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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 treatment of patients. Original CIMT includes constraining of the non-paretic arm for 90% of the waking time, intensive task-oriented training, and behavioral strategies. Modified versions also apply constraining of the non-paretic arm and task-oriented training but not as intensive as original CIMT and behavioral strategies are mostly lacking. With forced use, only constraining of the non-paretic arm is applied. The original and modified types of CIMT have favorable results 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 there is no evidence for constraint alone (as used in forced use therapy). The type of CIMT, timing, or intensity of practice does not affect patient outcomes. Although the underlying mechanisms that drive original and modified CIMT are still poorly understood, findings from kinematic studies suggest that improvements introduced by original CIMT or mCIMT are mainly based on adaptation through learning to optimize the use of intact end-effectors by selection of patients with some voluntary motor control of wrist and finger extensors after stroke.

INTRODUCTION

16.9 million people worldwide have a first stroke every year, resulting in about 33 million stroke survivors and 5.9 million stroke-related deaths,¹ making stroke the second most common cause of death and one of the main causes of acquired adult disability.^{1,2} Around 80% of these survivors have motor impairments of the upper limb³ that gravely affect their ability to perform activities of daily living and their social participation. The severity of upper limb paresis is an independent determinant of the outcome of basic activities of daily living after stroke.⁴

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

Although several systematic reviews concerning have been done,⁶⁻¹³ there is no current meta-analysis of randomized controlled trials (RCTs) of (m)CIMT or forced use (without a structured exercise program) that includes thorough analyses of possible effect modifiers and small-study effects. Of available reviews, some have an incomplete literature search strategy,^{6,7,14} whereas others are restricted to a specific set of mCIMT interventions,¹⁵ dose-matched controlled interventions,¹³ a specific period after stroke,^{10,12} or a best-evidence synthesis based on the methodological quality of included trials.¹¹

In this review, first, we give a brief historical background and description of the original CIMT protocol. On the basis of a systematic review of the literature and subsequent meta-analysis of RCTs, we summarize the evidence for CIMT, mCIMT, and forced use therapy in adult patients with stroke. In a subsequent sensitivity analysis of included RCTs, we explore the effects of type of CIMT, dose of therapy, and timing of therapy after stroke. We then discuss the effects of assumed underlying mechanisms that drive (m)CIMT and propose criteria to select patients who will benefit most from (m)CIMT.

HISTORY OF CIMT

The theoretical framework for CIMT has a long history.^{16,17} In 1909, the German scientist Munk¹⁸ 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 required. This work was quickly followed by the classic studies by Ogden and Franz in 1917, who noted that monkeys move

freely after lesions to their pyramidal tract.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 rapidly accomplished. This finding suggests that the limitation was not inability but one of disuse. This concept of forced use was revived several decades later by Knapp²⁰ and in studies by Taub,²¹ who applied the deafferented monkey model by dorsal rhizotomy of the nerves of the upper limb, to show that these animals would not use an insensate limb unless a series of behavioral strategies were used to overcome learned non-use.

DEFINITION OF CIMT

The signature protocol for the original form of CIMT contains three components or treatment packages: first, intensive, graded practice of the paretic upper limb to enhance task-specific use of the affected limb for up to 6 hours a day for 2 weeks (i.e. shaping; Figure 7.1); second, constraint or forced use, with the non-paretic upper limb constraint in a mitt to promote the use of the

