Constraint-Induced Therapy

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers constraint-induced movement therapy (CIMT) medically necessary for the treatment upper limb hemiparesis in persons with stroke who have at least 10 degrees of active wrist and finger extension, and who have no sensory and cognitive deficits.

Aetna considers CIMT experimental and investigational for the treatment of motor disorders caused by the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established.

- Cerebral palsy
- Congenital hemiplegia
- Hemiplegia from brain tumors
- Multiple sclerosis
- Parkinson's disease
- Spinal cord injury
- Traumatic brain injury

Aetna considers CIMT in combination with peripheral nerve stimulation for the treatment of hemiparesis following stroke experimental and investigational because the effectiveness of this approach has not been established.
Aetna considers CIMT in combination with transcranial direct current stimulation for the treatment of congenital hemiparesis/chronic stroke experimental and investigational because the effectiveness of this approach has not been established.

Aetna considers CIMT in combination with transcranial magnetic stimulation for the treatment of congenital hemiparesis experimental and investigational because the effectiveness of this approach has not been established.

Aetna considers CIMT in combination with biofeedback (e.g., auditory or visual) for the treatment of hemiparesis following stroke experimental and investigational because the effectiveness of this approach has not been established.

Aetna considers constraint-induced aphasia/language therapy, alone or in combination with transcranial magnetic stimulation, experimental and investigational for the treatment of post-stroke aphasia or other indications because its effectiveness has not been established.

**Background**

Constraint-induced movement therapy (CIMT), also known as forced use movement therapy, is a therapeutic approach to rehabilitation of movement after stroke. It has purportedly been demonstrated to improve motor function in patients following cerebro-vascular accident (CVA). The intensity and schedule of delivery of CIMT is different from that of traditional physical rehabilitation approaches. Constraint-induced movement therapy entails a family of rehabilitation techniques with an underlying goal of inducing individuals with stroke to markedly increase the use of a more-affected upper extremity (UE) for many hours a day over a period of 2 to 3 weeks. The principal therapy involves constraining movements of the less-affected arm with a sling for 90% of waking hours for the duration of therapy, while intensively training use of the more-affected arm.

Constraint-induced movement therapy has been employed for patients with chronic and sub-acute CVA, chronic traumatic brain injury, incomplete spinal cord injury, cerebral palsy, fractured hip, phantom limb pain, as well as musicians with focal hand dystonia. Although the improvement in motor function produced by CIMT in chronic stroke patients has been postulated to be associated with a shift in laterality of motor cortical activation toward the undamaged hemisphere, the exact mechanisms supporting rehabilitation-induced motor recovery are unclear.
In a randomized study \((n = 66)\), van der Lee et al (1999) reported a small improvement in motor impairment in patients with chronic hemiparesis treated with CIMT. In another randomized study \((n = 20)\), Dromerick et al (2000) found that CIMT resulted in a marked improvement in motor impairment.

Pierce et al (2004) examined the effectiveness of a program of traditional outpatient neurological rehabilitation that included home forced use. In total, 17 patients with chronic stroke and 1 patient with sub-acute stroke \((\text{mean time post-stroke} = 27.6 \text{ months})\) completed an individualized program consisting of seven 2-hour treatment sessions composed of 1 hour of occupational therapy and 1 hour of physical therapy. Therapy sessions were completed over a 2- to 3-week period and included instruction on the use of a restraining mitt at home during functional activities. The authors stated that the preliminary results suggested that the forced-use component of CIMT may be effective when applied within a traditional outpatient rehabilitation program.

In an observer-blinded randomized control trial \((n = 69)\), Suputtitada et al (2004) reported that CIMT of unaffected upper extremities has an advantage over conservative treatment for chronic stroke patients. The CIMT group received 6 hours of daily affected-upper-extremity training and restrained unaffected upper extremities for 5 days per week, totally 2 weeks. The control group received bimanual-upper-extremity training by conservative neuro-developmental technique without restrained unaffected upper extremities for 2 weeks. These authors concluded that CIMT may be an effective technique of improving motor activity and exhibiting learned non-use.

In a single-blinded randomized controlled trial, Page et al (2004) determined the effectiveness of a modified CIMT protocol for patients with chronic stroke. A total of 17 patients who experienced stroke more than 1 year before study entry and who had upper-limb hemiparesis and learned non-use enrolled in this study. Seven patients participated in structured therapy sessions emphasizing more affected arm use in valued activities, 3 times a week for 10 weeks. Their less affected arms were also restrained 5 days/week for 5 hours (modified CIMT). Four patients received regular therapy with similar contact time to modified CIMT. Six patients received no therapy (control). These investigators concluded that modified CIMT may be an effective method of improving function and use of the more affected arms of chronic stroke patients.

The findings of Suputtitada et al (2004) and Page et al (2004) are in agreement with the observations of Van Peppen et al (2004) and Yen et al (2005). Van Peppen and colleagues noted that there is strong evidence for therapies that are focused on functional training of the upper limb such as CIMT in improving functional outcomes after stroke; while Yen and associates reported that modified CIMT is useful in improving the function of the affected upper...
extremity in stroke patients (n = 30). Subjects in the modified CIMT group received a 2-week course of modified CIMT that entailed massed training of the affected arm without any physical restriction of the intact one.

Stein (2004) stated that younger stroke patients appear to have a greater ability to recover from stroke and are likely to benefit substantially from treatments that facilitate plasticity-mediated recovery. The use of new exercise treatments, such as CIMT, robot-aided rehabilitation, and partial body weight supported treadmill training are being studied intensively, and are likely to ultimately be incorporated into standard post-stroke rehabilitation.

Moreover, in a randomized controlled pilot study (n = 10), Page et al (2005) compared the effectiveness of modified CIMT to traditional rehabilitation in acute stroke patients exhibiting upper limb hemiparesis (less than 14 days post-stroke). Five patients were administered modified CIMT, consisting of structured therapy emphasizing more affected arm use in valued activities 3 days/week for 10 weeks and less affected arm restraint 5 days/week for 5 hours. Five other patients received half sessions of traditional motor rehabilitation for the affected arm, which included affected limb manual dexterity exercises and stretching, as well as compensatory strategies with the unaffected limb. The traditional rehabilitation regimens occurred 3 days/week for 10 weeks. These researchers concluded that modified CIMT is a promising regimen for improving more affected limb use and function in acute CVA. However, larger confirmatory studies need to be performed.

The Veterans Health Administration's clinical practice guideline for the management of stroke rehabilitation (2003) noted that the use of CIMT should be considered for a select group of patients, i.e., those with 20 degrees of wrist extension and 10 degrees of finger extension, who have no sensory and cognitive deficits.

Guidelines from the British Intercollegiate Stroke Working Party state that "[c]onstraint-induced therapy to increase the use of the affected arm should be considered in patients with at least 10 degrees of active wrist and finger extension, who are more than a year post-stroke and who can walk independently without an aid."

Ottawa Panel Guidelines (2006) state that "there is sufficient evidence to recommend the use of CIMT during the acute, subacute, or chronic phases of rehabilitation for improving dexterity, motor function, and functional status in stroke patients capable of some active finger and wrist extension."
Although CIMT has been demonstrated to provide a small positive effect on upper limb function in patients who require upper limb training for hemiplegia following stroke, a systematic evidence review (Lannin et al, 2005) has questioned the statistical and clinical significance of this effect. The systematic evidence review also notes that existing studies have only compared the effectiveness of CIMT to compensatory or bimanual training techniques, and not to techniques designed to practice re-training isolated active movement in the hemiplegic arm.

In a systematic review of randomized controlled trials on CIMT following stroke, Hakkennes and Keating (2005) stated that results indicate that CIMT may improve upper limb function following stroke for some patients when compared to alternative or no treatment. The authors stated that rigorous evaluation of CIMT using well-designed and adequately powered trials is required to evaluate the efficacy of different protocols on different stroke populations and to assess impact on quality of life, cost and patient/care-giver satisfaction.

Constraint-induced movement therapy is being investigated for use in other conditions, including cerebral palsy (CP).

In a randomized, controlled study, Taub et al (2004) evaluated the applicability of CIMT to young children with CP (n = 18, aged 7 to 96 months). Patients were randomly assigned to receive either pediatric CIMT or conventional treatment. Pediatric CIMT involved promoting increased use of the more-affected arm and hand by intensive training (using shaping) of the more-impaired upper extremity for 6 hours/day for 21 consecutive days coupled with bi-valved casting of the child’s less-affected upper extremity for that period. Patients were followed for 6 months. The authors found that pediatric CIMT produced major and sustained improvement in motoric function in the young children with hemiparesis. The results of this trial are promising, but its finding needs to be validated by studies with larger sample size and longer follow-up to ensure that gains that might occur persist for over 2 years as proposed by Weinstein et al (2003).

In a review of CIMT and forced use in children with hemiplegia, Charles and Gordon (2005) stated that while both forced use and CIMT appear to be promising for improving hand function in children with hemiplegia, the data are limited. Substantially more work must be performed before this approach can be advocated for general clinical use.

