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Constraint-Induced Movement Therapy after Stroke

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Abstract

Constraint-induced movement therapy (CIMT) was developed to overcome upper limb impairments after stroke and is the most investigated intervention for treating stroke patients in the previous decades. This review describes the current evidence regarding: original CIMT and modified versions of CIMT (mCIMT). Meta-analysis showed strong evidence favoring both types of CIMT in terms of motor function, arm-hand activities and self-reported arm-hand functioning in daily life, immediately after treatment and at long-term follow-up, whereas no evidence was found for constraining alone (Forced Use (FU) therapy). No evidence was found that type of CIMT, intensity of practice or timing did affect outcome. Although the underlying mechanism that

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drive (m)CIMT is still poorly understood, recent kinematic conducted studies suggests that improvements introduced by original CIMT or mCIMT are mainly based on adaptation by learning to optimize the use of intact end-effectors by selecting patients with some voluntary motor control of wrist and finger extensors post stroke.

Keywords

stroke; rehabilitation; upper limb; Constraint-induced movement therapy; forced use; systematic review; meta-analysis

Introduction

Worldwide, 16.9 million people suffer a first stroke each year, resulting in about 33 million stroke survivors and 5.9 million stroke-related death (1) making stroke the second or third most common cause of death and one of the main causes of acquired adult disability. (1, 2) Approximately 80% of these survivors have motor impairments of the upper limb(3) that gravely affect their ability to perform activities of daily living (ADL), as well as social participation. Previously we showed that the severity of upper limb paresis is an independent determinant of the outcome of basic activities of daily living (ADL) post stroke. (4)

A recent systematic review of 467 trials showed that the effectiveness of most interventions for the upper and lower limbs is driven by repetition and principles of task- and context-specific motor learning. (5) Constraint-induced movement therapy (CIMT) or modified versions of CIMT (mCIMT) are currently considered the most effective treatment regimens in physical therapy to improve the outcome of the upper paretic limb. (2, 5)

Although several systematic reviews concerning have been conducted in the past, (6-13) there is no recent meta-analysis of RCTs of (m)CIMT including thorough analyses of possible effect modifiers and small-study effects. Of the currently available reviews, some suffer from an incomplete literature search strategy,(6, 7, 14) while others are restricted to a specific set of modified versions of CIMT(15), dose-matched controlled interventions(13), a specific period post stroke(10, 12), or a best-evidence synthesis based on the methodological quality of included trials. (11)

In the present review, first, we will briefly give a historical background and description of the original CIMT protocol. Based on a systematic review of the literature and subsequent metaanalysis of randomized controlled trials (RCTs), we will summarize the evidence for CIMT, mCIMT and Forced Use (FU) therapy in adult patients with stroke. In a subsequent sensitivity analysis of included RCTs, we will explore the effects of (1) CIMT type, (2) dosage of therapy, and (3) timing of therapy post stroke. Subsequently, we will discuss the effects of in light of assumed underlying mechanisms that drives (m)CIMT and criteria for selecting patients that will benefit most from (m)CIMT. Finally, we will summarize our findings and offer suggestions for further research.

The theoretical framework for CIMT has a long history.(16, 17) The German scientist Munk (1909) (18) was the first to document that non-human primates would use an impaired

(deafferented) upper extremity if forced to do so, when the movement was purposeful and relevant. This work was quickly followed by the classical studies by Ogden and Franz (1917) who observed monkeys freely moving following pyramidal tract lesions.(19) Somewhat serendipitously, rather than by design, these animals were forced to use the hemiparetic upper extremity after immobilization of the better limb, which they were rapidly able to accomplish. This observation the authors to suggest that the limitation was not as much an inability as it was one of disuse. This concept of “forced use” (FU) was resurrected several decades later by Knapp(20) and in elegant studies by Taub(21), who applied the deafferented monkey model to show that these animals would not use the insensate limb unless a series of behavioral strategies was employed that resulted in ‘overcoming learned non-use’ (Fritz et al.(17) for more detail).

