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Review

Early-phase dose articulation trials are underutilized for post-stroke motor recovery: A systematic scoping review

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ABSTRACT

Background: To enable development of effective interventions, there is a need to complete systematic early-phase dose articulation research. This scoping review aimed to synthesize dose articulation research of behavioral motor interventions for stroke recovery.
Methods: MEDLINE and EMBASE were systematically searched for dose articulation studies. Preclinical experiments and adult clinical trials were classified based on the discovery pipeline and analyzed to determine which dose dimensions were articulated (time, scheduling or intensity) and how they were investigated (unidimensional vs multidimensional approach). Reporting of dose, safety and efficacy outcomes were summarized. The intervention description, risk of bias, and quality was appraised.
Results: We included 41 studies: 3 of preclinical dose preparation (93 rodents), 2 Phase I dose ranging (21 participants), 9 Phase IIA dose screening (198 participants), and 27 Phase IIB dose finding (1879 participants). All studies adopted a unidimensional approach. Time was the most frequent dimension investigated (53%), followed by intensity (29%), and scheduling (18%). Overall, 95% studies reported an efficacy outcome; however, only 65% reported dose and 45% reported safety. Across studies, 61% were at high risk of bias, and the average percentage reporting of intervention description and quality was 61% and 67%, respectively.
Conclusion: This review highlights a need to undertake more high-quality, early-phase studies that systematically articulate intervention doses from a multidimensional perspective in the field of behavioral motor stroke recovery. To address this gap, we need to invest in adapting early phase trial designs, especially Phase I, to support multidimensional dose articulation.

1. Introduction

The volume of stroke recovery research has increased exponentially over recent decades, with a noticeable shift toward later-phase clinical trials. Appropriate application of Phase III trials can determine the therapeutic efficacy of an intervention through adequately powered studies [1]. To achieve this, interventions should first investigate the biological basis for recovery, safety, and feasibility with a systematic phased approach [1].

Behavioral motor interventions for stroke recovery are complex, with multiple inter-related components that collectively aim to address a specific post-stroke impairment [2]. A rationale (theoretical and biological) to justify the selection of components is required to have confidence in trial results. Previous stroke recovery trials have often evaluated relatively low doses of therapy (~ 30 min/day) [3] and/or recruited participants at late post-stroke stage (> 6 months)[4]. Determining whether the therapy was ineffective in terms of how much, when or what was delivered is

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difficult. Dose (how much) is considered a key component to systematically investigate prior to intervention testing in later-phase trials, but optimizing dose for the best recovery continues to be a challenge [3]. Lack of consideration for the complexity of dose is a potential reason for neutral Phase III trial results [3]. A framework for complex intervention development exists, detailing a broad process of development, feasibility, implementation and evaluation [5]. This framework informs researchers about what to do but not how to go about it. In particular, it does not outline a systematic approach to investigate the individual components, such as dose, within the development stage. To address this gap, we previously defined a systematic discovery pipeline approach [6] based on the principles and clinical trial phases in the US Food and Drug Administration (FDA) [1] guidelines for clinical research. This pipeline serves to address an international consensus recommendation [3] that defined the need to systematically investigate dose.

To apply this pipeline approach, a clear definition of dose is necessary. In pharmaceutical interventions, dose refers to the amount of drug delivered to elicit a physiological response and may vary in terms of scheduling or intensity. For non-pharmacological interventions, the identification and operationalization of dose is more challenging. In the context of behavioral motor interventions, the challenges stem from the increased complexity of interventions, with dose dimensions often poorly quantified or controlled within the study design [7]. Preclinical experiments have tended to consider dose in terms of repetitions (e.g., number of reaches) [3]. Largely for pragmatic reasons, clinical trials usually focus on time in therapy environment [8]. For this review, we used the most common definitions reported in the literature that capture recognized dose dimensions of behavioral motor interventions [9]. These include the following:

- dose dimensions, including:
  - time: time on task and time in therapy environment,
  - scheduling: number of sessions/day, number of days/week, intervention duration, and
  - intensity: level of task difficulty, e.g., repetitions/minute, rating of perceived exertion or amount of rest period;
- dose articulation studies aim to investigate dose by manipulating one or more dose dimensions while keeping others fixed;
- discovery pipeline [6] demonstrates a systematic phased approach that links preclinical and clinical dose articulation studies within their appropriate phases.

A clear understanding of the multiple dose dimensions and a systematic approach to guide their investigation is key to align stroke recovery research with international consensus recommendations [3]. A lack of early phase research that systematically articulates the multiple dose dimensions can result in expensive Phase III trials that do not have a clear justification for dose. Skipping steps in the development of complex, behavioral motor interventions is a barrier to advancing stroke recovery research. Therefore, we must first understand how much early-phase dose articulation research has been completed in the context of behavioral motor interventions for stroke recovery.

2. Identifying the research question

The objective of this scoping review was to address what is known about dose articulation in preclinical and clinical stroke recovery, focusing on behavioral motor interventions. Our aims were to synthesize the literature on dose articulation in preclinical and clinical research, and discuss how well dose articulation designs adopted by individual studies address their stated research aim.

2.1. Methods

We followed an established 5-stage methodological framework [10,11]: identifying the research question, identifying relevant studies, study selection, charting the data, and collating, summarizing and reporting the results. This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses scoping review (PRISMA-ScR) guidelines [12] and adheres to the prespecified protocol [6].

2.2. Identifying relevant studies

MEDLINE and EMBASE were systematically searched for articles published in English up to August 6, 2020 (strategy in Supplement File 1, Appendix A). Reference lists of relevant studies including systematic reviews were hand-searched. For scientific and pragmatic reasons, the preclinical search was restricted to upper-limb behavioral motor interventions (reaching/retrieval; see Supplement File 1, Appendix A, for rationale). Terms for the preclinical search included words related to stroke, recovery, reaching, and animals and for the clinical search included stroke, recovery, dose, and early phase designs.

2.3. Study selection

Included studies had an explicit aim to articulate dose of a behavioral motor intervention during any phase of stroke recovery [3,13] (eligibility criteria in Supplement File 1, Appendix A). These studies ranged from preclinical experiments to Phase IIB clinical trials as per systematic discovery pipeline [6]. Studies of drug intervention, non-invasive brain stimulation, systematic reviews and conference abstracts were excluded. Search results were managed in Covidence. Given the large volume of articles, one author (ED) screened title/abstracts with a low tolerance to take articles through to full-text screening. Two authors screened full-text articles (ED/DC preclinical; ED/KH clinical). Discrepancies were first discussed to achieve consensus and otherwise with a third reviewer (LC).