In an open-label, pilot study (n = 6), Tuite and colleagues (2005) reported that CIMT did not produce any substantial or consistent kinematic improvements in the affected limb of patients with Parkinson’s disease (Hoehn and Yahr stage II to III).
In a pilot study (n = 9), Naylor and Bower (2005) assessed the effectiveness of modified CIMT in young children with hemiplegia. Assessment was at entry to the study and subsequently at 4-weekly intervals. A 4-week baseline period with no hand treatment, controlling for maturation, was followed by a 4-week treatment period and a second 4-week period with no hand treatment to measure carry-over. Treatment consisted of twice-weekly 1-hour sessions of structured activities with a therapist and a home program for non-treatment days. Only verbal instruction and gentle restraint of the unaffected arm were used to encourage use of the affected arm. Patients (6 males, 3 females; median age of 31 months, range of 21 to 61 months) presenting with congenital spastic hemiplegia (5 right side, 4 left side) were involved in the study. Changes in hand function were evaluated with the Quality of Upper Extremity Skills Test. Improvement was seen throughout the study with statistical significance, using the Wilcoxon signed rank test, of 0.01 immediately after treatment. Results of this pilot study suggested that this modification of CIMT may be an effective way of treating young children with hemiplegia. The authors noted that future work is planned to consolidate and develop these results.

In a single-blinded, randomized, controlled study (n = 22), Charles and colleagues (2006) examined the effectiveness of CIMT, modified to be child-friendly, in children with hemiplegic CP. Patients (8 females, 14 males; mean age of 6 years and 8 months; range of 4 to 8 years) were randomized to either an intervention group (n = 11) or a delayed treatment control group (n = 11). Children wore a sling on their non-involved upper limb for 6 hours per day for 10 out of 12 consecutive days and were engaged in play and functional activities. Children in the treatment group demonstrated improved movement efficiency and dexterity of the involved upper extremity, which were sustained through the 6-month evaluation period, as measured by the Jebsen-Taylor Test of Hand Function and fine motor-subtests of the Bruininks-Oseretsky Test of Motor Proficiency (p < 0.05 in both cases). Initial severity of hand impairment and testing compliance were strong predictors of improvement. Care-givers reported significant increases in involved limb frequency of use and quality of movement. However, there was no change in strength, sensibility, or muscle tone (p > 0.05 in all cases). Results of this study suggested that for a carefully selected subgroup of children with hemiplegic CP, CIMT modified to be child-friendly, appears to be effective in improving movement efficiency of the involved upper extremity.

It is interesting to note that the children in the control group who subsequently received CIMT did not improve after the intervention. There was no difference between the pre-test and 6-month follow-up scores for this group before cross-over, thus, a ceiling effect is unlikely. The authors stated that overall CIMT improved involved arm and hand function in a select group of children with hemiplegic CP. However, this intervention may not be advisable for all children with hemiplegia. The child’s age and severity of hand function need to be considered. Determining if forced-use is more appropriate for some ages and CIMT more appropriate for others, as well as determining the optimal dose response and potential adverse effects, is also important.
In a Cochrane review on the use of CIMT in the treatment of the upper limb in children with hemiplegic CP, Hoare et al (2007) found a significant treatment effect using modified CIMT in a single trial. A positive trend favoring CIMT and forced-use was also demonstrated. The authors concluded that given the limited evidence, the use of CIMT, modified CIMT and forced-use should be considered experimental in children with hemiplegic CP. They noted that further research using adequately powered randomized controlled trials, rigorous methodology and valid and reliable outcome measures is essential to provide higher level support of the effectiveness of CIMT for children with hemiplegic CP.

A systematic evidence review by Huang and colleagues (2009) concluded that evidence demonstrated an increased frequency of use of the upper extremity following CIMT for children with hemiplegic CP. The author found, however, that the critical threshold for intensity that constituted an adequate dose could not be determined from the available research. A total of 21 studies were included in the review (n = 168, range of 1 to 41): 5 randomized controlled trials (RCTs; n = 114); 2 pretest post-test design with control group (n = 16); 3 1-group pretest post-test designs (n = 27); 3 single-subject studies (n = 11); and 8 case report designs (n = 11). The RCTs and pretest post-test study designs had validity scores between 7 and 11 out of 16. The 2 1-group designs that were assessed had scores of 5 and 7 out of 11. Study duration ranged from 1 week to 18 months. Four studies allowed computation of effect size and 1 additional study provided effect size (eta values) within the paper. One of these studies reported 5 outcome measures at the body functions and structure level of which one (Modified Ashworth Scale – shoulder) was statistically significant (p < 0.05). These 5 studies reported a total of 14 different activity level outcomes of which 5 were statistically significant (p < 0.05): Caregiver Functional Use Survey -- How frequently (1 study); Assisting Hand Assessment (one study); Emerging Behaviour Scale (1 study); Pediatric Motor Activity Log – Amount of use (1 study); and WeeFIM Self-Care (1 study). All significant effect size values were medium to large (d = 0.6 to 1.16). The other 16 studies reported positive outcomes in fine motor and functional activities post treatment and up to 12 months follow-up. A critique of this systematic evidence review by the Centre for Reviews and Dissemination (2010) noted that the primary study sizes were small and the conclusions of this systematic evidence review were based on a small number of good-quality studies. The CRD critique concluded: "Given the uncertainties around the review methodologies used, potential that relevant studies were missed and paucity and variability in the evidence presented, the authors conclusions are unlikely to be reliable."

Mark and colleagues (2008) examined if CIMT may benefit chronic upper extremity hemiparesis in progressive multiple sclerosis (MS). A total of 5 patients with progressive MS, who had chronic upper extremity hemiparesis and evidence for learned non-use of the paretic limb in the life situation, underwent 30 hours of repetitive task training and shaping for the paretic limb over 2 to 10 consecutive weeks, along with physical restraint of the less-affected arm and a "transfer
package" of behavioral techniques to reinforce treatment adherence. Subjects showed significantly improved spontaneous, real-world limb use at post-treatment and 4 weeks post-treatment, along with improved fatigue ratings and maximal movement ability displayed in a laboratory motor test. The authors concluded that these findings suggested for the first time that slowly progressive MS may benefit from CIMT. Moreover, they stated that further studies are needed to determine the retention of treatment responses.

Sakzewski and co-workers (2009) systematically reviewed the effectiveness of non-surgical upper-limb therapeutic interventions for children with congenital hemiplegia. The Cochrane Central Register of Controlled Trials, Medline, CINAHL, AMED, Embase, PsycINFO, and Web of Science were searched up to July 2008. Data sources were randomized or quasi-randomized trials and systematic reviews. A total of 12 studies and 7 systematic reviews met the selection criteria. Trials had strong methodological quality (Physiotherapy Evidence Database [PEDro] scale greater than or equal to 5), and systematic reviews rated strongly (AMSTAR [Assessment of Multiple Systematic Reviews] score greater than or equal to 6). Four interventions were identified: (i) intra-muscular botulinum toxin A (Botox) combined with upper-limb training; (ii) CIMT; (iii) hand-arm bi-manual intensive training; and (iv) neurodevelopmental therapy. Data were pooled for upper-limb, self-care, and individualized outcomes. There were small-to-medium treatment effects favoring intra-muscular Botox and occupational therapy, neurodevelopmental therapy and casting, CIMT, and hand-arm bi-manual intensive training on upper-limb outcomes. There were large treatment effects favoring intra-muscular Botox and upper-limb training for individualized outcomes. No studies reported participation outcomes. The authors concluded that no one treatment approach seems to be superior; however, Botox injections provide a supplementary benefit to a variety of upper-limb-training approaches. They stated that additional research is needed to justify more-intensive approaches such as CIMT and hand-arm bi-manual intensive training.

In a prospective, repeated-measures design study, Brunner and colleagues (2011) examined eligibility for modalities such as CIMT and modified CIMT (mCIMT) in the sub-acute phase after stroke and defined the share of patients who should be offered this treatment. A total of 100 consecutive patients with arm paresis 1 to 2 weeks post-stroke were screened. Eligible for CIMT were patients who were cognitively intact, medically stable, and able to extend the wrist and 3 fingers 10° as a lower limit. The active range of motion was registered, and motor function was assessed by the Action Research Arm Test (ARAT) and the Nine Hole Peg Test at 1 to 2 weeks, 4 weeks, and 3 months post stroke. From 100 patients, 54 were excluded from motor assessment, mostly due to cognitive impairments. Of the remaining 46 patients, 21 (46 %) were eligible according to motor function of the hand at 1 to 2 weeks post-stroke, whereas in the other patients motor function was either too good or too poor. The share of patients eligible declined
to 31% after 4 weeks and 15% after 3 months. Within 3 months, 60% reached reasonable dexterity, expressed by an ARAT score greater than or equal to 51, all receiving standard rehabilitation. The authors concluded that results indicate that eligibility for CIMT or mCIMT should not be considered before 4 weeks post-stroke because much improvement in arm function was shown to occur during the first month post-stroke with standard rehabilitation.