Defining CIMT

The signature protocol for the original form of CIMT contains three components or ‘treatment packages’: (1) intensive graded practice of the paretic upper limb aimed at enhancing task-specific use of the affected limb for up to 6 hours a day for 2 weeks (i.e., shaping) (Figure 1); (2) constraining or FU of the non-paretic upper limb with a mitt to promote the use of the more impaired limb during 90% of the waking hours; and (3) adherence-enhancing behavioral methods designed to transfer the gains obtained in the clinical setting or laboratory to the patients' real-world environment (i.e., transfer package). (22, 23) Thus, CIMT uses operant training techniques applied in the context of rehabilitation medicine, (24) while FU does not rely upon any conditioning. (25, 26) Since its introduction, the first proof of the original CIMT concept was investigated in 9 chronic stroke patients by Edward Taub and colleagues. (27) Their positive findings regarding motor function, dexterity and self-reported arm-hand use in daily life were later replicated in a multicenter trial of 222 stroke patients.(28-30) Trials by other research groups have applied “modified” forms of CIMT (mCIMT) that vary in dosage, timing and composition of therapy. While embracing the fundamental components of the original form of CIMT, these modifications are typically characterized by distributed training protocols with reduced time spent in training, less time during which the non-paretic upper limb is restrained, and absence of a transfer package including a contract with the patient, but a larger number of training days. (31, 32) Treatment sessions for mCIMT vary from 30 minutes(33-35) to 6 hours(36-44) a day, and from 2(45) to 7(46) sessions a week, for 2(23, 36-45, 47-56) to 12 weeks. The wide variety of these adaptations justifies a systematic review and subsequent meta-analysis of trials applying original or mCIMT. The definitions and description of rehabilitation terminology for (m)CIMT in the present review are summarized in supplementary web appendix 1.

Effects of (m)CIMT

CIMT has been investigated in 51 RCTs,(23, 28-31, 33-82) including 1784 patients with adult stroke, but only 15 trials included patients within the first three months post stroke.(34, 45, 47, 49, 50, 52, 53, 56, 59, 66, 67, 69, 76, 78, 82) Panel 1 shows the used search strategy and selection criteria used for this systematic review of the literature. For details about the search strategy, methods and flow-chart, see supplementary web appendix 2 to 4.

Original CIMT

Original CIMT, although seen as the ‘gold standard’ of CIMT, has been investigated in merely one RCT(28-30) and included patients beyond 3 months post stroke (see for details of the included trial of original CIMT supplementary web appendix 4). Significant positive medium effect sizes post intervention were found for arm-hand activities, self-reported amount of arm-hand use in daily life and self-reported quality of arm-hand movement in daily life as shown in Figure 2 (see also supplementary web appendix 6). The favorable effects of original CIMT for these three outcomes were sustained at follow-up (4 months) as shown in Figure 3 (see also supplementary web appendix 7). In addition, significant positive effect sizes in the long term were found for quality of life related to hand function and quality of life related to ADL.

Modified versions of CIMT

Contrary to original CIMT, mCIMT has been investigated in a vast amount of RCTs (n=44; N=1397) (For details of included mCIMT trials see supplementary web appendix 4).(23, 31, 33-58, 61-64, 66, 70-78, 80-82) In favor of mCIMT, significant positive small to medium summary effect sizes (SEs) have been found post intervention in terms of motor function of the paretic arm, muscle tone, arm-hand activities, self-reported amount of arm-hand use in daily life, self-reported quality of arm-hand movement in daily life, and basic ADL (Figure 2) (see also supplementary web appendix 6). No significant summary effect sizes were found for grip strength, sensibility, pain, quality of life related to hand function, and quality of life related to ADL (Figure 2) (See supplementary web appendix 6). The effects were sustained at follow-up (mean 21.58 (SD 13.21) weeks) for motor function of the paretic arm, arm-hand activities, self-reported amount of arm-hand use in daily life, and self-reported quality of arm-hand movement in daily life, but not for muscle tone or basic ADL (Figure 3) (see also supplementary web appendix 7).

Forced use

Forced use therapy was investigated in 6 RCTs (N=165)(59, 60, 65, 67-69, 79) (see supplementary web appendix 5) and did not show an added value for self-reported amount of arm-hand use in daily life and self-reported quality of arm-hand movement in daily life (Figure 2) (see also supplementary web appendix 6).