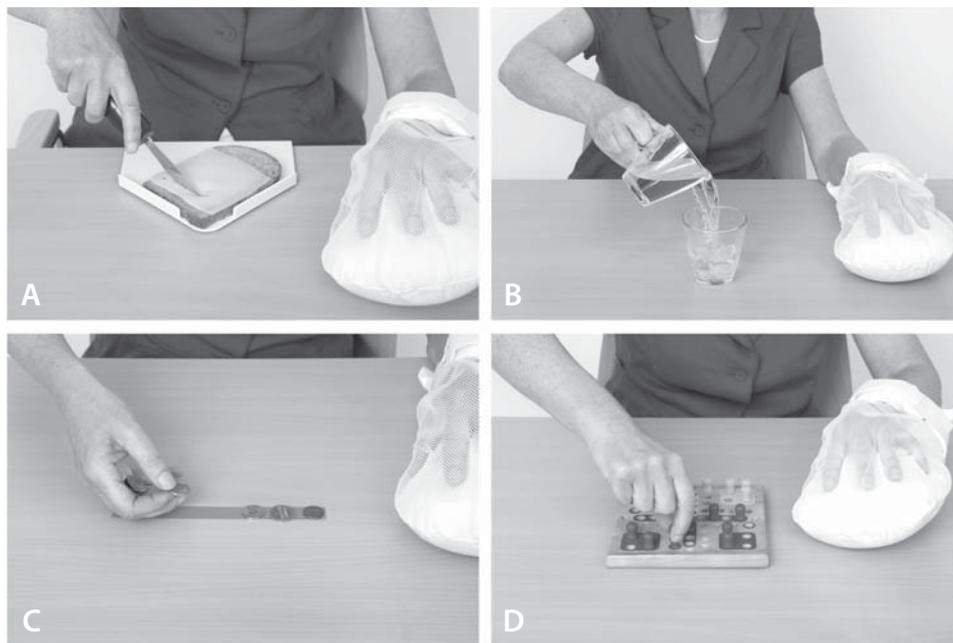


Figure 7.1 Task-oriented practices with the paretic limb in constraint-induced movement therapy (CIMT) Practices include cutting bread (A), pouring water (B), picking up and placing back money (C), and playing a game (D). Use of the unaffected limb is restricted by a padded mitt.

more impaired limb during 90% of the hours awake; and third, 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 whereas forced use does not rely upon any conditioning.^{25,26} Taub and colleagues²⁷ investigated the first proof of the original concept of CIMT in nine patients with chronic stroke. Their positive findings about motor function, dexterity, and self-reported arm-hand use in daily life were repeated in a multicenter trial of 222 patients with stroke.²⁸⁻³⁰ Trials by other research groups have applied mCIMT that vary in dose, timing, and composition of therapy. Although fundamental components of the original form of CIMT were applied, these modifications are typically characterized by distributed training protocols with less time spent in training, less time during which the non-paretic upper limb is restrained, and no transfer package or a contract with the patient, but more training days.^{31,32} Treatment sessions for mCIMT vary from 30 minutes³³⁻³⁵ to 6 hours³⁶⁻⁴⁴ a day, and from 2⁴⁵ to 7⁴⁶ sessions a week, for between 2^{23,36-45,47-56} to 12 weeks. Because of the wide variety of these adaptations, a systematic review and subsequent meta-analysis of trials applying original CIMT or mCIMT is needed. Panel 7.1 summarizes definitions and description of rehabilitation terminology for (m)CIMT in this review.

EFFECTS OF CIMT

CIMT has been investigated in 51 RCTs,^{23, 28-31,33-82} and in 1784 adult patients with stroke, but only 15 trials included patients within the first 3 months after stroke.^{34,45,47,49,50,52,53,56,59, 66,67,69,76,78,82}

Panel 7.2 gives a quick overview of the search strategy and selection criteria for our systematic review, while the Supplementary Web Appendix provides further details about the search strategy, methods, and flow chart.

ORIGINAL CIMT

Original CIMT, although seen as the gold standard, has been investigated in only one RCT²⁸⁻³⁰ that included patients who had had a stroke more than 3 months previous to enrolment in the trial (Supplementary Web Appendix). After CIMT, significant positive medium to large effect sizes were reported 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 (Figure 7.2; Supplementary Web Appendix). Additionally, significant positive effects in the long term were reported for quality of life related to hand function and activities of daily living (Figure 7.3; Supplementary Web Appendix).

Panel 7.1 Definitions and description of rehabilitation terms

Original constraint-induced movement therapy (CIMT) – A form of rehabilitation therapy that consists of three components: immobilization of the non-paretic arm with a padded mitt for 90% of the waking hours; task-oriented training with a high number of repetitions for about 6 hours a day during 10 consecutive working days; and, behavioral strategies to improve both compliance and transfer of the practiced activities from the clinical setting to the patient’s home environment.^{22,127}

Modified CIMT (mCIMT) – This therapy does not include the three components of original CIMT, but is restricted to repetitive, task-specific training of the paretic arm, including shaping procedures, applied in a different dose, combined with constraining of the non-affected hand by a padded mitt, glove, or splint.