2.4. Charting the data

We implemented separate data charting forms for preclinical experiments and clinical trials. Two members (ED/LC) of the research team classified included studies to the most appropriate discovery pipeline phase based on their stated aim [6]. Data were extracted for study information, population information, dose dimensions, study outcomes, intervention description, risk of bias, and quality.

Study information included aim, design, type of intervention (upper limb, lower limb, exercise or function defined in Supplement File 2, Appendix B), dose definition, and outcome timepoints. Data extracted on population information included sample size, sex, age, and phase of recovery per consensus guidelines [3,13]. For reference, the recovery phases for rodents were hyperacute 0–24 h, acute 1 to 5 days, early subacute 5 days to 4 weeks, late subacute 30 to 60 days, or chronic $>$ 60 days, and for non-human primates hyperacute 0 to 24 h, acute 1 to 7 days, early subacute 7 days to 6 weeks, late subacute 6 weeks to 3 months or chronic $>$ 3 months [3]. The clinical recovery phases were defined as hyperacute 0 to 24 hr, acute 1 to 7 days, early subacute 7 days to 3 months, late subacute 3 to 6 months or chronic $>$ 6 months [13].

Dose, safety, and efficacy outcomes were extracted. Consistent with the aims of early-phase dose articulation research, all studies (preclinical to Phase IIB) should report at least dose and safety outcomes. Dose outcomes included reporting one or more of the dose dimensions of time, intensity and schedule (as reported

above). We classified adverse events, including pain, fatigue or withdrawals due to prescribed dose, as safety outcomes. Intervention and dose efficacy outcomes were drawn from clinical measures (e.g., Fugl Meyer Assessment) used to determine the effect of the intervention or dose of intervention provided.

Preclinical intervention descriptions were evaluated by using Animal Research: Reporting of in vivo Experiments (ARRIVE), and the Template for Intervention Description and Replication checklist (TIDieR) was used to evaluate clinical trials. Preclinical risk of bias was rated by using Systematic Review Centre for Laboratory Animal Experimentations (SYRCLE). For clinical trials, the Cochrane Risk of Bias tool 2 (Cochrane RoB2) was used for all randomized controlled trials and the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) for all other designs. The Early Phase Research Quality Checklist (EPRQC) [6] was used to rate the quality of all included studies according to their discovery pipeline phase. The EPRQC was also used to determine whether the stated dose articulation aim was appropriately investigated within an experiment or trial. References for preclinical and clinical rating tools are reported in Supplement File 1, Appendix A).

One author (ED) critically appraised the included experiments and trials with these tools, and a second author (DC preclinical, KH clinical, LC quality) reviewed a random sample ($\geq$ 15%) for reliability.

2.5. Collating, summarizing and reporting the results

Results were tabulated according to the discovery pipeline [6]. Data were analyzed to determine what dose dimensions were articulated (time, scheduling or intensity) and how they were investigated (unidimensional vs multidimensional). Reporting of dose, safety and efficacy outcomes was documented as present or absent. In addition to preclinical dose preparation, we applied the conventional trial phases as outlined in the discovery pipeline [6]: Phase I dose ranging, Phase IIA dose screening, Phase IIB dose finding (response), and Phase IIB dose finding (optimal) to determine the appropriate intervention description and risk of bias and quality tool [6]. The process for rating is outlined in Supplement File 1 (Appendix A).

3. Results

We included 42 studies after full text review (Fig. 1). There was one repeat sample [14], which was a secondary analysis of a Phase IIB clinical trial [4]. Therefore, 41 independent study samples remained for analysis: 3 preclinical experiments (93 rodents) and 37 clinical trials (2098 participants).

All preclinical experiments focused on the upper limb as directed by the search strategy. Most clinical trials aimed to investigate the dose of an upper-limb intervention (60%), followed by the lower limb (21%), exercise (11%), and general function (8%) (results table in Supplement File 2, Appendix B). Intervention was most common in the early subacute or chronic phase of stroke recovery [13] (49% and 37% respectively; results table in Supplement File 2, Appendix B). Despite all studies aiming to investigate the dose of a behavioral motor intervention, a definition of dose was provided in only 24% of included studies. Common phrases used within the studies included "dose response relationship", "high dose/intensity", "low dose/intensity", and "dose effect". However, the definitions reported were not consistent (e.g., dose was considered to include "frequency, intensity, time, and type"[15] as parameters in one trial but defined as a "duration based measure"[16] in another trial). All studies investigated dose from a unidimensional perspective, either screening a dose regimen of fixed dimensions or manipulating one dose dimension while keeping the other dimensions fixed within the regimen (Table 1). Time was the most common dimension manipulated (53%), followed by intensity (29%) and scheduling (18%) (Table 1).

The reported outcomes for each included study are outlined in Table 1. Most studies (95%) reported an efficacy outcome, but only 65% reported a dose outcome and a fewer 45% reported a safety outcome. In all, 27% of studies reported all outcomes (efficacy, dose and safety). Most commonly, studies reported dose and efficacy together (34%), followed by only efficacy (22%), safety and efficacy (12%) and lastly dose and safety (5%). The dose articulation aim for each included study is reported in Supplement File 2 (Appendix B). Preclinical experiments aimed to understand the impact or efficacy of different dose intensities, and the investigation of dose was usually one part of multiple experiments

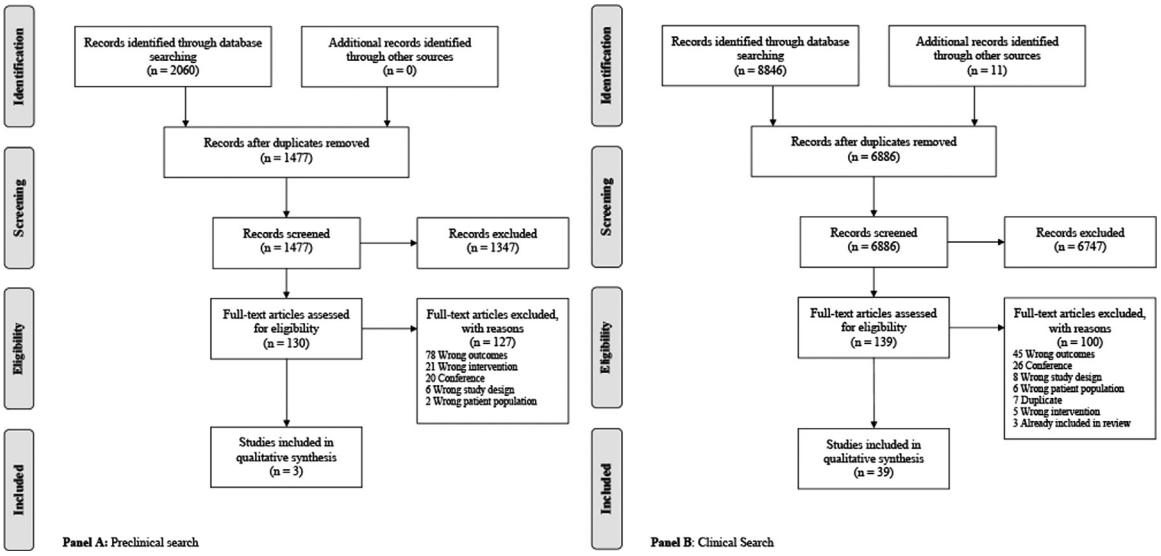

Fig. 1. PRISMA-ScR Flow Diagram.