In a systematic review, Nijland et al (2011) stated that CIMT is a commonly used intervention to improve upper limb function after stroke. However, the effectiveness of CIMT and its optimal dosage during acute or sub-acute stroke is still under debate. To examine the literature on the effects of CIMT in acute or sub-acute stroke. A literature search was performed to identify RCTs; studies with the same outcome measure were pooled by calculating the mean difference. Separate quantitative analyses for high-intensity and low-intensity CIMT were applied when possible. Five RCTs were included, comprising 106 participants. The meta-analysis demonstrated significant mean differences in favor of CIMT for the Fugl-Meyer arm, the Action Research Arm Test, the Motor Activity Log, Quality of Movement and the Grooved Pegboard Test. Non-significant mean difference in favor of CIMT were found for the Motor Activity Log, Amount of Use. Separate analyses for high-intensity and low-intensity CIMT resulted in significant favorable mean differences for low-intensity CIMT for all outcome measures, in contrast to high-intensity CIMT. This meta-analysis demonstrated a trend toward positive effects of high-intensity and low-intensity CIMT in acute or sub-acute stroke, but also suggests that low-intensity CIMT may be more beneficial during this period than high-intensity CIMT. However, these results were based on a small number of studies. Therefore, they concluded that more trials are needed applying different doses of therapy early after stroke and a better understanding is needed about the different time windows in which underlying mechanisms of recovery operate.

Constraint-induced aphasia therapy (CIAT) is an intensive language training program. According to the American Stroke Association (2006), this short-term therapy takes the 3 principles of CIMT and applies them to speech therapy. In speech therapy, constraint means avoiding the use of compensatory strategies such as gesturing, drawing, writing, etc.; forced use means communicating by talking; and massed practice means 2 to 4 hours of speech therapy a day. Preliminary investigations suggested that these principles may be effective in aphasia rehabilitation, but research is still very early. Thus, CIAT is provided in a communicative environment constraining patients to practice systematically speech acts with which they have difficulty. It has been used in the treatment of chronic aphasia.

Szafarski and colleagues (2008) stated that CIAT offers potential benefits to individuals with history of aphasia-producing ischemic stroke. In a pilot study, these investigators implemented the original German CIAT protocol, refined the treatment program, and attempted to confirm its
effectiveness in patients with chronic aphasia. They translated and modified the original CIAT protocol to include a hierarchy of individual skill levels for semantic, syntactic, and phonological language production, while constraining non-use behaviors. A total of 3 male subjects with moderate-to-severe post-stroke aphasia received CIAT 3 to 4 hours/day for 5 consecutive days. Pre- and post-testing included formal language evaluation, linguistic analysis of story retell, and mini-Communication Activity Log (mini-CAL). Substantial improvements in comprehension and verbal skills were noted in 2 subjects with an increase in the total number of words (31 % and 95 %) and in number of utterances for story retell task (57 % and 75 %). All subjects reported an improvement on at least 1 linguistic measure. No subjective improvements on mini-CAL were noted by any of the subjects. The authors concluded that given that the duration of treatment was only 1 week, these linguistic improvements in post-stroke aphasia subjects were remarkable. The results indicated that the CIAT protocol used in this study may be a useful tool in language restoration following stroke. The authors stated that these preliminary findings should be confirmed in a larger, randomized study.

Cherney and associates (2008) summarized evidence for intensity of treatment and constraint-induced language therapy (CILT) on measures of language impairment and communication activity/participation in individuals with stroke-induced aphasia. A systematic search of the aphasia literature using 15 electronic databases (e.g., PubMed, CINAHL) identified 10 studies meeting inclusion/exclusion criteria. A review panel evaluated studies for methodological quality. Studies were characterized by research stage (i.e., discovery, efficacy, effectiveness, cost-benefit/public policy research), and effect sizes (ESs) were calculated wherever possible. In chronic aphasia, studies provided modest evidence for more intensive treatment and the positive effects of CILT. In acute aphasia, 1 study evaluated high-intensity treatment positively; no studies examined CILT. Four studies reported discovery research, with quality scores ranging from 3 to 6 of 8 possible markers. Five treatment efficacy studies had quality scores ranging from 5 to 7 of 9 possible markers. One study of treatment effectiveness received a score of 4 of 8 possible markers. The authors concluded that although modest evidence exists for more intensive treatment and CILT for individuals with stroke-induced aphasia, the results of this review should be considered preliminary.

Allen et al (2012) stated that aphasia effects up to 38 % of acute stroke patients. For many of these individuals, this condition persists far beyond the acute phase. These researchers evaluated the effectiveness of therapeutic interventions for aphasia initiated more than 6 months post stroke. A literature search was conducted for articles in which aphasia treatments were initiated more than 6 months post stroke. Searches were conducted in multiple databases including MEDLINE, Scopus, CINAHL, and EMBASE. A total of 21 RCTs met the inclusion criteria. There is good evidence to suggest that the use of computer-based treatments, constraint-induced therapy, intensity of therapy, group language therapies, and training
conversation/communication partners are effective treatments for chronic aphasia. Repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and the use of the drugs piracetam, donepezil, memantine, and galantamine have also demonstrated evidence that they are effective treatments of aphasia 6 months or more post-stroke onset. Neither filmed language instruction nor the drug bromocriptine has been shown to be effective in treating chronic aphasia. The authors concluded that there is evidence to support the use of a number of treatments for chronic aphasia post stroke. Moreover, they stated that further research is needed to fully support the use of these interventions and to explore the effectiveness of other aphasia interventions in the chronic stage.

Sterling et al (2013) noted that studies with adult stroke patients showed that structural neuroplastic changes are correlated with clinical improvements due to CIMT. In a pilot study, these researchers examined if comparable changes occur in children with CP receiving CIMT. A total of 10 children (6 boys) with congenital hemiparesis (mean age of 3 years, 3 months) underwent magnetic resonance imaging (MRI) scans 3 weeks before, immediately before, and immediately after receiving 3 weeks of CMT. Longitudinal voxel-based morphometry was performed on MRI scans to determine gray matter change. In addition, the Pediatric Motor Activity Log-Revised was administered at these time points to assess arm use in daily life before and after treatment. Children exhibited large improvements after CIMT in spontaneous use of the more-affected arm (p < 0.001, $d' = 3.24$). A significant increase in gray matter volume occurred in the sensorimotor cortex contralateral to the more-affected arm ($p = 0.04$); there was a trend for these changes to be correlated with motor improvement ($r = 0.63, p = 0.063$). Trends were also observed for increases in gray matter volume in the ipsilateral motor cortex ($p = 0.055$) and contralateral hippocampus ($p = 0.1$). No significant gray matter change was seen during the 3 weeks before treatment. These findings suggested that CIMT produces gray matter increases in the developing nervous system and provide additional evidence that CIMT is associated with structural remodeling of the human brain while producing motor improvement in patients with disabling central nervous system diseases.

Mark et al (2013) evaluated in a preliminary manner the feasibility, safety, and effectiveness of CIMT of persons with impaired lower extremity use from MS. A referred sample of ambulatory adults with chronic MS ($n = 4$) with at least moderate loss of lower extremity use (average item score of less than or equal to 6.5/10 on the functional performance measure of the Lower Extremity Motor Activity Log [LE-MAL]) were included in this study. Constraint-induced movement therapy was administered for 52.5 hours over 3 consecutive weeks (15 consecutive weekdays) to each patient. The primary outcome was the LE-MAL score at post-treatment. Secondary outcomes were post-treatment scores on laboratory assessments of maximal lower extremity movement ability. All the patients improved substantially at post-treatment on the LE-MAL, with smaller improvements on the laboratory motor measures. Scores on the LE-MAL
continued to improve for 6 months afterward. By 1 year, patients remained on average at post-treatment levels. At 4 years, 50% of the patients remained above pre-treatment levels. There were no adverse events, and fatigue ratings were not significantly changed by the end of treatment. The authors concluded that the findings of this initial trial of lower extremity CIMT for MS indicates that the treatment can be safely administered, is well-tolerated, and produces substantially improved real-world lower extremity use for as long as 4 years afterward. They stated that further trials are needed to determine the consistency of these findings.

In a randomized, single-blind, parallel-group study, Sickert et al (2014) examined the effectiveness of a modified CIAT schedule and included patients with sub-acute stroke. The results were compared to those of patients who received identically intensive treatment focusing on conventional aphasia therapy. A total of 50 patients were treated with the authors' modified version of CIAT and 50 received a standard aphasia therapy at the same intensity and duration. Inclusion criteria were clinical diagnosis of first-ever stroke, aphasia in the sub-acute stage and German speakers. Language function was evaluated using the Aachen Aphasia Test and the Communicative Activity Log directly before therapy onset, after the training period and at 8-week and 1-year follow-ups. Patients of both groups improved significantly in all sub-tests of the Aachen Aphasia Test Battery. The improvements remained stable over a 1-year follow-up period. Patients and relatives of both groups rated daily communication as significantly improved after therapy. The authors concluded that both CIAT and conventional therapy performed with equal intensity are effective methods for patients with sub-acute aphasia. The modified CIAT schedule is practical in an everyday therapeutic setting. They stated that these findings indicated that a short-term intensive therapy schedule in the early aphasia stage leads to substantial improvements in language functions.