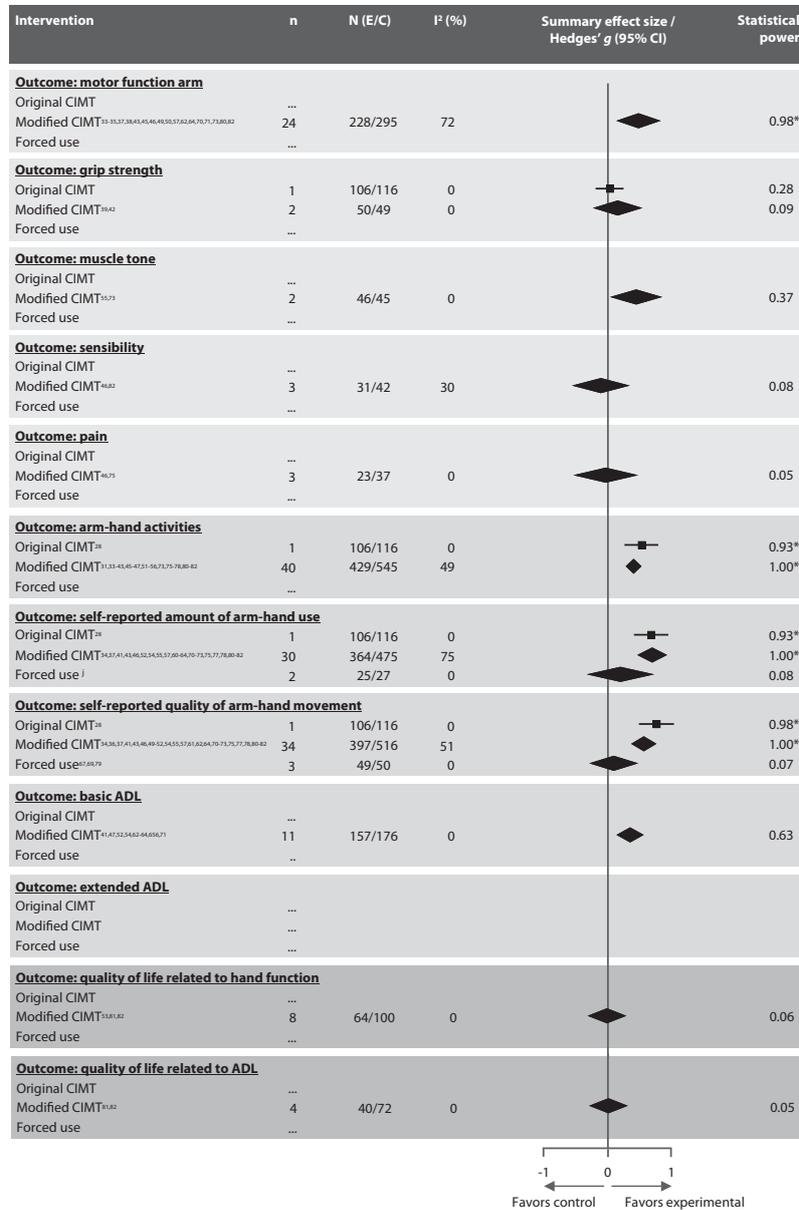
Forced use therapy – An intervention that is limited to immobilization of the nonparetic arm to increase the amount of use of the paretic limb. No formal behavioral training (shaping) is specified in the treatment protocol.

Intensity of original and modified CIMT – Number of hours spent in supervised exercise therapy.^{128,129}

Treatment contrast – Time spent on exercise therapy for the experimental group minus that for the control group.¹²⁸

Panel 7.2 Search strategy and selection criteria

We identified relevant publications of English, French, German, or Dutch by searching PubMed, EMBASE, 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). We searched all databases from inception to September 24, 2013. 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). We included articles that were of adult stroke patients; that used a randomised controlled trial design including those with a two-group parallel, multiarm parallel, crossover, cluster, or factorial design; in which the experimental intervention conformed to the definitions of original constraint-induced movement therapy (CIMT), modified CIMT (mCIMT), or forced use; in which the comparator was usual care, another intervention, the same intervention with a different dose, or no intervention; and in which outcomes were measured after intervention or at follow-up.