Table 1
Dose dimensions and reported outcomes for included studies.

Reference Author, Country, Sample size	Dose dimensions[a]				Reported outcomes		
	Fixed vs. Manipulated	Time	Schedule	Intensity	Dose	Safety	Efficacy
Preclinical: dose preparation							
Bell 2015 [26]	Fixed	15 min	5 d/w, 2 w	Aim 100 reps	✓	×* [*]	✓
USA, $n = 27$[b]	Manipulated		0 vs 1 vs 2 s/d				
Jeffers 2018 [27]	Fixed	15 min	3 s/d, 5 d/w, > 3 w	45-min rest	✓	×* [*]	✓
Canada, $n = 27$[b]	Manipulated						
MacLellan 2011 [28]	Fixed	240 min	1 s/d, 5 d/w, 6w		✓	×* [*]	✓
Canada, $n = 39$[c]	Manipulated			Limited pellets vs unlimited pellets			
Clinical: Phase I, dose ranging							
Colucci 2017 [24]	Fixed		1 s/d, 5 d/w, 2 w		✓	✓	×*
UK, $n = 15$	Manipulated			50 vs 100 vs 167 vs 251 vs 209 reps			
Dite 2015 [23]	Fixed		1 s/d, 3 d/w, 12 w		✓	✓	✓
Australia, $n = 6$	Manipulated	360 vs 630 vs 750 min					
Clinical: Phase IIA, dose screening							
Banina 2020 [29]	Fixed	90 min	1 s/d, 5 d/w, 2 w		✓	×*	✓
Canada, $n = 41$	Manipulated						
Birkenmeier 2010 [17]	Fixed	60 min	1 s/d, 3 d/w, 6 w	Aim > 300 reps	✓	✓	✓
USA, $n = 15$	Manipulated						
Carl 2016 [30]	Fixed	30 min	1 s/d, 1 d/w, 3 w		✓	✓	×*
USA, $n = 18$	Manipulated			30- vs 60- vs 90-sec rest			
Milot 2019 [31]	Fixed	60 min	1 s/d, 3 d/w, 4w	BRPE 12-13/20 progress to 15-60/20 by 4 w.	✓	✓	✓
Canada, $n = 12$	Manipulated						
Nordin 2019 [32]	Fixed	90 min	1 s/d, 1 d/w, 12 w		✓	✓	✓
Exercise, $n = 41$	Manipulated						
Norouzi-Gheidar 2019 [33]	Fixed		1 s/d, 2–3 d/w, 4w	Aim 70% score on games	✓	✓	✓
Canada, $n = 18$	Manipulated	Usual care vs usual care + 30 min					
Schneider 2019 [34]	Fixed	60 min	1 s/d, 6 d/w, 4w		✓	✓	✓
Upper limb, $n = 20$	Manipulated						
Vinstrup 2018 [35]	Fixed		1s	3 reps/s	✓	×*	✓
Denmark, $n = 18$	Manipulated			Easy vs moderate vs hard resistance			
Waddell 2014 [36]	Fixed	60 min	1 s/d, 4 d/w, length of admission	Aim > 300 reps/s	✓	✓	✓
USA, $n = 15$	Manipulated						
Clinical: Phase IIB, dose finding (response)							
Allison 2007[37]	Fixed	45 min	5 d/w, length of admission		×*	✓	✓
UK, $n = 17$	Manipulated		1 s/d vs 2 s/d				
Bowden 2002 [38]	Fixed	20 min	Length of admission	110/125% self-selected walking speed. 75% of 1RM. 60–80% of max HR	✓	×*	✓
USA, $n = 35$	Manipulated		Usual care vs usual care + 6 s/w				
Burgar 2011[39]	Fixed	60 min	5 d/w, 3 w		✓	×*	✓
USA, $n = 54$	Manipulated		1 s/d vs 2 s/d				
de Sousa 2019[40]	Fixed	120 vs 180–240 min			✓	✓	✓
Australia, $n = 30$	Manipulated		2 s/d, 5 d/w vs 4 s/d, 6 d/w				
Dromerick 2009 [41]	Fixed		5 d/w, 2 w		×*	✓	✓
USA, $n = 52$	Manipulated	120 vs 180 min					
Elsner 2018 [42]	Fixed		1s		×*	×*	✓
Germany, $n = 20$	Manipulated			1- vs 4-min rest			
GAPS 2004 [43]	Fixed		1 s/d, 5 d/w, 4w		✓	✓	✓
UK, $n = 70$	Manipulated	30–40 vs 60–80 min					
Han 2012[44]	Fixed		1 s/d, 5 d/w, 6 w		✓	×*	✓
China, $n = 32$	Manipulated	60 vs 120 vs 180 min					

Table 1 (*Continued*)