Impact of CIMT-type, dosage of therapy, and timing of therapy post stroke and small study effects

Sensitivity analysis shows no significant differences in effect sizes between original and modified version of CIMT, dosage of (m)CIMT (additional time spent in exercise therapy 5(51) to 60 hours(28, 36, 38, 40, 42)(mean 46.8 hours), and timing of (m)CIMT when comparing trials that started within or beyond the first 3 months post stroke. In addition, these robust effects for (m)CIMT seems not to be influenced by small-study effects, publication bias, nor were they moderated by risk of bias (supplementary web appendix 6 and 7). Despite not finding evidence for small-study effects, meta-regression of mCIMT trials showed that methodological quality was a significant effect modifier for motor function post intervention and self-reported use in daily life at follow-up.

What drives (m)CIMT?

The underlying mechanism(s) that drive improvement by (m)CIMT are still poorly understood. Firstly, we expected that intensity of task-specific practice (expressed as treatment contrast in terms of duration) would be a significant moderator of (m)CIMT. However, as shown in this meta-analysis, we found no evidence that the type of (m)CIMT or treatment contrast - which amounted a mean of 47 hours - mattered. The absence of effects of treatment contrast between trials does not imply that dosing of CIMT therapy is not important. However, patients in (m)CIMT trials did practice much more intensively each day than is usual. In addition, Wolf and colleagues showed in a retrospective analysis of 169 participants that the intensity of supervised original CIMT was modified by the amount of repetitive task practice and also to some extent by the initial severity of motor impairment on the WMFT.(83) This finding suggests that the effects of the therapy dose are confounded by the initial severity of neurological deficits. Possible risks of bias, like blinding of assessors, did not seem to influence lack of difference between dose-matched trials and non-dose matched trials. These findings are in agreement with a recent trial(82) and meta-analysis(84) showing that dose-matched trials of mCIMT in which the control group received an equal dose of bilateral arm training failed to report significant differences in overall effect sizes. Despite the finding that (m)CIMT may increase short-term(50, 85) and long-term cortical activation patterns, (42, 50, 86), the underlying mechanisms responsible for improvements require further investigation. In particular, uncertainty continues to exist about how observed improvements in motor performance after (m)CIMT relate to recruitment of cortical activation patterns in the contralesional and ipsilesional cortex after stroke, as revealed by Transcranial Magnetic Stimulation (TMS)(42, 86, 87) and functional Magnetic Resonance Imaging (fMRI) (88-90) (See for a critical review: Buma et al. (91)). For example, recent studies suggest that improved hand function assessed by WMFT is accompanied by increased recruitment of ipsilesional somatosensory cortex. (89, 90) Although significant neural correlates have been found with upper extremity measurements, such as WMFT, these studies do not address the question how cortical changes relate to the quality of motor performance in terms of 'neural repair' or using compensation strategies. (See for a review: Buma et al.(92)) For example, a recent controlled proof of concept study of Kitago and colleagues failed to show significant changes in coordinative measures of the paretic arm and wrist after (m)CIMT in chronic stroke, despite clinically meaningful functional improvements in ARAT scores.(93) (See also references (33, 35, 37, 38, 43, 46, 57, 62, 64, 70-72, 80) (35)) This observation further suggests that improvements introduced by original CIMT or mCIMT are mainly based on learning to optimize the use of intact end-effectors (i.e., compensation strategies). These findings also suggest that the enhanced cortical neuroplasticity found by TMS(42, 86, 87) and fMRI(90) in the subacute(49, 50) and chronic post stroke phases(42, 87) may reflect learned non-use and compensatory skill learning rather than "true neurological repair" or "recovery" of impairments (see also references (14, 92, 94)). This assumption is further supported by some recent longitudinal 3D-kinematic studies showing that the number of degrees of freedom that patients can engage while performing meaningful tasks, such as reaching, is mainly completed in the first 8 weeks post stroke. (94, 95) These improvements in intra-limb coordination are accompanied by a significant reduction in patients' variability(94) and improvement in the

smoothness(95) of their motor performance. Interestingly, the 3D-kinematic improvements closely follow the clinical time course of impairments such as synergism(94, 96, 97) and are also restricted to the first 3 months post stroke.(98, 99) Interestingly, the present meta-analysis further suggests that the effects of mCIMT on motor function of the arm such as FMA-arm scores is restricted to trials that started within this time window of 3 months post stroke (Table 1 and supplementary web appendix 6 and 7) (References (34, 45, 49, 50, 82)). This finding is in agreement with the growing evidence from animal studies in which the first weeks after stroke onset are characterized by increased levels of homeostatic neuroplasticity (100)

Who should be selected for (m)CIMT?