In a pilot study, McConnell et al (2014) examined the acceptability and effectiveness of reduced intensity CIMT in children with CP. Children (9 to 11 years of age) with hemiplegia underwent 5 baseline assessments followed by 2 weeks CIMT; 6 further assessments were performed during treatment and follow-up phases. The primary outcome was the Melbourne Assessment of Unilateral Upper Limb Function (MUUL). Quantitative data were analyzed using standard single-subject methods and qualitative data by thematic analysis. Four of the 7 participants demonstrated statistically significant improvements in MUUL (3 to 11%, p < 0.05); 2 participants achieved significant improvements in active range of motion but strength and tone remained largely unchanged. Qualitative interviews highlighted limitations of the restraint, importance of family involvement, and coordination of treatment with education. The authors concluded that reduced intensity CIMT may be effective for some children in this population; however it is not suitable for all children with hemiplegia. The findings of this small (n = 7) pilot study need to be validated by well-designed studies.
On behalf of the European network for Health Technology Assessment (EUnetHTA), Eliasson et al (2014) provided an overview of what is known about CIMT in children with unilateral CP; identified current knowledge gaps, and provided suggestions for future research. A total of 9 experts participated in a consensus meeting. A comprehensive literature search was conducted and data were summarized before the meeting. The core model produced by the (EUnetHTA) was used as a framework for discussion and identified critical issues for future research. All models of CIMT have demonstrated improvements in the upper limb abilities of children with unilateral CP. A consensus was reached on 11 important questions to be further explored in future studies. The areas of highest priority included the effect of dosage, the effect of repeated CIMT, and the impact of predictive factors, such as age, on the response to CIMT. Consensus suggestions for future study designs and the use of validated outcome measures were also provided. The authors concluded that the CIMT construct is complex, and much remains unknown. It is unclear if a specific model of CIMT demonstrates superiority over others and whether dosage of training matters. Moreover, they stated that future research should build upon existing knowledge and aim to provide information that will help implement CIMT in various countries with different healthcare resources and organizational structures.

An UpToDate review on “Management and prognosis of cerebral palsy” (Miller, 2014) states that “Constraint-induced movement therapy (CIMT) -- For children with hemiplegic CP, CIMT promotes function of the affected limb by encouraging its use through intermittent restraint of the unaffected limb during therapeutic tasks. The method of restraint varies from holding a child's hand, to casting, and the length of time in the restraint varies from 1 to 24 hours a day. "Forced use" is a variation of CIMT in which the limb's use is encouraged only by placement of the contralateral restraint; no additional therapeutic tasks are assigned to the affected limb. Because the methods and outcomes used varied considerably among these trials, it is unclear which specific CIMT techniques are clinically useful”.

Johnson and colleagues (2014) stated that the initial version of CIAT I consisted of a single exercise. In a pilot study, these researchers evaluated the feasibility for future trials of an expanded and restructured protocol (CIAT II) designed to increase the effectiveness of CIAT I. The subjects were 4 native English speakers with chronic stroke who exhibited characteristics of moderate Broca’s aphasia. Treatment was carried out for 3.5 hours/day for 15 consecutive weekdays. It consisted of 3 components: (i) intensive training by a behavioral method termed shaping using a number of expressive language exercises in addition to the single original language card game, (ii) strong discouragement of attempts to use gesture or other non-verbal means of communication, and (iii) a transfer package of behavioral techniques to promote transfer of treatment gains from the laboratory to real-life situations. Participation in speech in the life situation improved significantly after treatment. The effect sizes (i.e., d’) in
this domain were greater than or equal to 2.2; $d'$ values greater than or equal to 0.8 are considered large. Improvement in language ability on a laboratory test, the Western Aphasia Battery-Revised did not achieve statistical significance, although the effect size was large -- that is, 1.3 (13.1 points). The authors concluded that the results of this pilot study suggested in preliminary fashion that CIAT II may produce significant improvements in everyday speech. The findings of this small ($n = 4$) pilot study need to be validated by well-designed studies.

Martin et al (2014) examined (i) the feasibility of administering a modified CILT (mCILT) treatment session immediately after transcranial magnetic stimulation (TMS); and (ii) if this combined therapy could improve naming and elicited propositional speech in chronic, non-fluent aphasia. Two chronic stroke patients with non-fluent aphasia (mild-moderate and severe) each received 20 minutes of repetitive TMS (rTMS) to suppress the right pars triangularis, followed immediately by 3 hours of mCILT (5 days/week for 2 weeks). Each patient had received TMS alone, 2 to 6 years prior. Language evaluations were performed pre- TMS+mCILT, and post- at 1 to 2 months, and 6 or 16 months. Both patients showed significant improvements in naming pictures, and elicited propositional speech at 1 to 2 months post- TMS+mCILT. The improved naming was still present at 6 months post- TMS+mCILT for patient 2; but not at 16 months post- TMS+mCILT for patient 1. The authors concluded that it is feasible to administer mCILT for 3 hours immediately after a TMS session. However, it is unknown if the significant improvements in naming pictures, and elicited propositional speech were associated with the second series of TMS, or this first series of mCILT, or a combination of both. They stated that a larger, sham-controlled clinical trial is needed.

Chen et al (2014) evaluated the research literature on the effectiveness of CIMT on improving arm function in children with CP, and assessed the association between the study effect size and the characteristics of the patients and intervention protocol. These researchers performed a systematic literature search in PubMed, PsycINFO, Cochrane, CINAHL, Web of Science, and TRIP Database up to May 2014. Studies employing RCT design, children with CP, comparing CIMT with another intervention with a focus on arm function, and upper-extremity measures were included in this review. Methodological quality was evaluated using the PEDro scale. The literature search resulted in 27 RCTs with good methodological quality that compared CIMT with other intervention therapy. Overall, CIMT provided a medium beneficial effect ($d = 0.546; p<0.001$) when compared with conventional therapy. For the subgroup analyses, presence of a dose-equivalent comparison group, intervention location, and time of follow-up were significant factors. Studies examining CIMT effect without a dose-equivalent comparison group showed a large effect in children with CP, but studies with a dose-equivalent group only showed a small effect. Children who received home-based CIMT had a better improvement in arm function than those who received CIMT elsewhere.
Sakzewski and colleagues (2014) reviewed the effectiveness of non-surgical upper limb therapies for children with unilateral CP. Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Embase, the Cochrane Central Register of Controlled Trials, and PubMed were searched to December 2012. Randomized controlled or comparison trials were included. A total of 42 studies evaluating 113 UL therapy approaches (n = 1,454 subjects) met the inclusion criteria. Moderate to strong effects favoring intramuscular injections of botulinum toxin A and occupational therapy (OT) to improve UL and individualized outcomes compared with OT alone were identified. Constraint-induced movement therapy achieved modest to strong treatment effects on improving movement quality and efficiency of the impaired UL compared with usual care. There were weak treatment effects for most outcomes when constraint therapy was compared with an equal dose (amount) of bi-manual OT; both yielded similar improved outcomes. Newer interventions such as action observation training and mirror therapy should be viewed as experimental. The authors concluded that there is modest evidence that intensive activity-based, goal-directed interventions (e.g., CIMT, bi-manual training) are more effective than standard care in improving UL and individualized outcomes. There is little evidence to support block therapy alone as the dose of intervention is unlikely to be sufficient to lead to sustained changes in UL outcomes. There is strong evidence that goal-directed OT home programs are effective and could supplement hands-on direct therapy to achieve increased dose of intervention. Moreover, these investigators noted that a number of potential limitations exist with the current evidence for upper limb interventions; generally, studies continued to report small sample sizes.

Leafblad and Van Heest (2015) presented research from the last 5 years on the pathophysiology and treatment of upper extremity sequelae of CP. The development of new treatments of CP-affected limbs, utilizing the brain's inherent neuroplasticity, remains an area of promising and active research. Functional MRI scans have evaluated the role of neuroplasticity in adapting to the initial central nervous system insult. Children with CP appear to have greater recruitment of the ipsilateral brain for motor and sensory functions of the affected upper limb. Studies have also shown that CIMT resulted in localized increase in gray matter volume of the sensori-motor cortex contralateral to the affected arm targeted during rehabilitation. The authors stated that recent therapy interventions have emphasized the role of home therapy programs, the transient effects of splinting, and the promise of CIMT and bi-manual hand training.

Eliasson and Holmefur (2015) noted that there is evidence that modified CIMT (mCIMT) has a short-term positive effect on hand function in children with unilateral CP, but the long-term effect is unknown. These researchers examined if a single block of mCIMT (2 hrs/day for 2 months) at age 2 to 3 years influences the course of development of bi-manual hand function at around 8 years of age. A convenience sample of 45 children (24 males and 21 females) with unilateral CP and mean (SD) age at first assessment 32 months (13 months) was included in this study. The
participants were divided into the mCIMT group (n = 26) and the reference group (no mCIMT; n = 19). Brain lesion characteristics were available for 32 children. The children were measured repeatedly with the Assisting Hand Assessment (AHA) for a mean period of 4 years and 6 months. Development curves were created and compared with a non-linear mixed effects model. Children who were receiving mCIMT had an upper limit of development of bi-manual hand function that was 8.5 AHA units higher than in the reference group (p = 0.022). However, when controlling for brain lesion characteristics and baseline in a subgroup of 32 children, the difference was considerably smaller and no longer significant. The authors concluded that mCIMT may have a positive impact on long-term development of bimanual hand function, but the results are inconclusive and further research is needed.