Reference Author, Country, Sample size	Dose dimensions[a]				Reported outcomes		
	Fixed vs. Manipulated	Time	Schedule	Intensity	Dose	Safety	Efficacy
Hornby 2019 [15]	Fixed	40 min	1 s/d, 35 d/w, 8w		✓	✓	✓
USA, *n* = 97	Manipulated			30–40% vs 70–80% HRR			
Hsieh 2011 [16]	Fixed	90-105 min	1 s/d, 5 d/w, 4w		×*	✓	✓
Taiwan, *n* = 18	Manipulated			900 vs 1800 reps			
Hsieh 2012 [45]	Fixed	90-100 min	1 s/d, 5 d/w, 4w		×*	✓	✓
Taiwan, *n* = 54	Manipulated			375–500 vs 750–1000 reps			
Hsu 2010 [46]	Fixed		1 s/d, 5 d/w, 4w		×*	×*	✓
Taiwan, *n* = 66	Manipulated	0 vs 30 vs 60 min					
Hsu 2012 [47]	Fixed		1 s/d, 5 d/w, 4w		×*	×*	✓
Taiwan, *n* = 95	Manipulated	0 vs 15 vs 30 vs 60 min					
Hunter 2011 [48]	Fixed		1 s/d, 5 d/w, 2 w		✓	✓	✓
UK, *n* = 76	Manipulated	0 vs 30 vs 60 vs 120 min					
Kowalczewski 2007 [49]	Fixed		1 s/d, 5 d/w, 34 w		✓	×*	✓
UK, *n* = 19	Manipulated	15 vs 60 min					
Lang 2016 [4]	Fixed	60 min	1 s/d, 4 d/w, 8 w		✓	×*	✓
Waddell 2017 [14]	Manipulated			3200 vs 6400 vs 9600 vs > 9600 reps			
USA, *n* = 85							
Lincoln 1999 [50]	Fixed		1 s/d, 5 d/w, 5 w		✓	×*	✓
UK, *n* = 282	Manipulated	30–45 vs 54–79 min					
Page 2012 [51]	Fixed		1 s/d, 5 d/w, 8 w		×*	×*	✓
USA, *n* = 32	Manipulated	30 vs 60 vs 120 min					
Patel 2019[52]	Fixed		1 s/d, 5 d/w	200–300 reps	×*	✓	✓
USA, *n* = 13	Manipulated	180 vs 240 min					
Tong 2019[53]	Fixed		7 d/w, 2 w		✓	×*	✓
China, *n* = 248	Manipulated	<90 vs 180 min					
Winstein 2019 [54]	Fixed		1 s/d, 4 d/w, 15 w		×*	×*	✓
USA, *n* = 45	Manipulated	0 vs 900 vs 1800 vs 3600 min					
Wu, 2019 [55]	Fixed	30–90 min	5 d/w, 2 w		×*	×*	✓
China, *n* = 32	Manipulated		1 s/d vs 3 s/d				
Clinical: Phase IIB, dose finding (optimal)							
Di Lauro 2003 [56]	Fixed		12 s/d, 5 d/w, 2 w		×*	×*	✓
Italy, *n* = 60	Manipulated	45 vs 120 min					
Doucet 2013 [57]	Fixed	20–40 min	1 s/d, 4 d/w, 4 w		×*	×*	✓
USA, *n* = 16	Manipulated			20 Hz e-stim vs 40 Hz e-stim			
Partridge 2000 [58]	Fixed		1 s/d, 5 d/w, 6 w		×*	×*	✓
UK, *n* = 114	Manipulated	30 vs 60 min					
Rodgers 2003 [59]	Fixed		1 s/d, 5 d/w, 6 w		✓	×*	✓
UK, *n* = 123	Manipulated	Usual care vs usual care + 30 min					
Sivenius 1985 [60]	Fixed		2 s/d		✓	×*	✓
Finland, *n* = 95	Manipulated						

d: day/; d/w, day/week; HR, heart rate; HRR, heart rate reserve; Hz: Hertz; NR: not reported; 1RM: one repetition maximum; s: sessions; reps: repetitions; reps/s: repetitions/sessions; sec: seconds; s/d: sessions/day; s/w: sessions/week; w: week; BRPE: Borg Rating of Perceived Exertion Scale.

[a] Dose dimensions defined as fixed, remain stable or consistent throughout study or manipulated, articulated or change within study.

[b] Results from experiment 1 only.

[c] Results from experiment 2 only.

[*] Safety outcomes related to stroke inducement reported but no safety outcomes reported for intervention.

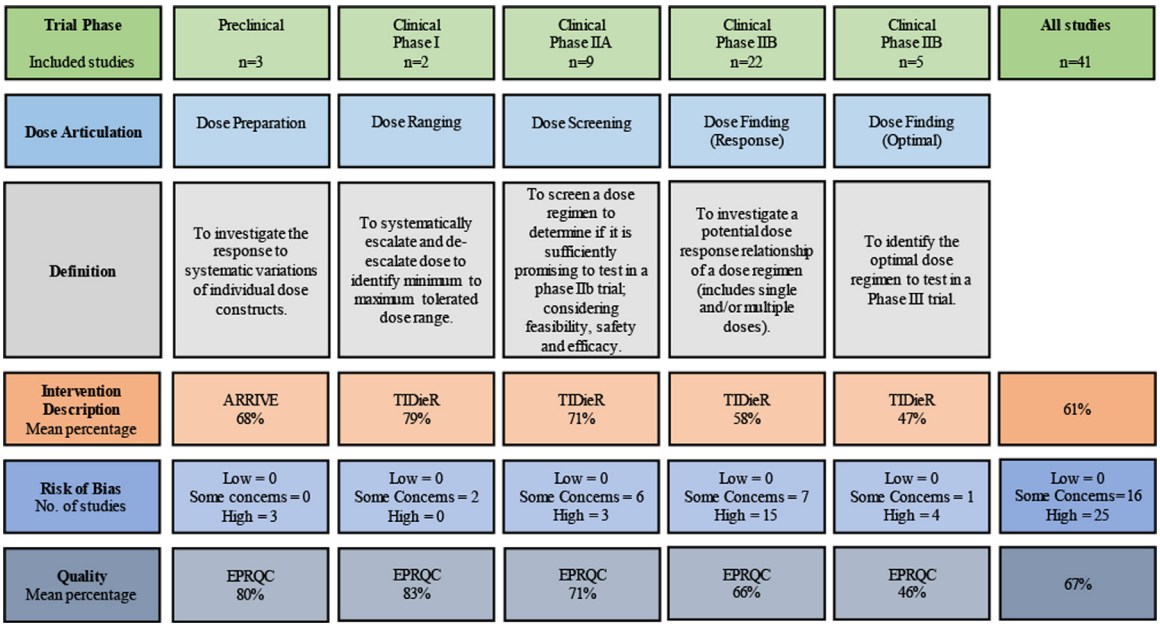

Fig. 2. Discovery pipeline including intervention description, risk of bias and quality outcomes.

that aimed to determine efficacy. All preclinical experiments reported dose and efficacy; however, intervention safety outcomes were not reported. Phase I trials aimed to determine the maximum tolerated dose with rule-based designs; dose and safety outcomes were consistently reported. The aim of Phase IIA trials focused on safety and feasibility of high repetitions or intensity of dose. All Phase IIA trials reported dose, but 2 did not report safety outcomes. Phase IIB dose-finding (response) trials predominately aimed to determine the effect of dose on motor outcomes, through a randomized controlled trial. All dose–response trials reported efficacy; however, dose outcomes were reported in only half, and fewer (41%) reported safety outcomes. Most Phase IIB dose finding (optimal) trials aimed to compare the effect of different doses. Efficacy outcomes were reported by all dose optimization trials, but dose outcomes were reported in only 40%, and no trials reported safety outcomes. Thus, the frequency of dose and safety outcome reporting decreased along the discovery pipeline.