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Figure 7.2 Forest plot of effects of constraint-induced movement therapy (CIMT), modified CIMT and forced use after intervention

Classified according to the International Classification of Functioning, disability and health (ICF; WHO). Diamonds represent the overall effect sizes after pooling the standardised mean differences (SDM) based on an adjusted Hedges' *g*. If pooling was not possible, the individual SMD is shown. The Supplementary Web Appendix shows Hedges' *g* (95% CI) in numbers. Background colors represent the different ICF-categories: body functions (light grey), activities (mid grey), and participation (dark grey). * Indicates sufficient statistical power ($1-\beta \geq 0.80$). CI, Confidence Interval; ADL, Activities of Daily Living; C, Control Group; CIMT, Constraint-Induced Movement Therapy; E, Experimental Group.

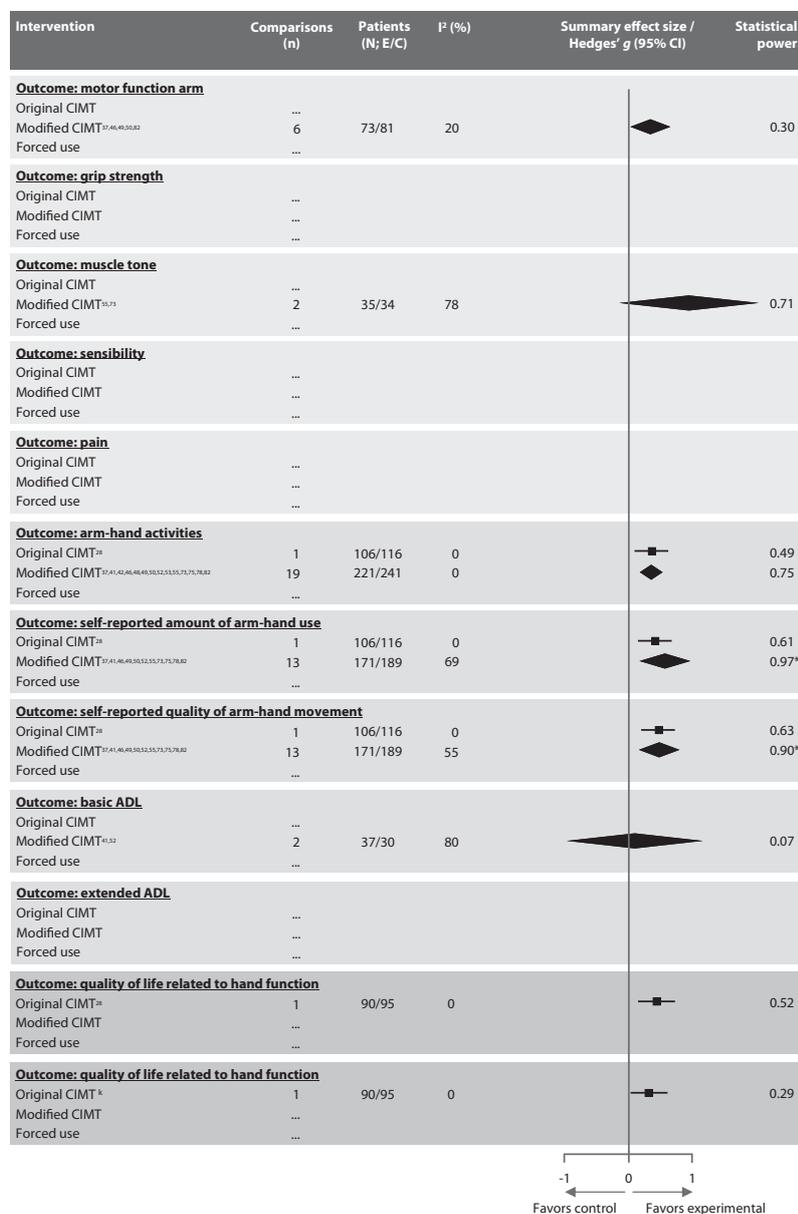


Figure 7.3 Forest plot of the effects of constraint-induced movement therapy (CIMT), modified CIMT, and forced use in the long term

Classified according to the International Classification of Functioning, disability and health (ICF; WHO). Diamonds represent the overall effect sizes after pooling the standardised mean differences (SDM) based on an adjusted Hedges' *g*. If pooling was not possible, the individual SMD is shown. The Supplementary Web Appendix shows Hedges' *g* (95% CI) in numbers. Background colors represent the different ICF-categories: body functions (light grey), activities (mid grey), and participation (dark grey). * Indicates sufficient statistical power ($1-\beta \geq 0.80$). CI, Confidence Interval; ADL, Activities of Daily Living; C, Control Group; CIMT, Constraint-Induced Movement Therapy; E, Experimental Group.