An UpToDate review on “Management and prognosis of cerebral palsy’ (Miller, 2015) states that “Constraint-induced movement therapy (CIMT) -- For children with hemiplegic CP, CIMT promotes function of the affected limb by encouraging its use through intermittent restraint of the unaffected limb during therapeutic tasks. The method of restraint varies from holding a child's hand, to casting, and the length of time in the restraint varies from 1 to 24 hours a day. "Forced use" is a variation of CIMT in which the limb's use is encouraged only by placement of the contralateral restraint; no additional therapeutic tasks are assigned to the affected limb. Because the methods and outcomes used varied considerably among these trials, it is unclear which specific CIMT techniques are clinically useful”.

Furthermore, the United Cerebral Palsy (2015) states that “Accumulating research reports have generally shown a favorable response to CIMT, although questions remain about what is the critical level of intensity of therapy necessary for a positive effect (how much? how frequently?). As with any new therapy, another important question is whether it is superior to what is already available and being implemented, perhaps at less expense”.

The Children’s Hemiplegia and Stroke Association (CHASA, 2015) states that “Impaired hand function is among the most functionally disabling symptoms of hemiplegia in children (also known as unilateral cerebral palsy). Evidence-based treatment approaches are generally lacking. However, recent approaches providing intensive upper extremity training appear promising. This review describes two such approaches, constraint-induced movement therapy (CIMT) and bimanual training (hand-arm bimanual intensive therapy, HABIT)”.

Also, Wikipedia (last updated April 21, 2015) notes that “Recently, the possible benefits of cortical reorganization has led to studies of CIMT on children because neuroplasticity is even greater among children than adults. Particular interest is growing in CIMT for children who have cerebral palsy where one arm is more affected than the other”.
Chorna and co-workers (2015) noted that CP is the most common physical disability in childhood. It is a disorder resulting from sensory and motor impairments due to perinatal brain injury, with lifetime consequences that range from poor adaptive and social function to communication and emotional disturbances. Infants with CP have a fundamental disadvantage in recovering motor function: they do not receive accurate sensory feedback from their movements, leading to developmental disregard. Constraint-induced movement therapy is one of the few effective neurorehabilitative strategies that may potentially overcome developmental disregard. This study is a RCT of children 12 to 24 months corrected age studying the effectiveness of CIMT combined with motor and sensory-motor interventions. The study population will comprise 72 children with CP and 144 typically developing children for a total of 216 children. All children with CP, regardless of group allocation will continue with their standard of care occupational and physical therapy throughout the study. The research material collected will be in the form of data from high-density array event-related potential scan, standardized assessment scores and motion analysis scores. The study protocol was approved by the Institutional Review Board. The findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.

In a systematic review and meta-analysis, Chiu and Ada (2016) examined if CIMT improves activity and participation in children with hemiplegic CP. Does it improve activity and participation more than the same dose of upper limb therapy without restraint? Is the effect of CIMT related to the duration of intervention or the age of the children? The experimental group received CIMT (defined as restraint of the less affected upper limb during supervised activity practice of the more affected upper limb). The control group received no intervention, sham intervention, or the same dose of upper limb therapy. Measures of upper limb activity and participation were used in the analysis; CIMT was more effective than no/sham intervention in terms of upper limb activity (standard mean difference [SMD] 0.63, 95 % CI: 0.20 to 1.06) and participation (SMD 1.21, 95 % CI 0.41 to 2.02). However, CIMT was no better than the same dose of upper limb therapy without restraint either in terms of upper limb activity (SMD 0.05, 95 % CI: -0.21 to 0.32) or participation (SMD -0.02, 95 % CI: -0.34 to 0.31). The effect of CIMT therapy was not related to the duration of intervention or the age of the children. The authors concluded that this review suggested that CIMT was more effective than no intervention, but no more effective than the same dose of upper limb practice without restraint.

In a RCT with masked assessment, Christmas and colleagues (2018) examined the feasibility and short-term efficacy of caregiver-directed CIMT to improve upper limb function in young children with hemiplegic CP. Caregiver-directed CIMT was administered using either 24-hour short-arm restraint device (prolonged) or intermittent holding restraint during therapy (manual).
Primary measures included AHA at 10 weeks; secondary measures included adverse events (AEs), Quality of Upper Extremity Skills Test and Pediatric QOL Inventory. Feasibility measures include recruitment, retention, data completeness and adherence. About 62/81 (72 %) of eligible patients in 16 centers were randomized (prolonged restraint n = 30; manual restraint n = 32) with 97 % retention at 10 weeks. The mean change at 10 weeks on the AHA logit-based 0 to 100 unit was 9.0 (95 % confidence interval (CI): 5.7 to 12.4; p < 0.001) for prolonged restraint and 5.3 (95 % CI: 1.3 to 9.4; p = 0.01) for manual restraint with a mean group difference of 3.7 (95 % CI: -1.5 to 8.8; p = 0.156) (AHA smallest detectable difference = 5 units). No serious related AEs were reported. There were no differences in secondary outcomes. More daily therapy was delivered with prolonged restraint (60 versus 30 minutes; p < 0.001); AHA data were complete at baseline and 10 weeks. The authors concluded that caregiver-directed CIMT is feasible and associated with improvement in upper limb function at 10 weeks; more therapy was delivered with prolonged than with manual restraint, warranting further testing of this intervention in a longer term trial.

In a randomized, blinded, sham-controlled clinical trial, Gillick and associates (2018) examined the safety, feasibility, and efficacy of tDCS combined with CIMT in children and young adults with unilateral CP. A total of 20 subjects were randomized to receive active or sham tDCS. The intervention consisted of 10 consecutive weekday sessions of tDCS applied to the non-lesioned hemisphere (20 mins) concurrently with CIMT (120 mins). Participants, care-givers, and interventionists were blinded to group assignment. The primary safety outcome investigated AEs. The primary behavioral outcome was the AHA. All 20 participants (mean age = 12.7 years, range of 7.4 to 21.6 years) were evaluated for the primary outcomes. No serious AEs occurred, and the most commonly reported minor AEs were headache and itchiness. Both groups demonstrated a significant improvement in hand function after the intervention, although no significant effect of tDCS was observed (between-group difference = -2.18, 95 % CI: -6.48 to 2.12], p = 0.30). Although hand function improved overall, no significant differences between intervention groups were found. Children with preserved corticospinal tract circuitry from the lesioned hemisphere, compared to those without, showed greater improvement in hand function (MD = 3.04, 95 % CI: -0.64 to 6.72], p = 0.099). The authors concluded that the findings of this study demonstrated the safety and feasibility of serial sessions of tDCS, and presented preliminary evidence for the effect of CST circuitry on outcomes following tDCS/CIMT. They stated that future work in children with unilateral cerebral palsy should focus on the optimal dosing and consider individual brain circuitry when describing response to combined interventions.

Spinal Cord Injury
In a case study, Kim and colleagues (2015) examined effects of modified CIMT (m-CIMT) and functional bi-manual training, when applied to a patient with incomplete spinal cord injury (SCI), on upper extremity function and daily activities. One patient, diagnosed with C4 incomplete SCI, underwent physical therapy with CIMT for 3 hours and task-oriented bi-manual training for 1 hour, per day. This combined 4-hour session was performed 5 times a week, for 3 weeks, totaling 15 sessions. Upper extremity function was measured using the Manual Function Test (MFT) and Box & Block Test (BBT). Additionally, Spinal Cord Independence Measure Version III (SCIM-III) and Short Form 36 Health Survey (SF-36) were used to assess functional outcomes. Mobility of the hand and overall function of upper extremities were enhanced following intervention. Moreover, the subject's quality of life and ability to carry out daily activities also improved. The authors concluded that modified CIMT and bi-manual training was effective in enhancing upper extremity function and performance of daily routines in a patient with incomplete SCI. Moreover, they stated that further studies, recruiting multiple subjects, should focus on m-CIMT using diverse methods, performed during the course of daily activities.

Peripheral Nerve Stimulation and Constraint-Induced Movement Therapy

Carrico and associates (2016) stated that constraint-based therapy and peripheral nerve stimulation (PNS) can significantly enhance movement function after stroke. No studies have investigated combining these interventions for cases of chronic, mild-to-moderate hemiparesis following stroke. These researchers examined the effects of PNS paired with a modified form of CIT on upper extremity movement function after stroke. A total of 19 adult stroke survivors with mild-to-moderate hemiparesis more than 12 months after stroke received 2 hours of either active (n = 10) or sham (n = 9) PNS preceding 4 hours of modified CIT (10 sessions). Active PNS enhanced modified CIT more than sham PNS (significance at p < 0.05), both immediately after intervention (Wolf Motor Function Test: p = 0.006 (timed score); p = 0.001 (lift score); Fugl-Meyer Assessment: p = 0.022; Action Research Arm Test: p = 0.007) and at 1-month follow-up (Wolf Motor Function Test: p = 0.025 (timed score); p = 0.007 (lift score); Fugl-Meyer Assessment: p = 0.056; Action Research Arm Test: p = 0.028). The authors concluded that pairing PNS with modified CIT can lead to significantly more improvement in upper extremity movement function than modified CIT alone. Moreover, they stated that future research is recommended to help establish longitudinal effects of this paired intervention, particularly as it affects movement function and daily life participation.