An important inclusion criterion for the original CIMT trial was that patients showed some voluntary extension at the wrist and some minimal extension at the metacarpophalangeal and interphalangeal joints at baseline.(28) Within this selection criterion one may discriminate between higher-functioning participants who demonstrate at least 20° of wrist extension and at least 10° of active extension of each metacarpophalangeal and interphalangeal joint of all digits, and lower-functioning participants who shows at least 10° of active wrist extension, at least 10° of thumb abduction/extension, and at least 10° of extension in at least 2 additional digits. Preferably, these movements had to be repeated 3 times in 1 minute. (101)

Although severity of stroke was not tested formally in this review, the ability to extend one or more fingers of the paretic side seems to be natural due to the fact that active repetition of movements and activities is not possible when there is no function at all. Recent transcranial magnetic stimulation (TMS) (86) and diffusion tensor imaging (DTI) (102, 103) studies have shown that voluntary wrist and, particularly, finger extension are highly associated with the integrity of the corticospinal tract (CST) system. This motor function is the strongest clinical predictor of the return of some dexterity in the first days post stroke. (103-106) Accordingly, Fritz and colleagues showed in 55 chronic stroke subjects that initial presence of finger extension was the only significant predictor of outcome of the WMFT after applying original CIMT. (107) Accordingly, the selection of patients with some extension of wrist and fingers should be seen as a key factor determining the potential for change(103, 105) and reversal of learned non-use by CIMT after stroke. (107) In addition, due to concerns about the safety of the restraint by a sling or splint applied in the original form of CIMT, (36) which might prevent adequate protective reactions to control standing balance, the restraint has been replaced by a padded mitt,(108) and patients should be able to stand for at least 2 minutes with or without support. (16) Other, more general criteria, included a Mini-Mental State Examination (MMSE) score of ≥ 24 , no major medical problems that could interfere with participation, no history of previous stroke, no excessive pain or spasticity in the paretic extremity, enough stamina to participate, and age above 18 years. (16) Collectively, these inclusion criteria suggest that (m)CIMT is best restricted to patients with a mild to moderate paresis with a predominantly favorable prognosis for dexterity early post stroke. To date, about 10% (range 3(53) to 90%(59)) of the initially screened patients of included trials in the present review was eligible for (m) CIMT.

Synthesizing current evidence of (m)CIMT

From systematic review of the literature and subsequent meta-analyses it is clear that modified versions of CIMT (n=44) and FU (n=6) have been investigated in several mainly small, underpowered trials, whereas original CIMT has only been investigated in one sufficiently powered landmark trial. (28) Despite the heterogeneity among the forms of mCIMT applied, meta-analyses show that original and modified versions of CIMT have a robust, clinically meaningful impact on patient's outcomes for arm-hand activities, self-reported amount and quality of arm-hand use in daily life, and basic ADL, making (m)CIMT one of the most effective interventions for the upper paretic limb post stroke. (5) For example, an anchor-based change of 12 to 17 points (21-30%) in dexterity following the ARAT is considered as 'clinically important' or 'meaningful' in patients measured within the first month post stroke. (109), whereas in chronic stroke victims, a distribution-based change of about 6 points (10%) is found as clinically meaningful on the ARAT (110). This finding further emphasizes that the minimal clinically important difference (MCID) of used upper extremity measures such as ARAT and WMFT are not only context specific but also dynamic in time.(109)

With the exception of muscle tone and basic ADL, the significant positive effects were sustained in the longer term, even though the size of SESs decreased after ending (m)CIMT. In addition, original CIMT showed evidence of benefits in long-term health-related quality of life.(28)

This review also suggests that (m)CIMT has no significant effects on grip strength, sensibility, pain, or health-related quality of life post intervention. However, the statistical power underpinning the evidence was limited by the insufficient numbers of patients in (m)CIMT trials using these outcomes. A summary of findings in terms of body functions, activities and participation is shown in Table 1.

This review also suggests that, based on RCTs in which the only difference between the experimental and control groups was wearing a mitt on the less affected arm without a structured exercise program (i.e. FU), no superiority to the outcome was found. This finding suggests that procedures involving shaping, repetitive exercises and instructions for behavioural change are the most important components of (m)CIMT. Despite the large number of trials identified, sensitivity analyses showed no significant differences between types of CIMT regimen, timing of (m)CIMT post stroke, or treatment contrast between experimental and control groups.