MCIMT

mCIMT has been investigated in many RCTs (n=44; N=1397) (the Supplementary Web Appendix provides details of included mCIMT trials).^{23,31,33-58,61-64,66,70-78,80-82} Significant positive medium to large summary effect sizes have been reported for motor function of the paretic arm, muscle tone, arm-hand activities, self-reported amount of arm-hand use in daily life and self-reported quality of arm-hand movement in daily life, and basic activities of daily living after mCIMT (Figure 7.2; Supplementary Web Appendix). No significant summary effect sizes were noted for grip strength, sensibility, pain, and quality of life related to hand function or quality of life related to activities of daily living (Figure 7.2; Supplementary Web Appendix). The effects were sustained at follow-up (mean 21.58 [SD 13.21] weeks) for motor function of the paretic arm, arm-hand activities, and 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 activities of daily living (Figure 7.3; Supplementary Web Appendix).

FORCED USE THERAPY

Forced use therapy was investigated in 6 RCTs (N=165)^{59,60,65,67-69,79} (Supplementary Web Appendix) but did not show an increased value for self-reported amount of arm-hand use in daily life and self-reported quality of arm-hand movement in daily life (Figure 7.2; Supplementary Web Appendix).

EFFECTS OF TYPE, DOSE, AND TIMING OF CIMT AFTER STROKE AND SMALL STUDY EFFECTS

Sensitivity analysis showed no significant differences in effect sizes between original CIMT and mCIMT, dose of (m)CIMT (additional time spent in exercise therapy between 5 hours⁵¹ and 60 hours^{28,36,38,40,42} [mean 46.8 hours]), and timing of (m)CIMT when comparing trials that started within or after the first 3 months from when a patient had a stroke. Additionally, robust effects for (m)CIMT do not seem to be affected by small-study effects or publication bias, or moderated by risk of bias (Supplementary Web Appendix). Although we noted no evidence for small-study effects, a meta-regression of mCIMT trials showed that methodological quality was a significant effect modifier for motor function after intervention and self-reported use in daily life at follow-up.

WHAT DRIVES IMPROVEMENTS BY CIMT AND MCIMT?

The underlying mechanisms that drive improvement by (m)CIMT are still poorly understood. First, we expected that intensity of task-specific practices (expressed as differences in treatment duration) would be a significant moderator of CIMT. However, our meta-analysis showed no evidence that the type of CIMT or differences in treatment times between groups within a trial – which amounted to a mean of 47 hours – had an effect. 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 every day than is usual in stroke rehabilitation. Additionally, in a retrospective analysis of 169 participants Wolf and colleagues⁸³ showed that the intensity of supervised original CIMT was modified by the amount of repetitive task practice, and to some extent by the initial severity of motor impairment recorded on the Wolf Motor Function Test (WMFT). This finding suggests that the effects of the therapy dose are confounded by the initial severity of neurological deficits. Possible risks of bias, such as blinding of assessors, did not seem to affect the difference between dose-matched trials and non-dose matched trials. These findings accord with a trial⁸² and meta-analysis⁸⁴ showing that dose-matched trials of mCIMT, in which the control group received an equal dose of bilateral arm training, did not record significant differences in overall effect sizes.

Although (m)CIMT may increase short-term^{50,85} and long-term cortical activation patterns,^{42,50,86} the underlying mechanisms responsible for improvements need further investigation. In particular, uncertainty continues to exist about how improvements in motor performance after (m)CIMT relate to cortical activation patterns in the contralesional and ipsilesional cortex after stroke, as shown by transcranial magnetic stimulation (TMS)^{42,86,87} and functional magnetic resonance imaging (fMRI)⁸⁸⁻⁹¹. For example, findings from studies suggest that improved hand function assessed by WMFT is accompanied by increased recruitment of neural networks in the ipsilesional somatosensory cortex.^{89,90} Although significant neural correlates have been reported with upper extremity measurements, such as WMFT, these studies do not address the question of how cortical changes relate to the quality of motor performance in terms of neural repair or use of compensation strategies.⁹² For example, in a controlled proof of concept study, Kitago and colleagues⁹³ did not show significant changes in coordinative measures of the paretic arm and wrist after (m)CIMT in chronic stroke, despite clinically meaningful functional improvements in Action Research Arm Test (ARAT) scores. This finding 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). Furthermore, the enhanced cortical neuroplasticity shown by TMS^{42,86,87} and fMRI⁹⁰ in the subacute^{49,50} and chronic poststroke phases^{42,87} might show learned non-use and compensatory skill learning rather than true neurological repair or recovery of impairments.^{14,92,94}