Fig. 2 illustrates results at the trial phase level. The proportion was lower for preclinical (7%), Phase I (5%), and Phase IIA (22%) studies than Phase IIB studies (66%). The systematic translation of findings along the discovery pipeline (i.e., one phase informing the next) was poorly demonstrated. The justification of dose for Phase I trials included preclinical experiments but also later-phase clinical trials. No included Phase IIA trials were based on dose outcomes of a Phase I trial, and only one Phase IIB trial [4] tested dose outcomes from a published Phase IIA trial[17].

The mean intervention description score was 61% (ARRIVE 68%, TIDieR 61%; Fig. 2) despite 78% of studies being published after 2010. There were 5 ARRIVE questions (7/8/10/11/18) that all preclinical experiments failed to sufficiently report, covering experiment information and animals, sample size, and interpretation of results. No included clinical trials reported modifications to the intervention (TIDieR Question 10), and only 40% reported fidelity (TIDieR Question 12). Intervention description results by question are reported in Supplement File 2 (Appendix B). The overall risk of bias scores (SYRCLE, ROBINS-I, Cochrane RoB2) demonstrated that most studies were at high risk of bias (SYRCLE $n = 3/3$, ROBINS-I $n = 3/11$, Cochrane RoB2 $n = 19/27$, Fig. 3). Quality appraisal using the EPRQC gave an overall mean score of 67%. The quality scores declined for each trial phase along the discovery pipeline. Justification for the dose regimen (19% EPRQC Question 6B) and the starting dose (21% EPRQC Question 5B) were the lowest reported across preclinical experiments and clinical trials, followed by whether studies differentiate between causality related and unrelated adverse events (37% EPRQC Question 3). Quality results by question and phase are reported in Supplement File 2 (Appendix B).

4. Discussion

This review found a disproportionally small number of early-phase studies that investigated dose in comparison to the volume of published behavioral motor stroke recovery research [13,18]. Preclinical experiments and Phase I clinical trials represented 12% of included studies, highlighting a gap early in the discovery pipeline. All studies adopted a unidimensional dose articulation approach (i.e., the investigation of a single dose dimension), and most focused on upper-limb interventions as compared with other domains (lower limb, exercise, function). Preclinical experiments were all at high risk of bias but in comparison to clinical trials, did marginally better at intervention reporting and dose articulation. Outcome reporting of dose and safety declined along the discovery pipeline, as did intervention description, risk of bias, and quality scores.

Early phase stroke recovery research has adopted a unidimensional approach to investigate dose of behavioral motor interventions. In this review, studies most commonly selected time as the dimension to manipulate, with the outcome usually reported as time in therapy environment. This provided limited information regarding actual work performed [19]. The intervention domain should guide the researcher to select multiple dose dimensions to investigate, building a comprehensive dose outcome. For example, time spent actively working and repetitions per minute could provide a measure of time and intensity respectively for an upper-limb trial. The idea that dose is multidimensional is not new in the field [9]; Lang et al. previously reported that "optimal dosing will not likely be a single value" [7]. To successfully complete

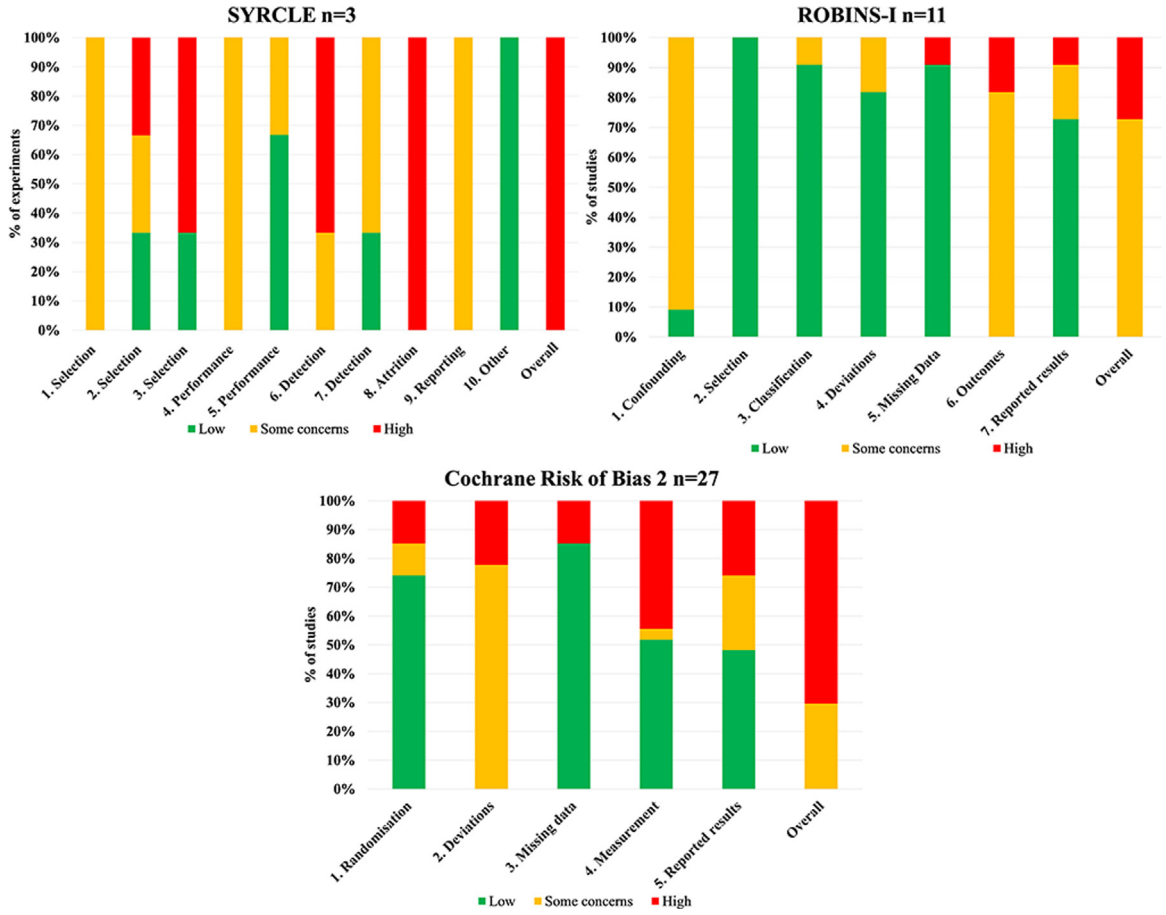

Fig. 3. Risk of bias.

multidimensional, early-phase dose articulation research, we need to establish a consistent dose definition that operationalizes the multiple dimensions that can be applied to preclinical and clinical stroke recovery research.

