in shoulder subluxation. Improper positioning in bed, lack of support in the upright position, and pulling on the hemiplegic arm during transfers all contribute to glenohumeral subluxation. Inferior subluxation commonly occurs secondary to prolonged downward pull on the arm, against which hypotonic muscles offer little resistance (Chaco & Wolf, 1971). It has long been assumed that if shoulder subluxation is not corrected, a pattern of traction on the flaccid shoulder will result in pain, decreased range of motion, and contracture. Patients with shoulder subluxation may not have HSP and patients with HSP may not have shoulder subluxation. The failure to consistently report an association may be due in part to a failure to examine the contribution of other probable etiological factors occurring concurrently.

Conclusion
The association between shoulder subluxation and hemiplegic shoulder pain is unclear.

4.5.2 Spasticity and Contractures

The relationship between spasticity and HSP has been explored in several observational studies. In an early study, van Ouwenaller et al. (1986) identified spasticity as "*the prime factor and the one most frequently encountered in the genesis of shoulder pain in the hemiplegic patient*." In patients followed for one year after stroke, the authors identified a much higher incidence of shoulder pain in spastic (85%) than in flaccid (18%) hemiplegia. Poulin de Courval et al. (1990) similarly reported that subjects with shoulder pain had significantly more spasticity of the affected limb than those without pain.

The internal rotators of the shoulder predominate but are one of the last areas of shoulder function to recover. Motor units are not appropriately recruited during recovery, yielding the simultaneous co-contraction of agonist and antagonist muscles. A shortened agonist in the synergy pattern becomes stronger and the constant tension of the agonist can become painful; stretching of these tightened spastic muscles causes more pain. Tightened muscles inhibit movement, reduce range of motion, and prevent other movements, especially at the shoulder where external rotation of the humerus is necessary for arm abduction greater than 90°. Muscles that contribute to spastic internal rotation/adduction of the shoulder include the subscapularis, pectoralis major, teres major, and latissimus dorsi. However, two muscles in particular have been implicated as most often being spastic leading to muscle imbalance: (1) subscapularis and (2) pectoralis major.



Conclusions

Hemiplegic shoulder pain may be associated with spastic muscle imbalance and contracted shoulder. There is high variability in the reported frequency of hemiplegic shoulder pain. Sustained positioning and static stretching of the hemiplegic shoulder may not be effective in reducing pain or improving motor function.

Active therapies for the hemiplegic shoulder may be effective in reducing pain, increasing range of motion, and improving motor function.

While a wide variety of options are available, it is unclear which is the most effective.

4.5.3 Electrical Stimulation in Hemiplegic Shoulder Pain

A recent meta-analysis examined 10 RCTs to determine the effect of NMES on shoulder subluxation and pain in both "early" (<6 months) and "late" (>6 months) stroke patients (Vafadar et al., 2015). Analyses revealed that conventional therapy with NMES was more effective than conventional therapy alone at preventing/reducing shoulder subluxation, although its effectiveness was not significant in the "late" subgroup.

Highlighted Study

Church C, Price C, Pandyan AD, Huntley S, Curless R, Rodgers H. Randomized controlled trial to evaluate the effect of surface neuromuscular electrical stimulation to the shoulder after acute stroke. Stroke 2006; 37(12):29995-3001.

RCT (9) N=176	E: sNMES C: Sham sNMES	• Action Research Arm Test (-) • Motricity Index: C (+) • Frenchay Arm Test: C (+) • Pain (-)

Conclusions
Surface neuromuscular electrical stimulation may be effective in reducing subluxation and improving range of motion in the hemiplegic shoulder, although its effectiveness may be negatively correlated with stroke onset.
Intramuscular neuromuscular electrical stimulation may be effective in reducing hemiplegic shoulder pain, although its effectiveness may be negatively correlated with stroke onset.
Transcutaneous electrical nerve stimulation may be effective in improving range of motion in the hemiplegic shoulder, although it may only be effective at higher intensity.
Functional electrical stimulation may be effective in reducing subluxation and improving motor function in the hemiplegic shoulder.

4.5.4 Botulinum Toxin Injections for the Hemiplegic Shoulder

Subscapularis spasticity is characterized by shoulder ROM being most limited by pain on external rotation, causing a spastic muscle imbalance around the shoulder in many cases. Pectoralis muscle spasticity, characterized by limitation of ROM on shoulder abduction, is seen to a lesser extent but causes a similar muscle imbalance. Intra-articular injections of botulinum toxin and other agents have been used in an effort to treat spastic muscles, reduce imbalance, and relieve HSP.

A Cochrane review by Singh and Fitzgerald (2010) examined five RCTs evaluating the efficacy of botulinum toxin for treating post-stroke shoulder pain. The authors determined that treatment was associated with reductions in pain at three and six months following injection, but not at one month.

Conclusion
Botulinum toxin may be effective in reducing pain and improving range of motion in the hemiplegic shoulder, but only when delivered in higher doses.

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