This assumption is further supported by longitudinal three dimensional 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 poststroke.^{94,95} Improvements in intra-limb coordination are accompanied by a significant reduction in variability⁹⁴ and improvement in the smoothness⁹⁵ of motor performance. The three-dimensional kinematic improvements closely follow the clinical time course of neurological recovery such as patients' improved ability to dissociate from pathologic upper limb synergies^{94,96,97} which are also restricted to the first 3 months after stroke.^{98,99} Our meta-analysis further suggests that the effects of mCIMT on motor function of the arm such as Fugl-meyer Assessment arm scores, is mainly restricted to trials that started within 3 months after stroke (Figure 7.4; Supplementary Web Appendix).^{34,45,49,50,82} This finding is in agreement with the increased 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 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 higher-functioning participants who show at least 20° of wrist extension and 10° of active extension of each metacarpophalangeal and interphalangeal joint for all digits can be distinguished from lower-functioning participants who show at least 10° of active wrist extension, 10° of thumb abduction or extension, and 10° of extension in a minimum of two additional digits. Preferably, these movements had to be repeated three times in 1 minute.¹⁰¹

Although severity of stroke was not formally tested in the present review, the ability to extend one or more fingers of the paretic side seems to be 'natural' because active repetition of movements and activities is not possible when there is no function. Findings from TMS⁸⁶ and diffusion tensor imaging^{102,103} studies have shown that voluntary wrist and, particularly, finger extension are highly associated with the integrity of the corticospinal tract system. This type of motor function is the strongest clinical predictor for the return of some dexterity in the first days after stroke.¹⁰³⁻¹⁰⁶ Fritz and colleagues¹⁰⁷ showed in 55 patients with chronic stroke that initial ability of finger extension was the only significant predictor of outcomes for the WMFT after applying original CIMT. The selection of patients with some extension of wrist and fingers should be regarded as a key factor determining the potential for change^{103,105} and reversal of learned non-use by CIMT after stroke.¹⁰⁷ Additionally, because of 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 was replaced by a padded mitt,¹⁰⁸ and patients should be able to stand for at least 2 minutes with or without support.¹⁶ More general criteria were a Mini-Mental State Examination (MMSE) score of 24 or more, no major medical problems that could interfere with participation, no history of disabling stroke, no excessive pain or spasticity in the paretic extremity, enough stamina to participate, and age older than 18 years.¹⁶ Collectively, these criteria suggest that (m)CIMT is best restricted to patients with a mild to moderate paresis with a predominantly favorable chance for for dexterity early after stroke. About 10% (range from 3%⁵³ to 90%⁵⁹) of initially screened patients of included trials in this review were eligible for (m)CIMT.

SYNTHESIS OF EVIDENCE ABOUT CIMT

mCIMT (44 trials) and forced use (6 trials) have been investigated in several, mainly small, under-powered trials, whereas original CIMT has been investigated in only one sufficiently powered landmark trial.²⁸ Despite the heterogeneity in the forms of mCIMT applied, findings from meta-analyses show that original and modified versions of CIMT have a robust, clinically meaningful effect on patient outcomes for arm-hand activities, self-reported amount and quality of arm-hand use in daily life, and basic activities of daily living, making (m)CIMT one of the most effective interventions for the upper paretic limb after stroke (Figure 7.4).⁵ For example, an anchor-based change of 12–17 points (21–30%) in dexterity on the ARAT is regarded as clinically important or meaningful in patients who are measured within the first month after stroke,¹⁰⁹ whereas in patients with chronic stroke-related deficits, a distribution-based change of about 6 points (10%) in dexterity is clinically meaningful.¹¹⁰ This finding further emphasizes that the minimal clinically important difference 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 activities of daily living, the significantly positive effects of mCIMT (i.e. motor function of the paretic arm, arm-hand activities, amount of arm-hand use in daily life, and quality of arm-hand use in daily life) were sustained in the long term, even though the magnitude of the summary effect sizes decreased at follow up. Additionally, original CIMT had benefits for long term health-related quality of life.²⁸