Transcranial Direct Current Stimulation and Constraint-Induced Movement Therapy

Gillic et al (2015b) stated that perinatal stroke occurs in more than 1 in 2,500 live-births and resultant congenital hemiparesis necessitates investigation into interventions that may improve long-term function and decreased burden of care beyond current therapies. Constraint-induced
movement therapy (CIMT) is recognized as an effective hemiparesis rehabilitation intervention. Transcranial direct current stimulation (tDCS) as an adjunct treatment to CIMT may potentiate neuroplastic responses and improve motor function. These researchers described the methodology of a clinical trial in children designed as a placebo-controlled, serial-session, non-invasive brain stimulation trial incorporating CIMT. The primary hypotheses are (i) that no serious adverse events will occur in children receiving non-invasive brain stimulation, and (ii) that children in the stimulation intervention group will show significant improvements in hand motor function compared to children in the placebo stimulation control group. This trial is a randomized, controlled, double-blinded clinical trial, and 20 children and/or young adults (age of 8 to 21 years) with congenital hemiparesis, will be enrolled. The intervention group will receive 10 2-hour sessions of tDCS combined with CIMT and the control group will receive sham stimulation with CIMT. The primary outcome measure is safety assessment of tDCS by physician evaluation, vital sign monitoring and symptom reports. Furthermore, hand function will be evaluated using the Assisting Hand Assessment, grip strength and assessment of goals using the Canadian Occupational Performance Measure. Neuroimaging will confirm diagnoses, cortico-spinal tract integrity and cortical activation; motor cortical excitability will also be examined using transcranial magnetic stimulation techniques. The authors noted that combining non-invasive brain stimulation and CIMT interventions has the potential to improve motor function in children with congenital hemiparesis beyond each intervention independently. Such a combined intervention has the potential to benefit an individual throughout their lifetime.

In a pilot, double-blind, sham-controlled, randomized trial, Rocha and associates (2016) examined if the addition of anodal tDCS on the affected hemisphere or cathodal tDCS on unaffected hemisphere to m-CIMT would be superior to constraints therapy alone in improving upper limb function in chronic stroke patients. A total of 21 patients with chronic stroke were randomly assigned to receive 12 sessions of either (i) anodal, (ii) cathodal or (iii) sham tDCS combined with m-CIMT. Fugl-Meyer assessment (FMA), motor activity log scale (MAL), and handgrip strength were analyzed before, immediately, and 1 month (follow-up) after the treatment. Minimal clinically important difference (mCID) was defined as an increase of greater than or equal to 5.25 in the upper limb FMA. An increase in the FMA scores between the baseline and post-intervention and follow-up for active tDCS group was observed, whereas no difference was observed in the sham group. At post-intervention and follow-up, when compared with the sham group, only the anodal tDCS group achieved an improvement in the FMA scores. ANOVA showed that all groups demonstrated similar improvement over time for MAL and handgrip strength. In the active tDCS groups, 7/7 (anodal tDCS) 5/7 (cathodal tDCS) of patients experienced mCID against 3/7 in the sham group. The authors concluded that the findings of this study supported the merit of association of m-CIMT with brain stimulation to augment clinical gains in rehabilitation after stroke. However, the anodal tDCS appeared to have greater impact
than the cathodal tDCS in increasing the m-CIMT effects on motor function of chronic stroke patients. These preliminary findings need to be validated by well-designed studies.

In a Cochrane review, Elsner and colleagues (2016) evaluated the effects of tDCS on activities of daily living (ADLs), arm and leg function, muscle strength and cognitive abilities (including spatial neglect), drop-outs and adverse events in people after stroke. These investigators searched the Cochrane Stroke Group Trials Register (February 2015), the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library; 2015, Issue 2), Medline (1948 to February 2015), Embase (1980 to February 2015), CINAHL (1982 to February 2015), AMED (1985 to February 2015), Science Citation Index (1899 to February 2015) and 4 additional databases. In an effort to identify further published, unpublished and ongoing trials, they searched trials registers and reference lists, hand-searched conference proceedings and contacted authors and equipment manufacturers. This is the update of an existing review. In the previous version of this review these researchers focused on the effects of tDCS on ADLs and function. In this update, they broadened their inclusion criteria to compare any kind of active tDCS for improving ADLs, function, muscle strength and cognitive abilities (including spatial neglect) versus any kind of placebo or control intervention. Two review authors independently assessed trial quality and risk of bias and extracted data. If necessary, they contacted study authors to ask for additional information; and collected information on drop-outs and adverse events from the trial reports. These researchers included 32 studies involving a total of 748 participants aged above 18 years with acute, post-acute or chronic ischemic or hemorrhagic stroke. They also identified 55 ongoing studies. The risk of bias did not differ substantially for different comparisons and outcomes. They found 9 studies with 396 participants examining the effects of tDCS versus sham tDCS (or any other passive intervention) on the primary outcome measure, ADLs after stroke. These investigators found evidence of effect regarding ADL performance at the end of the intervention period (SMD 0.24, 95 % CI: 0.03 to 0.44; inverse variance method with random-effects model; moderate quality evidence); 6 studies with 269 participants assessed the effects of tDCS on ADLs at the end of follow-up, and found improved ADL performance (SMD 0.31, 95 % CI: 0.01 to 0.62; inverse variance method with random-effects model; moderate quality evidence). However, the results did not persist in a sensitivity analysis including only trials of good methodological quality. One of the secondary outcome measures was upper extremity function: 12 trials with a total of 431 participants measured upper extremity function at the end of the intervention period, revealing no evidence of an effect in favor of tDCS (SMD 0.01, 95 % CI -0.48 to 0.50 for studies presenting absolute values (low quality evidence) and SMD 0.32, 95 % CI -0.51 to 1.15 (low quality evidence) for studies presenting change values; inverse variance method with random-effects model). Regarding the effects of tDCS on upper extremity function at the end of follow-up, the authors identified 4 studies with a total of 187 participants (absolute values) that showed no evidence of an effect (SMD 0.01, 95 % CI: -0.48 to 0.50; inverse variance method with random-effects model; low quality evidence); 10 studies with 313
participants reported outcome data for muscle strength at the end of the intervention period, but in the corresponding meta-analysis there was no evidence of an effect; 3 studies with 156 participants reported outcome data on muscle strength at follow-up, but there was no evidence of an effect. In 6 of 23 studies (26 %), drop-outs, adverse events or deaths that occurred during the intervention period were reported, and the proportions of drop-outs and adverse events were comparable between groups (risk difference (RD) 0.01, 95 % CI: -0.02 to 0.03; Mantel-Haenszel method with random-effects model; low quality evidence; analysis based only on studies that reported either on drop-outs, or on adverse events, or on both). However, this effect may be under-estimated due to reporting bias. The authors concluded that at the moment, evidence of very low to moderate quality is available on the effectiveness of tDCS (anodal/cathodal/dual) versus control (sham/any other intervention) for improving ADL performance after stroke. However, there are many ongoing randomized trials that could change the quality of evidence in the future. They stated that future studies should particularly engage those who may benefit most from tDCS after stroke and in the effects of tDCS on upper and lower limb function, muscle strength and cognitive abilities (including spatial neglect). Drop-outs and adverse events should be routinely monitored and presented as secondary outcomes. They should also address methodological issues by adhering to the Consolidated Standards of Reporting Trials (CONSORT) statement.

In a pilot study, Andrade and colleagues (2017) compared the effects of tDCS at different cortical sites (premotor cortex [PMC] and motor primary cortex [M1]) combined with CIMT for treatment of stroke patients. A total of 60 patients were randomly distributed into 3 groups: Group A, anodal stimulation on PMC and CIMT; Group B, anodal stimulation on M1 and CIMT; and Group C, sham stimulation and CIMT. Evaluations involved analysis of functional independence, motor recovery, spasticity, gross motor function, and muscle strength. A significant improvement in primary outcome (functional independence) after treatment in the PMC group followed by M1 group and sham group was observed. The same pattern of improvement was highlighted among all secondary outcome measures regarding the superior performance of the PMC group over M1 and sham groups.