The lack of dose articulation studies included in the review also suggests that the field has overlooked the importance of conducting research along the discovery pipeline [6]. A systematic phased approach is required to develop new pharmaceutical interventions [1]. This approach provides regulatory bodies [1] with key information (i.e., safe and tolerable dose range) to inform the approval of new pharmaceutical interventions. Phase IIB trials included in this review skipped trial phases in the discovery pipeline, which meant dose (feasibility and tolerability) and safety outcomes were inadequately explored. This finding was previously discussed by Dobkin et al., [20] who reported that rehabilitation trials have tended to "move forward in random increments compared to the FDA process for drug approval". Skipping trial phases can result in inadequate justification of the dose selected for inclusion in later-phase efficacy trials (i.e., not based on a safe and tolerable dose range). A recent review found that only 36 of 194 randomized controlled stroke recovery trials provided a justification (i.e., earlier phase study) for intervention dose [21]. The adoption of a systematic discovery pipeline approach should result in more early-phase studies (preclinical, Phase I and Phase IIA) and fewer Phase III trials being completed. From this process, the resulting Phase III trials will have been developed based on a safe and tolerable dose, allowing confidence that the results truly reflect the intervention outcome.

Reporting of outcomes varied along the pipeline. Preclinical experiments and clinical Phase I/IIA trials consistently reported dose outcomes. There was a steep drop off at Phase IIB study, with less than half reporting dose outcomes, despite a stated dose articulation aim. The actual dose achieved can affect intervention efficacy and research replication. Safety outcomes also followed a similar pattern of reporting along the pipeline. Reporting safety outcomes is critical for all behavioral motor intervention trials because interventions cannot be assumed safe [22]. Although the purpose of a Phase IIB trial does shift to focus on efficacy, this review demonstrated the need for better reporting of dose and safety even at this phase to ensure adequate justification of dose in later-phase trials.

Phase I trials were poorly represented in the overall results, with the 2 included trials [23,24] adopting a unidimensional approach to dose articulation. This finding highlights a lack of published Phase I, dose-ranging trials in the field of behavioral motor stroke recovery. A likely contributor to this research gap is a poor understanding of how to conduct a multidimensional Phase I trial. Classical Phase I trial designs have been developed in the pharmaceutical field to investigate the single dimension of "amount of drug" (usually measured in milligrams) [25]. To successfully investigate the dose of behavioral motor interventions, we need to understand the design attributes inherent in Phase I trials and adapt them for multidimensional dose articulation. Early-phase research, particularly the appropriate design and implementation of multidimensional Phase I trials, warrants further attention in behavioral motor stroke recovery.

There are some limitations to this review. The restriction of the preclinical inclusion criteria to yield a manageable number of search results could have resulted in missing some preclinical, dose-preparation experiments of other domains (e.g., lower limb). One person completed the first review of title and abstracts;

however, a low threshold was used to move papers to full-text review. Studies not published in English were also excluded. The strengths are the search for both preclinical experiments and clinical trials via the adoption a systematic discovery pipeline approach to understand the continuum of trial phases. Use of the EPRQC [6] also enabled rating the quality of included preclinical and clinical studies with a consistent tool.

5. Conclusions

This review highlights that early-phase dose articulation research of behavioral motor interventions for stroke recovery is in its infancy. There is a unique opportunity to adopt systematic processes and collaborate across the discovery pipeline (preclinical and clinical) to increase the volume of dose articulation research. Researchers in the field must consider how to adapt existing early-phase trial designs, with a particular focus on Phase I, to accommodate investigation of the multiple dimensions of dose.

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Contributions

ED and KH conceived the idea for this review and were involved in all aspects of study, with manuscript writing led by ED. LC and DC were involved in the study design, study selection, rating of studies, and manuscript editing. NL was involved in the study design, and manuscript editing. BC was involved in manuscript editing. All authors made significant intellectual contributions to the review.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rehab.2020.101469.