Overall, the methodological quality or treatment contrast did not significantly affect our results, however small mCIMT trials with lower methodological quality did significantly overestimate the post intervention scores on motor function, while self-reported amount of arm-hand use in daily life showed overestimation of its effect sizes in the long term (see supplementary web appendix 6).

These findings further extend the knowledge of the effectiveness of CIMT and hypothetical accompanying mechanisms from previous reviews,(6-10, 12, 13, 15, 111) by determining the effects and especially their sustainability on all domains of the ICF, based on well-

powered meta-analyses. The post intervention effects on the activities level were confirmed, but the present review also shows that the effects are maintained for at least 4-5 months after termination of the intervention. In addition, the present review showed strong evidence that CIMT has greater effects on motor function only when applied in the earlier stages post stroke, in which it is assumed that restitution of neurological functions is still possible, but that in the later phases CIMT solely influences arm-hand activities by learning to use adaptation strategies (i.e., compensation) to improve upper limb performance in ADLs.(14)

Limitations

The present systematic review has some limitations. First, we could only explore differential effects between original type of CIMT and mCIMT by using forest plots. However, the 44 mCIMT trials are heterogeneous in terms of content and intensity. Second, although we did not detect common threats to meta-analyses from small-study effects or publication bias, (112) we may have missed small negative trials. We synthesized only aggregate study level data obtained from cited studies of sufficient methodological quality (i.e., PEDro > 4). Including the 5 trials with low methodological quality would not have affected significantly the overall medium sized effects and conclusions in the present review. Unfortunately, we were unable to perform meta-analysis of individual patient data.(113) As a consequence, we were unable to investigate possible effect modifiers, such as arm dominance and the influence of cognitive limitations such as dyspraxia, age, or type of stroke. To investigate long-term effects, we pooled data from trials with different follow-up intervals. Also, our meta-analyses of measures such as grip strength and health-related quality of life were underpowered, so the effect of (m)CIMT on these outcomes remains unclear. Our sensitivity analyses should be interpreted with caution; due to uneven distribution across subgroups and in some cases inclusion of only one trial in a subgroup, these analyses should mainly be seen as indications.(114)

Analyses of the statistical power of pooled trials showed that about half of the statistical analyses for (m)CIMT and FU post intervention and in the longer term are sufficiently powered (supplementary web appendix 5 and 6). The lack of statistical power applies more to the pooled trials that started within the first three months post stroke, as well for those studies that investigated the sustainability of (m)CIMT.

Finally, the optimal dosage of (m)CIMT remains unclear, but should range between the numbers as described in the section 'The CIMT protocol'. Although not tested formally in this review due to the lack of a sufficient number of RCTs, the use of a transfer package to enhance intensity of practice could be considered.

Future directions

The present review shows that only 15 out of the 51 trials provided mCIMT within the first weeks post stroke, whereas all these RCTs were small, phase II trials. This finding suggests that more mCIMT trials are needed preferably starting within the first days post stroke using different doses of upper limb training. There is growing evidence from animal studies that the brain shows increased neuroplasticity in the early phases post stroke. This finding suggests that normalization of motor control by true neurological recovery could be

maximized within this time window.(92, 93, 100) Results from several animal studies(100, 115-117) suggest that (m) CIMT in the first weeks after stroke may enhance up-regulation of growth promoting factors such as protein 43, synaptophysin and other brain derived neurotrophic factors. (117) In addition, Zhao and colleagues recently showed that applying (m) CIMT from weeks 1 to 3 post stroke significantly suppressed the up-regulation of growth inhibiting factors such as Nogo-A, Nogo receptors and RhoA expressed in the peri-infarct cortex in Wistar rats.(117) In these animals, mCIMT resulted in significant structural post-synaptic plastic changes in the denervated cervical spinal cord. (117) Applying mCIMT for 4 weeks directly after stroke fosters reorganization of the somatosensory cortex and its neural network.(118) One emerging question is whether the structural plasticity introduced by early applied mCIMT also leads to true neurological repair beyond the existing mechanisms of spontaneous neurological recovery in the first phase post stroke.(92) The limited time window of neural mechanisms assumed to play a role in the natural logarithmic pattern of spontaneous neurological recovery of body functions (or reduction in impairments) may further underline the need for more RCTs with intensive serial assessments in time early post stroke. Preferably, to improve our understanding of skill acquisition by mCIMT, these observed improvements in repeated assessments should be associated with serial measures of kinematics, biomechanics and non-invasive neuroimaging techniques post stroke.(2, 92)