Moreover, the authors stated that the results of this preliminary study should be interpreted with caution, given some limitations. Although the goal has been to compare the efficacy of tDCS in PMC and M1 after stroke, these researchers could not guarantee that there has not been a cumulative effect of PMC stimulation reaching M1 and vice versa. Due to the existence of intra- and inter-individual variations that interfere with the effects of neuro-stimulation, similar studies drew attention to this limitation related to the focal power of the technique, so that a current propagation effect from one region to another could not be definitively excluded. However, it is important to note that these investigators had used several strategies to locate PMC and M1 in distinct ways (e.g., reduced electrode size, use of standardized coordinates in previous studies.
for localization of target regions, use of MRI applied individually for each patient, as well as procedural repetition at each stimulation session). However, future studies should take into account variations in current density according to individual differences. Another point that should be considered is that the experimental design did not include neurophysiological measures; thus, these researchers could not determine the causal relationship between the integrity of the spinal cortical tract and improvement in patients’ functionality, according to the stimulated area. Considering that the patients included in this study did not present significant variations in relation to the clinical parameters at baseline, the different benefits achieved by the studied groups suggested that the differences were due to manipulation of the experimental variable, i.e., the locus of stimulation, as the sample was homogeneous. However, the authors reinforced that it was not possible to measure the role of cortical excitability on the efficacy of tDCS in both PMC and M1 in this pilot study. The improvement achieved by the stimulation of alternative areas as verified in the present study could contribute to the design of clinical trials with larger samples and the use of more specific techniques such as diffusion tensor imaging and biomarkers.

Constraint-Induced Movement Therapy for the Treatment of Hemiplegia from Brain Tumors

In a pilot study, Sparrow and colleagues (2017) examined the feasibility of a 3-week CIMT program in children with brain tumors and UE hemiplegia and described resultant change in extremity use. Affected arm use, health-related QOL, and parent-reported feasibility of program participation were measured before and after the intervention and at a 3-month follow-up visit. All 9 participants completed the entire study. The quality and amount of affected arm use improved significantly; gains were maintained at the 3-month follow-up evaluation. Some parents (44%) reported that program participation was difficult; however, all reported satisfaction with the program. Participants did not experience negative changes in health-related QOL during the intervention, indicating that they tolerated the program well. The authors concluded that the findings from this small (n = 9) pilot study suggested that a child with hemiplegia as a result of a brain tumor can adhere to and benefit from a CIMT program. These preliminary findings need to be validated by well-designed studies.

Constraint-Induced Movement Therapy in Combination With Biofeedback (e.g., Auditory or Visual) for the Treatment of Hemiparesis Following Stroke

In a pilot RCT, Bang (2016) examined the effects of modified mCIMT combined with auditory feedback for trunk control on UE function and ADL among subacute stroke patients with moderate impairment. A total of 20 subjects with hemiparesis were randomly assigned to either the mCIMT combined with auditory feedback group (n = 10) or the control group (n = 10). The mCIMT combined with auditory feedback group received the mCIMT protocol training at the
same time as the auditory feedback for control of the compensatory movement of the trunk. The control group only received the mCIMT protocol. Each group underwent 20 (1 hour/day) intervention sessions (5 days/week for 4 weeks). The mCIMT combined with auditory feedback group exhibited greater changes in the ARAT (p = 0.027; 95 % CI: 0.429 to 6.171), Fugl-Meyer Assessment upper extremity (p = 0.034; 95 % CI: 0.360 to 8.039), modified Barthel Index (p=0.003; 95 % CI: 3.465 to 14.536), and amount of use of motor activity log (p = 0.009; 95 % CI: 0.78 to .476) compared to the control group. There were no significant differences in the quality of movement (p = 0.054, 95 % CI: -0.005 to 0.457) and modified Ashworth Scale (p = 0.288; 95 % CI: -0.583 to 0.183) grades between the 2 groups. The authors concluded that the findings from this pilot study suggested that mCIMT combined with auditory feedback for trunk control was more helpful in improving the UE function than mCIMT alone in subacute stroke patients with moderate impairment. These preliminary findings need to be validated by well-designed studies.

Seok and colleagues (2016) examined the synergic effects of short-term CIMT and visual biofeedback training (VBT) in subacute stroke patients. A total of 32 subacute stroke patients were enrolled and randomly assigned to 1 of 3 groups: (i) short-term CIMT with VBT, (ii) VBT only, and (iii) control groups. These researchers applied CIMT for 1 hour daily during VBT instead of the ordinary restraint time, referred to as “short-term” CIMT. Short-term CIMT with VBT group received simultaneous VBT with CIMT, whereas the VBT the only group received VBT without CIMT for 1 hour a day for 2 weeks. The control group received conventional OT alone. Patients underwent the Purdue Pegboard Test, the JAMAR grip strength test, the Wolf Motor Function Test, the Fugl-Meyer Assessment (upper extremity), Motricity index and the Korean version of Modified Barthel Index test to evaluate motor functions of the hemiplegic upper limb at baseline, post-treatment, and 2 weeks after treatment. No significant differences were observed between short-term CIMT with VBT and VBT only groups. Both groups showed significantly higher scores compared to the control group in the WMFT and FMA tests. However, the short-term CIMT with VBT group showed significant improvement (p < 0.05) compared with the control group in both grasp and pad pinch at post-treatment and 2 weeks after treatment while the VBT only group did not. The authors concluded that short-term CIMT with VBT group did not show significant improvement of hemiplegic upper limb function of subacute stroke patients, compared to VBT only group. They stated that larger sample sizes and different restraint times are needed to clarify the effect.

This study had several drawbacks: (i) it is not advisable to generalize these findings in subacute stroke patients with hemiplegic upper limb because of the small sample size (n = 32), (ii) since these researchers followed-up patients for only 2 weeks after treatment, no long-term effects were evaluated, (iii) these investigators could not examine functional recovery in stroke patients with severe cognitive impairment or spasticity because they
used the Mini-Mental Status Examination, MAS scale, and manual muscle test to screen the patients initially, and (iv) they did not examine the correlation between functional recovery and cortical re-organization by using imaging study (e.g., MRI).

Multiple Sclerosis

Mark et al (2018) examined if CIMT can produce comparable results with a progressive disorder such as MS. These researchers conducted a preliminary phase-II RCT of CIMT versus a program of complementary and alternative medicine (CAM) treatments for persons with MS, to evaluate their effect on real-world disability. A total of 20 adults with hemiparetic MS underwent 35 hours of either CIMT or CAM over 10 consecutive weekdays. The primary clinical outcome was change from pretreatment on the MAL. The CIMT group improved more on the MAL (2.7 points, 95% CI: 2.2 to 3.2) than did the CAM group (0.5 points, 95% CI: -0.1 to 1.1; p < 0.001). These results did not change at 1-year follow-up, indicating long-term retention of functional benefit for CIMT. The treatments were well-tolerated and without AEs. The authors concluded that these findings suggested that CIMT can increase real-world use of the more-affected arm in patients with MS for at least 1 year.

In a pilot RCT, Barghi et al (2018) examined if CIMT can also induce increases in white matter integrity in patients with MS. A total of 20 adults with chronic hemiparetic MS were randomized to receive either CIMT or CAM treatment. Structural white matter change was assessed by tract-based spatial statistics (TBSS); measures included fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). CIMT and CAM groups did not differ in pre-treatment disability or expectancy to benefit. As noted in the companion paper (Mark et al, 2018), the MAL improved more after CIMT than CAM (p < 0.001); the within-group effect size for CIMT was 3.7 (large $d' = 0.57$), while for CAM it was just 0.7. Improvements in white matter integrity followed CIMT and were observed in the contralateral corpus callosum (FA, p < 0.05), ipsilateral superior occipital gyrus (AD, p < 0.05), ipsilateral superior temporal gyrus (FA, p < 0.05), and contralateral corticospinal tract (MD and RD, p < 0.05). The authors concluded that CIMT produced a very large improvement in real-world limb use and induced white matter changes in patients with hemiparetic MS when compared with CAM. They stated that these findings suggested in preliminary fashion that the adverse changes in white matter integrity induced by MS might be reversed by CIMT.

Transcranial Magnetic Stimulation and Constraint-Induced Movement Therapy for the Treatment of Congenital Hemiparesis
In a factorial-design, blinded, RCT, Kirton and colleagues (2016) examined if the addition of rTMS and/or CIMT to intensive therapy increases motor function in children with perinatal stroke and hemiparesis. Subjects were hemiparetic children (aged 6 to 19 years) with MRI-confirmed perinatal stroke. All completed a 2-week, goal-directed, peer-supported motor learning camp randomized to daily rTMS, CIMT, both, or neither. Primary outcomes were the Assisting Hand Assessment and the Canadian Occupational Performance Measure at baseline, and 1 week, 2 and 6 months post-intervention. Outcome assessors were blinded to treatment. Interim safety analyses occurred after 12 and 24 participants. Intention-to-treat analysis examined treatment effects over time (linear mixed effects model). All 45 participants completed the trial. Addition of rTMS, CIMT, or both doubled the chances of clinically significant improvement. Assisting Hand Assessment gains at 6 months were additive and largest with rTMS + CIMT ($\beta$ coefficient = 5.54 [2.57 to 8.51], $p = 0.0004$). The camp alone produced large improvements in Canadian Occupational Performance Measure scores, maximal at 6 months (Cohen d = 1.6, $p = 0.002$); QOL scores improved. Interventions were safe and well-tolerated with no decrease in function of either hand. The authors concluded that hemiparetic children participating in intensive, psychosocial rehabilitation programs can achieve sustained functional gains; addition of CIMT and rTMS increased the chances of improvement.