References

[1] U.S. Food and Drug Administration. Step 3: Clinical Research; 2018 [Accessed 2019. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies].
[2] Walker MF, Hoffmann TC, Brady MC, Dean CM, Eng JJ, Farrin AJ, et al. Improving the development, monitoring and reporting of stroke rehabilitation research: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. Int J Stroke 2017;12:472–9. http://dx.doi.org/10.1177/1747493017711815.
[3] Bernhardt J, Hayward K, Dancause N, Lannin N, Ward N, Nudo R, et al. A stroke recovery trial development framework: Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable. Int J Stroke 2019;14:792–802. http://dx.doi.org/10.1177/1747493019879657.
[4] Lang CE, Strube MJ, Bland MD, Waddell KJ, Cherry-Allen KM, Nudo RJ, et al. Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial. Ann Neurol 2016;80:342–54. http://dx.doi.org/10.1002/ana.24734.
[5] Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655. http://dx.doi.org/10.1136/bmj.a1655.
[6] Dalton E, Churilov L, Lannin NA, Corbett D, Hayward K. Dose Articulation in Preclinical and Clinical Stroke Recovery: Refining a Discovery Research Pipeline and Presenting a Scoping Review Protocol. Front Neurol 2019;10:1148. http://dx.doi.org/10.3389/fneur.2019.01148.
[7] Lang CE, Lohse KR, Birkenmeier RL. Dose and timing in neurorehabilitation. Curr Opin Neurol 2015;28:549–55. http://dx.doi.org/10.1097/wco.0000000000000256.
[8] Lohse KR, Pathania A, Wegman R, Boyd LA, Lang CE. On the Reporting of Experimental and Control Therapies in Stroke Rehabilitation Trials: A Systematic Review. Arch Phys Med Rehabil 2018;99:1424–32. http://dx.doi.org/10.1016/j.apmr.2017.12.024.
[9] Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. Interventions for improving upper limb function after stroke. Cochrane Database Syst Rev 2014;11:CD010820. http://dx.doi.org/10.1002/14651858.cd010820.pub2.
[10] Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8:19–32. http://dx.doi.org/10.1080/1364557032000119616.
[11] Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implementation Sci 2010;5:69. http://dx.doi.org/10.1186/1748-5908-5-69.
[12] Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018. http://dx.doi.org/10.7326/m18-0850.
[13] Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. Int J Stroke 2017;12:444–50. http://dx.doi.org/10.1177/1747493017711816.
[14] Waddell KJ, Strube MJ, Bailey RR, Klaesner JW, Birkenmeier RL, Dromerick AW, et al. Does Task-Specific Training Improve Upper Limb Performance in Daily Life Poststroke? Neurorehabili Neural Repair 2017;31:290–300. http://dx.doi.org/10.1177/1545968316680493.
[15] Hornby T, Henderson C, Plawecki A, Lucas E, Lotter J, Holthus M, et al. Contributions of Stepping Intensity and Variability to Mobility in Individuals Poststroke. Stroke 2019;50:2492–9. http://dx.doi.org/10.1161/strokeaha.119.026254.
[16] Hsieh Y, Wu C, Liao W, Lin K, Wu K, Lee C. Effects of treatment intensity in upper limb robot-assisted therapy for chronic stroke: a pilot randomized controlled trial. Neurorehabil Neural Repair 2011;25:503–11. http://dx.doi.org/10.1177/1545968310394871.
[17] Birkenmeier RL, Prager EM, Lang CE. Translating Animal Doses of Task-Specific Training to People With Chronic Stroke in 1-Hour Therapy Sessions: A Proof-of-Concept Study. Neurorehabil Neural Repair 2010;24:620–35. http://dx.doi.org/10.1177/1545968310361957.
[18] Mayo NE, Kaur N, Barbic SP, Fiore J, Barclay R, Finch L, et al. How have research questions and methods used in clinical trials published in Clinical Rehabilitation changed over the last 30 years? Clin Rehabil 2016;30:847–64. http://dx.doi.org/10.1177/0269215515658939.
[19] Lohse KR, Lang CE, Boyd LA. Is More Better? Using Metadata to Explore Dose–Response Relationships in Stroke Rehabilitation. Stroke 2014;45:2053–8. http://dx.doi.org/10.1161/strokeaha.114.004695.
[20] Dobkin BH. Progressive Staging of Pilot Studies to Improve Phase III Trials for Motor Interventions. Neurorehabil Neural Repair 2009;23:197–206. http://dx.doi.org/10.1177/1545968309331863.
[21] Borschmann K, Hayward KS, Raffelt A, Churilov L, Kramer S, Bernhardt J. Rationale for Intervention and Dose Is Lacking in Stroke Recovery Trials: A Systematic Review. Stroke Res Treatment 2018;2018:1–9. http://dx.doi.org/10.1155/2018/8087372.
[22] Avert Trial Collaboration Group, Bernhardt J, Langhorne P, Lindley RI, Thrift AG, Ellery F, et al. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet 2015;386:46–55.
[23] Dite W, Langford ZN, Cumming TB, Churilov L, Blennerhassett JM, Bernhardt J. A Phase 1 exercise dose escalation study for stroke survivors with impaired walking. Int J Stroke 2015;10:1051–6. http://dx.doi.org/10.1111/ijs.12548.
[24] Colucci E, Clark A, Lang CE, Pomeroy VM. A rule-based, dose-finding design for use in stroke rehabilitation research: methodological development. Physiotherapy 2017;103:414–22. http://dx.doi.org/10.1016/j.physio.2016.<DOI>10.393.
[25] Tourneau CL, Lee JJ, Siu LL. Dose Escalation Methods in Phase I Cancer Clinical Trials. J Natl Cancer Inst 2009;101:708–20. http://dx.doi.org/10.1093/jnci/djp079.
[26] Bell JA, Wolke ML, Ortez RC, Jones TA, Kerr AL. Training Intensity Affects Motor Rehabilitation Efficacy Following Unilateral Ischemic Insult of the Sensorimotor Cortex in C57BL/6 Mice. Neurorehabil Neural Repair 2015;29:590–8. http://dx.doi.org/10.1177/1545968314553031.
[27] Jeffers MS, Karthikeyan S, Gomez-Smith M, Gasinzigwa S, Achenbach J, Feiten A, et al. Does Stroke Rehabilitation Really Matter Part B: An Algorithm for Prescribing an Effective Intensity of Rehabilitation. Neurorehabil Neural Repair 2018;32:73–83. http://dx.doi.org/10.1177/1545968317753074.
[28] MacLellan CL, Keough MB, Granter-Button S, Chernenko GA, Butt S, Corbett D. A Critical Threshold of Rehabilitation Involving Brain-Derived Neurotrophic Factor Is Required for Poststroke Recovery. Neurorehabil Neural Repair 2011;25:740–8. http://dx.doi.org/10.1177/1545968311407517.
[29] Baniña MC, Molad R, Solomon JS, Berman S, Soroker N, Frenkel-Toledo S, et al. Exercise intensity of the upper limb can be enhanced using a virtual rehabilitation system. Disabil Rehabilit Assistive Technol 2020;15:1–7. http://dx.doi.org/10.1080/17483107.2020.1765421.