Second, there is a need to investigate the assumptions of learned “misuse” when patients learn to use their end-effectors in a different adaptive way to normalize motor control early post stroke.(119) Such research should objectively and intensively monitor the quality of motor control in terms of temporal-spatial activation patterns of the upper limb and trunk using 3D-kinematics and EMG-controlled measures in addition to complementary clinical outcomes. (92) This approach would allow investigation of changes in end-effectors of the paretic arm and trunk during stroke recovery. (94) Preferably, these coordination measures should be related to neuronal correlates to allow appropriate interpretation of changes in neuroplasticity observed in animal studies. (92, 120, 121)

Third, additional research is needed to investigate possible detrimental effects of very high doses of early applied (m)CIMT (i.e., > 3 hours) within this time window of increased homeostatic neuroplasticity, as suggested by some studies among animals (122-124) and patients with stroke. (53) Interestingly, a recent meta-analysis involving 8 animal trials showed no significant inverse dose-response relationship of (m)CIMT on infarct volume (-3%, 95%CI 15-9; p= p=0.63).(121) This finding further emphasizes that animal models may help us to efficiently explore the biological basis of rehabilitation interventions, but also questions its generalizability to humans. (121)

Fourth, none of the identified trials reported the influence of phenotypic factors such as gender, age or type of stroke on the effects of (m) CIMT on outcome after stroke. One trial claimed larger effects for chronic stroke patients with sensory deficits and neglect. (37) Investigating the relation between individual patient characteristics and the effects of (m)CIMT requires meta-analysis of individual patient data to identify possible effect modification by patients' phenotypes.(113)

Fifth, most mCIMT trials lack transparency in the treatment protocol with respect to content, timing post stroke and therapy dosage. Fortunately, most journals now accept online submission of treatment protocols applied in trials. In addition, consensus is needed on the content and timing of test batteries applied to evaluate (m) CIMT. (2)

Finally, the barriers to implementation of (m)CIMT and factors which may enhance real-world use of the upper paretic limb require further investigation. (23) In view of the limited health care resources in most countries, and the increasing numbers of stroke survivors, there is a need to investigate the cost-effectiveness of (m)CIMT compared to usual care. (16) Adding therapy time will result in a concomitant increase in health-care costs, however effective therapy could potentially reduce rates of readmission to hospitals and admission to long-term care institutions. (125) In addition, innovative, adaptive forms of (m)CIMT, such as group sessions to reduce the staff-to-patient ratio and costs, self-training mCIMT programs (e.g., (126)), caregiver-support, and supervised practice by e-health support and telerehabilitation services, need to be investigated and compared with the usual face-to-face (m)CIMT regarding cost-benefit. (11)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel 1**Search strategy and selection criteria**

We identified relevant publications by searching PubMed, EBSCO *host*/Excerpta Medica Databank (EMBASE), EBSCO*host*/Cumulative Index of Nursing and Allied Health Literature (CINAHL), Wiley/Cochrane Library (Cochrane Database of Systematic Reviews [CDSR], Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Methodology Register [CMR], Database of Abstracts of Reviews of Effects [DARE], Health Technology Assessment Database [HTA], NHS Economic Evaluation Database [EED]) and Physiotherapy Evidence Database (PEDro) (all databases last searched 24-09-2013 by JMV). The indexing terms and free-text terms with synonyms and related terms in the title or abstract used were: “stroke” and “physical restraint” or “constraint-induced movement therapy” or “forced use” or “immobilization” or “learned nonuse” and “randomized controlled trial” or “reviews” (supplementary web appendix 2). One reviewer (JMV) screened the titles, abstracts, if relevant full-text publications, and references of included RCTs. The inclusion criteria were: (1) adult stroke patients; (2) RCT design, including those with a two-group parallel, multi-arm parallel, crossover, cluster or factorial design; (3) the experimental intervention conformed to the definitions of original CIMT, mCIMT, or FU; (4) the comparator was usual care, another intervention, the same intervention with a different dose, or no intervention; (5) outcomes were measured post intervention and/or at follow-up; and (6) publication in the English, French, German, or Dutch.