Our analysis suggests that (m)CIMT has no significant effects on grip strength, sensibility, pain, or health-related quality of life after intervention (Figure 7.4). However, the statistical power underpinning the evidence was limited by the insufficient number of patients in (m)CIMT trials using these outcomes.

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

Figure 7.4 Summary of evidence for constraint-induced movement therapy (CIMT), modified CIMT, and forced use

The evidence for original CIMT, modified CIMT, and forced use after intervention and in the long term (4–5 months) are summarized according to the International Classification of Function, disability and health model (ICF; WHO). Background colors show the different ICF-categories: body functions (light grey), activities (mid grey), and participation (dark grey). ✓, beneficial or likely to be beneficial based on significant positive summary effect sizes; x, uncertain benefit based on non-significant summary effect sizes; ?, unknown effect based on the inability to statistically pool data of RCTs. ADL, Activities of Daily Living; AOU, Self-reported Amount of Arm-hand Use in Daily Life; CIMT, Constraint-Induced Movement Therapy; QoL, Quality of Life; QOM, Self-reported Quality of Arm-hand Movement in Daily Life. * only beneficial or likely to be beneficial within the first 3 months after stroke.

7

Analysis of 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. forced use), showed no benefit. 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 after 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 methods of lower quality did significantly overestimate the post intervention scores for motor function, and self-reported amount of arm-hand use in daily life showed overestimation of its effect sizes in the long term (Supplementary Web Appendix).

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 determination of the effects and especially their sustainability on all domains of the International Classification of Functioning, disability and health, on the basis of sufficiently powered meta-analyses. Post intervention effects on a patient's activity level was reported (Figures 7.2 and 7.4), and we showed that effects are maintained for at least 4–5 months after termination of the intervention (Figures 7.3 and 7.4). Additionally, CIMT has greater effects on motor function only when applied in the earlier stages after stroke, in which it is assumed that restitution of neurological functions is still possible; however, when applied in later phases, CIMT solely affects arm-hand activities by learning to use adaptation strategies (i.e. compensation) to improve upper limb performance in activities of daily living.¹⁴

LIMITATIONS OF OUR ANALYSIS

Our review has some limitations. First, we could explore only differential effects between the original type of CIMT and mCIMT by use of forest plots (Figures 7.2 and 7.3). However, therapy applied in the 44 mCIMT trials are heterogeneous in terms of content and intensity. The duration of the treatment sessions, the number of treatment sessions, and the duration of the treatment period differed between RCTs, resulting in variations in the total time that patients spent in mCIMT. Second, although we did not detect common threats to meta-analyses such as small-study effects or publication bias.¹¹² However, we might have missed small negative trials. We synthesized only aggregate study level data obtained from cited studies of sufficient methodological quality (i.e. Physiotherapy Evidence Database score of >4 out of 10 points). Including the five trials with moderate methodological quality would not have significantly affected the overall medium-sized effects and conclusions in this review. Unfortunately, we were unable to perform meta-analysis of individual patient data.¹¹³ As a result, we could not investigate possible effect modifiers such as arm dominance, and the effect 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. Furthermore, 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 is unclear. Our sensitivity analyses should be interpreted with caution because of uneven distribution across subgroups,

and in some cases inclusion of only one trial in a subgroup; these analyses should therefore mainly be seen as indications.¹¹⁴

Analyses of the statistical power of pooled trials showed that about half of the analyses for (m)CIMT and forced use after intervention and in the longer term were sufficiently powered (Figures 7.2 and 7.3, and Supplementary Web Appendix). Low statistical power applies more to pooled trials that started within the first 3 months after stroke and for those investigations of the sustainability of (m)CIMT.

Finally, the optimum dose of mCIMT is not known, but treatment sessions for mCIMT should range between 30 minutes³³⁻³⁵ to 6 hours³⁶⁻⁴⁴ a day, and from 2⁴⁵ to 7⁴⁶ sessions a week, for between 2^{23,36-45,47-56} to 12 weeks. Although not tested formally in this review because of an insufficient number of RCTs, the use of a transfer package to enhance intensity of practice could be considered.