The authors noted that drawbacks of this study included a single-center trial and modest sample size ($n = 45$) that precluded examination of co-variates such as age, stroke type, and baseline disability. A ceiling effect for the AHA (3 participants scored 100) may have limited discriminatory ability in higher-functioning children. The AHA was also unable to specifically characterize what "clinically significant" improvement looked like across children with variable function and goals. The randomization imposed by peer grouping may be an unavoidable requirement to optimize psychosocial benefits in such trials; QOL measures improved but likely failed to capture meaningful psychosocial changes observed anecdotally. Most had never met another child with hemiparesis. They worked closely and intensively with age-matched peers, often in group settings. They shared goals, faced similar challenges, supported each other, and realized successes together. Such examples of personal growth were consistently reported by participants and parents. Measures to capture these effects in future interventional studies would enhance the quality of the data and associated conclusions.

In an accompanying editorial of the afore-mentioned study by Kirton et al (2016), Staudt and Gordon (2016) stated that "However, before implementing rTMS in clinical practice, more questions need to be answered. One critical point must be looked at in more detail: in contrast to adult hemiparetic stroke patients, who normally control their paretic hands via preserved crossed corticospinal projections from the lesioned hemisphere, a substantial portion of patients with congenital hemiparesis possess fast-conducting ipsilateral corticospinal projections from the contralesional hemisphere to the paretic hand. In some, these are the only projections to the
paretic hand (e.g., in patients with extensive hemispheric lesions, or after hemispherotomy). In these patients, interhemispheric inhibition between the 2 motor cortices cannot occur (there is only one), and it is, at least at first glance, counterintuitive to use rTMS to inhibit the one hemisphere controlling both hands. Of note, Kirton et al deliberately included 20 patients in whom they found such ipsilateral projections, 11 of whom underwent rTMS. Although it was stated that no deterioration of hand function was observed, the question remains whether rTMS really is an appropriate treatment option for this subgroup of patients, and if yes, what the modes of action in this constellation might be. However, the idea of inhibiting the contralesional hemisphere in these patients would be compatible with findings that CIMT in patients with only ipsilateral projections led to a reduction of synaptic activity during simple hand movements (measured by fMRI) and to a reduction in trans-synaptic excitability of the motor cortex (measured by single-pulse TMS). It would also be attractive to speculate that, if indeed inhibitory rTMS can be shown to be beneficial in these patients, it might act by helping to reduce the activity and excitability of the motor cortex controlling the paretic hand. We are therefore looking forward to more detailed analyses of the study by Kirton et al, which should specifically look at possible differences in the effects of rTMS (and maybe also of CIMT) on patients with contralateral and with ipsilateral corticospinal projections. In the end, we are confident that rTMS will eventually become yet another new tool in our “toolbox” for treating congenital hemiparesis. Not unlike CIMT and bimanual therapy, we will still have to find its specific contributions, most likely together with intensive therapies, as well as interventions acting on the impairment level (e.g., botulinum toxin or splinting). As in these other approaches, it is unlikely to be a “one-size-fits-all” treatment for congenital hemiparesis.”

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no specific CPT code for constraint-induced movement therapy or constraint-induced aphasia:</td>
<td></td>
</tr>
<tr>
<td>CPT codes not covered for indications listed in the CPB:</td>
<td></td>
</tr>
<tr>
<td>92507</td>
<td>Treatment of speech, language, voice, communication, and/or auditory processing disorder; individual [constraint-induced aphasia/language therapy alone or in combination with transcranial magnetic stimulation]</td>
</tr>
<tr>
<td>92508</td>
<td>group, 2 or more individuals [constraint-induced aphasia/language therapy alone or in combination with transcranial magnetic stimulation]</td>
</tr>
<tr>
<td>Other CPT codes related to the CPB:</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>0310T</td>
<td>Motor function mapping using non-invasive navigated transcranial magnetic stimulation (nTMS) for therapeutic treatment planning, upper and lower extremity [not covered for constraint-induced movement therapy in combination with transcranial direct current stimulation for the treatment of congenital hemiparesis/chronic stroke]</td>
</tr>
<tr>
<td>64555 - 64595</td>
<td>Neurostimulator peripheral nerve [not covered in combination with constraint induced movement therapy]</td>
</tr>
<tr>
<td>90867</td>
<td>Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management [not covered for constraint-induced movement therapy in combination with transcranial direct current stimulation for the treatment of congenital hemiparesis/chronic stroke]</td>
</tr>
<tr>
<td>90868</td>
<td>Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session [not covered for constraint-induced movement therapy in combination with transcranial direct current stimulation for the treatment of congenital hemiparesis/chronic stroke]</td>
</tr>
<tr>
<td>90869</td>
<td>Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management [not covered for constraint-induced movement therapy in combination with transcranial direct current stimulation for the treatment of congenital hemiparesis/chronic stroke]</td>
</tr>
<tr>
<td>95970 - 95975</td>
<td>Electronic analysis and programming of neurostimulator pulse generator [not covered in combination with constraint induced movement therapy]</td>
</tr>
<tr>
<td>97110</td>
<td>Therapeutic procedure, one or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility</td>
</tr>
<tr>
<td>97112</td>
<td>neuromuscular reeducation of movement, balance coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities</td>
</tr>
<tr>
<td>97140</td>
<td>Manual therapy techniques (e.g., mobilization/manipulation, manual lymphatic drainage, manual traction), one or more regions, each 15 minutes</td>
</tr>
<tr>
<td>97530</td>
<td>Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes</td>
</tr>
<tr>
<td>G0151</td>
<td>Services performed by a qualified physical therapist in the home health or hospice setting, each 15 minutes</td>
</tr>
<tr>
<td>S9131</td>
<td>Physical therapy; in home, per diem</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>I69.051 - I69.059, I69.151 - I69.159, I69.251 - I69.259, I69.351 - I69.359, I69.851 - I69.859, I69.951 - I69.959</td>
<td>Sequelae of cerebrovascular disease, hemiplegia and hemiparesis [not covered for constraint-induced movement therapy in combination with peripheral nerve stimulation or biofeedback for the treatment of hemiparesis following stroke]</td>
</tr>
<tr>
<td>C71.0 - C71.9</td>
<td>Malignant neoplasm of brain</td>
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<tr>
<td>G20</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>G21.11 - G21.9</td>
<td>Secondary parkinsonism</td>
</tr>
<tr>
<td>G35</td>
<td>Multiple sclerosis [motor tic disorders caused by MS]</td>
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<tr>
<td>G80.0 - G80.9</td>
<td>Cerebral Palsy</td>
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<tr>
<td>I63.00 - I63.9</td>
<td>Cerebral infarction [chronic stroke]</td>
</tr>
<tr>
<td>I69.020, I69.120, I69.220, I69.320, I69.820, I69.920</td>
<td>Sequelae of cerebrovascular disease, aphasia</td>
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<tr>
<td>R29.5</td>
<td>Transient paralysis</td>
</tr>
<tr>
<td>S02.0XX+ - S02.42X+, S02.600+ - S02.92X+</td>
<td>Fracture of skull and facial bones [traumatic brain injury]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>S02.0xxS, S02.10xS, S02.110S, S02.111S, S02.112S, S02.113S, S02.118S, S02.119S, S02.19xS, S02.2xxS, S02.3xxS, S02.400S, S02.401S, S02.402S, S02.411S, S02.412S, S02.413S, S02.42xS, S02.5xxS, S02.600S, S02.609S, S02.61xS, S02.62xS, S02.62xS, S02.63xS, S02.64xS, S02.65xS, S02.66xS, S02.67xS, S02.69xS, S02.8xxS, S02.91xS, S02.92xS</td>
<td>Sequela of fracture of skull and facial bones [traumatic brain injury]</td>
</tr>
<tr>
<td>S06.0x0+ -</td>
<td>Intracranial injury [traumatic brain injury]</td>
</tr>
<tr>
<td>S06.9x9+</td>
<td></td>
</tr>
<tr>
<td>S09.90x+</td>
<td>Unspecified injury of head [traumatic brain injury]</td>
</tr>
<tr>
<td>S14.0xx+ -</td>
<td>Injury of nerves and spinal cord at neck level</td>
</tr>
<tr>
<td>S14.9xx+</td>
<td></td>
</tr>
<tr>
<td>S24.0xx+ -</td>
<td>Injury of nerves and spinal cord at thorax level</td>
</tr>
<tr>
<td>S24.9xx+</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>S34.01x+</td>
<td>Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and</td>
</tr>
<tr>
<td>S34.9xx+</td>
<td>pelvis level</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


19. Lannin N, Thorpe K, Armstrong B. Constraint induced movement therapy does not provide clinically significant improvement in upper limb function following stroke. OT CATS: Occupational Therapy Critically Appraised Topics. Penrith, NSW; University of Western Sydney; 2004.


58. Miller G. Management and prognosis of cerebral palsy. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2014.


78. Bang DH. Effect of modified constraint-induced movement therapy combined with auditory feedback for trunk control on upper extremity in subacute stroke patients


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0665
Constraint-Induced Therapy

There are no amendments for Medicaid.