Figure 1. Constraint-induced movement therapy

Illustration of task-oriented practice with the paretic limb in a Constrained Induced Movement Therapy session. Use of the non-affected limb is restricted by a padded mitt.

Figure 2. Forest plot of constraint-induced movement therapy post intervention

This figure displays the summarized effects of original CIMT, modified CIMT and forced use post intervention, classified according to the International Classification of Functioning, disability and health (ICF; World Health Organization). Please consult supplementary web appendix 5 for Hedges' g (95%CI) in numbers. Background colors represent the different ICF-categories, body functions (pink), activities (blue), and participation (orange). The italic numbers in the statistical power column indicate sufficient power ($1-\beta \geq 0.80$). 95%CI, 95%

Confidence interval; ADL, Activities of daily living; C, Control group; CIMT, Constraint-induced movement therapy; E, Experimental group; N/A, Not applicable.

References: (a) 33-35, 37, 38, 43, 45, 46, 49, 50, 57, 62, 64, 70, 71, 73, 80, 82; (b) 39, 42; (c) 55, 73; (d) 46, 82; (e) 46, 75; (f) 28; (g) 31, 33-43, 45-47, 51-56, 73, 75-78, 80-82; (h) 28; (i) 34, 37, 41, 43, 46, 52, 54, 55, 57, 61-64, 70-73, 75, 77, 78, 80-82; (j) 67, 69; (k) 28; (l) 34, 36, 37, 41, 43, 46, 49-52, 54, 55, 57, 61, 62, 64, 70-73, 75, 77, 78, 80-82; (m) 67, 69, 79; (n) 41, 47, 52, 54, 62-64, 66, 71; (o) 53, 81, 82; (p) 81, 82.

Figure 3. Forest plot of constraint-induced movement therapy in the long term

This figure displays the summarized effects of original CIMT, modified CIMT and forced use in the long term (4-5 months), classified according to the International Classification of Functioning, disability and health (ICF; World Health Organization). Please consult supplementary web appendix 6 for Hedges' g (95% CI) in numbers. Background colors represent the different ICF-categories, body functions (pink), activities (blue), and participation (orange). The italic numbers in the statistical power column indicate sufficient power ($1-\beta \geq 0.80$). 95% CI, 95% Confidence interval; ADL, Activities of daily living; C,

Control group; CIMT, Constraint-induced movement therapy; E, Experimental group; N/A, Not applicable.

References: (a) 37, 46, 49, 50, 82; (b) 55, 73; (c) 28; (d) 37, 41, 42, 46, 48, 49, 50, 52, 53, 55, 73, 75, 78, 82; (e) 28 ; (f) 37, 41, 46, 49, 50, 52, 55, 73, 75, 78, 82; (g) 28; (h) 37, 41, 46, 49, 50, 52, 55, 73, 75, 78, 82; (i) 41, 52; (j) 28; (k) 28.

Table 1
Summary of evidence for constraint-induced movement therapy according to the ICF

In this table, the evidence for original CIMT, modified CIMT, and forced use post intervention and in the long term (4-5 months) are summarized according to the International classification of function, disability, and health model (ICF). ✓, beneficial or likely to be beneficial based on significant positive summary effect sizes; ×, uncertain benefit based on non-significant summary effect sizes; ?, unknown effect based on the inability to statistically pool data of RCTs; *, only beneficial or likely to be beneficial within the first 3 months post stroke. ADL, Activities of daily living; AOU, Self-reported amount of arm-hand use in daily life; CIMT, Constraint-induced movement therapy; FU, Forced use; QoL, Quality of life; QOM, Self-reported quality of arm-hand movement in daily life.

	Original CIMT		Modified CIMT		Forced use therapy	
	Post-intervention	Long term	Post-intervention	Long term	Post-intervention	Long term
Motor function arm	?	?	✓*	✓*	?	?
Grip strength	×	?	×	?	×	?
Muscle tone	?	?	✓	×	?	?
Sensibility	?	?	×	?	?	?
Pain	?	?	×	?	?	?
Arm-hand activities	✓	✓	✓	✓	?	?
AOU	✓	✓	✓	✓	×	?
QOM	✓	✓	✓	✓	×	?
Basic ADL	?	?	✓	×	?	?
QoL—hand function	?	✓	×	?	?	?
QoL—basic ADL	?	?	×	?	?	?