FUTURE DIRECTIONS

Our review shows that only 15 out of the 51 trials provided mCIMT within the first weeks after stroke, whereas all these 51 RCTs were small, phase II trials. More mCIMT trials are needed that preferably start within the first days after stroke and use different doses of upper limb training. Evidence from animal studies shows that the brain has increased neuroplasticity in the early phases after stroke, which suggests that normalization of motor control by true neurological recovery could be maximized within this time.^{92,93,100} Several animal studies^{100,115-117} suggest that (m)CIMT in the first weeks after stroke may enhance upregulation of growth promoting factors such as protein 43, synaptophysin, and other brain derived neurotrophic factors.¹¹⁷ Additionally, Zhao and colleagues¹¹⁷ showed that application of (m)CIMT from weeks 1 to 3 after stroke significantly suppressed the upregulation of growth inhibiting factors such as Nogo-A, Nogo receptors, and RhoA expressed in the peri-infarct cortex in Wistar rats. In these animals, mCIMT resulted in significant structural post-synaptic plastic changes in the denervated cervical spinal cord.¹¹⁷ Application of mCIMT for 4 weeks directly after stroke caused reorganization of the somatosensory cortex and its neural network.¹¹⁸ An 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 after stroke.⁹² The restricted time for neural mechanisms that are assumed to play a part in the non-linear pattern of spontaneous neurological recovery of body functions (or reduction in impairments) might emphasize the need for more RCTs with intensive serial assessments early after stroke. To improve knowledge about skill acquisition by mCIMT, improvements in repeated assessments should be associated with serial measures of kinematics, biomechanics, and non-invasive neuroimaging techniques after stroke.^{2,92}

Investigations are needed about assumptions of learned misuse when patients learn to use their end-effectors in a different adaptive way to normalize motor control early after 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 three-dimensional kinematics and electromyography-controlled measures, in addition to clinical outcomes.⁹² This approach would allow investigation of the adaptive changes in the unaffected parts (or: end-effectors) of the paretic arm and trunk during stroke recovery.⁹⁴ Coordination measures should be related to neuronal correlates to allow appropriate interpretation of changes in neuroplasticity noted in animal studies.^{92,120,121}

Additional research is also needed to investigate possible detrimental effects of very high doses of early applied (m)CIMT (i.e. >3 hours) within this time of increased homeostatic neuroplasticity, as suggested by some studies in animals¹²²⁻¹²⁴ and in patients with stroke.⁵³ However, a recent meta-analysis¹²¹ of eight animal trials showed no significant inverse dose-response relationship of mCIMT on infarct volume (-3%, 95% CI, -15-9; p=0.63). This finding not only further emphasizes that animal models might help to efficiently explore the biological basis of rehabilitation interventions, but also questions its generalizability to humans.¹²¹

No identified trials reported an effect of phenotypic factors such as sex, age or type of stroke, on the effects of (m)CIMT on outcome after stroke. Investigators of a trial claimed large effects for patients with chronic stroke with sensory deficits and neglect.³⁷ The relation between individual patient characteristics and the effects of (m)CIMT needs further meta-analysis of individual patient data to identify possible effect modification by patients' phenotypes.¹¹³

Most mCIMT trials do not have a transparent treatment protocol with regard to content, timing after stroke, and doses of therapy. Fortunately, investigators are now publishing their treatment protocols more often in journals. Additionally, consensus is needed on the content and timing of tests applied to assess (m)CIMT.²

Final, barriers to implementation (m)CIMT and factors that might enhance real-world use of the upper paretic limb need further investigation.²³ In view of the scarce health-care resources in most countries and increasing numbers of stroke survivors, the cost-effectiveness of (m)CIMT compared to usual care needs to be assessed.¹⁶ Additions to therapy time will result in a concomitant increase in health-care costs; however, effective therapy could reduce rates of readmission to hospitals and admission to long-term care institutions.¹²⁵ Furthermore, innovative, adaptive forms of (m)CIMT, such as group sessions to reduce the staff-to-patient ratio and costs, self-training mCIMT programs,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 for any cost-benefit.¹¹

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