[30] Carl DL, Boyne P, Rockwell B, Gerson M, Khoury J, Kissela B, et al. Preliminary safety analysis of high-intensity interval training (HIIT) in persons with chronic stroke. Appl Physiol Nutr Metab 2017;42:311–8. http://dx.doi.org/10.1139/apnm-2016-0369.
[31] Milot M-H, Léonard G, Corriveau H, Desrosiers J. Using the Borg rating of perceived exertion scale to grade the intensity of a functional training program of the affected upper limb after a stroke: a feasibility study. Clin Interv Aging 2019;14:9–16. http://dx.doi.org/10.2147/cia.s179691.
[32] Nordin NAM, Yusoff NAH, Singh DKA. Facilitating Exercise Engagement among Community Dwelling Stroke Survivors: Is a once Per Week Group Session Sufficient? Int J Environment Res Public Health 2019;16:4746. http://dx.doi.org/10.3390/ijerph16234746.
[33] Norouzi-Gheidari N, Hernandez A, Archambault PS, Higgins J, Poissant L, Kairy D. Feasibility, Safety and Efficacy of a Virtual Reality Exergame System to Supplement Upper Extremity Rehabilitation Post-Stroke: A Pilot Randomized Clinical Trial and Proof of Principle. Int J Environment Res Public Health 2019;17:113. http://dx.doi.org/10.3390/ijerph17010113.
[34] Schneider EJ, Ada L, Lannin NA. Extra upper limb practice after stroke: a feasibility study. Pilot Feasibil Stud 2019;5:156. http://dx.doi.org/10.1186/s40814-019-0531-5.
[35] Vinstrup J, Calatayud J, Jakobsen M, Sundstrup E, Jørgensen J, Casaña J, et al. Hand strengthening exercises in chronic stroke patients: Dose-response evaluation using electromyography. J Hand Ther 2017;31:111–21. http://dx.doi.org/10.1016/j.jht.2017.01.004.
[36] Waddell KJ, Birkenmeier RL, Moore JL, Hornby TG, Lang CE. Feasibility of High-Repetition. Task-Specific Training for Individuals With Upper-Extremity Paresis Am J Occup Ther 2014;68:444. http://dx.doi.org/10.5014/ajot.2014.011619.
[37] Allison R, Dennett R. Pilot randomized controlled trial to assess the impact of additional supported standing practice on functional ability post stroke. Clin Rehabil 2007;21:614–9. http://dx.doi.org/10.1177/0269215507077364.
[38] Bowden MG, Monsch ED, Middleton JA, Daughtry C, Powell T, Kraft SV, et al. The Difficulties of Incorporating Intensity Principles into Inpatient Stroke Rehabilitation. Arch Rehabil Res Clin Transl 2020;2:100052. http://dx.doi.org/10.1016/j.arrct.2020.100052.
[39] Charles GB, Peter SL, Scremin AME, Susan LG, Loos HFMVd, Deborah K, et al. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: Department of Veterans Affairs multisite clinical trial. J Rehabili Res Dev 2011;48:445. http://dx.doi.org/10.1682/jrrd.20.
[40] Sousa DGd, Harvey LA, Dorsch S, Varettas B, Jamieson S, Murphy A, et al. Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke: a randomised trial. J Physiother 2019;65:152–8. http://dx.doi.org/10.1016/j.jphys.2019.05.007.
[41] Dromerick AW, Lang CE, Birkenmeier RL, Wagner JM, Miller JP, Videen TO, et al. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS). Neurology 2009;73:195–201. http://dx.doi.org/10.1212/wnl.0b013e3181ab2b27.
[42] Elsner B, Schweder S, Mehrholz J. Immediate effects of rest periods on balance control in patients after stroke. A randomized controlled pilot trial. BMC Res Notes 2018;11:338. http://dx.doi.org/10.1186/s13104-018-3450-2.
[43] The Glasgow Augmented Physiotherapy Study g. Can augmented physiotherapy input enhance recovery of mobility after stroke? A randomized controlled trial. Clin Rehabil 2004;18:529–37. http://dx.doi.org/10.1191/0269215504cr768oa.
[44] Han Q, Wang Q, Meng P, Qi M. Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial. Clin Rehabil 2012;27:75–81. http://dx.doi.org/10.1177/0269215512447223.
[45] Hsieh Y, Wu C, Lin K, Yao G, Wu K, Chang Y. Dose–Response Relationship of Robot-Assisted Stroke Motor Rehabilitation. Stroke 2012;43:2729–34. http://dx.doi.org/10.1161/strokeaha.112.658807.
[46] Hsu S, Hu M, Wang Y, Yip P, Chiu J, Hsieh C. Dose-Response Relation Between Neuromuscular Electrical Stimulation and Upper-Extremity Function in Patients With Stroke. Stroke 2010;41:821–4. http://dx.doi.org/10.1161/strokeaha.109.574160.
[47] Hsu S, Hu M, Luh J, Wang Y, Yip P, Hsieh C. Dosage of neuromuscular electrical stimulation: Is it a determinant of upper limb functional improvement in stroke patients? J Rehabil Med 2012;44:125–30. http://dx.doi.org/10.2340/16501977-0917.
[48] Hunter S, Hammett L, Ball S, Smith N, Anderson C, Clark A, et al. Dose–Response Study of Mobilisation and Tactile Stimulation Therapy for the Upper Extremity Early After Stroke. Neurorehabil Neural Repair 2011;25:314–22. http://dx.doi.org/10.1177/1545968310390223.
[49] Kowalczewski J, Gritsenko V, Ashworth N, Ellaway P, Prochazka A. Upper-Extremity Functional Electric Stimulation–Assisted Exercises on a Workstation in the Subacute Phase of Stroke Recovery. Arch Phys Med Rehabil 2007;88:833–9. http://dx.doi.org/10.1016/j.apmr.2007.03.036.
[50] Lincoln N, Parry R, Vass C. Randomized, Controlled Trial to Evaluate Increased Intensity of Physiotherapy Treatment of Arm Function After Stroke. Stroke 1999;30:573–9. http://dx.doi.org/10.1161/01.str.30.3.573.
[51] Page SJ, Levin L, Hermann V, Dunning K, Levine P. Longer Versus Shorter Daily Durations of Electrical Stimulation During Task-Specific Practice in Moderately Impaired Stroke. Arch Phys Med Rehabil 2012;93:200–6. http://dx.doi.org/10.1016/j.apmr.2011.09.016.
[52] Patel J, Fluet G, Qiu Q, Yarossi M, Merians A, Tunik E, et al. Intensive virtual reality and robotic based upper limb training compared to usual care, and associated cortical reorganization, in the acute and early sub-acute periods post-stroke: a feasibility study. J Neuroeng Rehabil 2019;16:92. http://dx.doi.org/10.1186/s12984-019-0563-3.
[53] Tong Y, Cheng Z, Rajah G, Duan H, Cai L, Zhang N, et al. High Intensity Physical Rehabilitation Later Than 24 h Post Stroke Is Beneficial in Patients: A Pilot Randomized Controlled Trial (RCT) Study in Mild to Moderate Ischemic Stroke. Front Neurol 2019;10:113. http://dx.doi.org/10.3389/fneur.2019.00113.
[54] Winstein C, Kim B, Kim S, Martinez C, Schweighofer N. Dosage Matters. Stroke 2019. http://dx.doi.org/10.1161/strokeaha.118.023603.
[55] Wu W-X, Zhou C-Y, Wang Z-W, Chen G-Q, Chen X-L, Jin H-M, et al. Effect of Early and Intensive Rehabilitation after Ischemic Stroke on Functional Recovery of the Lower Limbs: A Pilot, Randomized Trial. J Stroke Cerebrovasc Dis 2020;29:104649. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2020.104649.
[56] Di Lauro A, Pellegrino L, Savastano G, Ferraro C, Fusco M, Balzarano F, et al. A randomized trial on the efficacy of intensive rehabilitation in the acute phase of ischemic stroke. J Neurol 2003;250:1206–8. http://dx.doi.org/10.1007/s00415-003-0185-2.
[57] Doucet B, Griffin L. High-versus low-frequency stimulation effects on fine motor control in chronic hemiplegia: a pilot study. Top Stroke Rehabil 2013;20:299–307. http://dx.doi.org/10.1310/tsr2004-299.
[58] Partridge C, Mackenzie M, Edwards S, Reid A, Jayawardena S, Guck N, et al. Is dosage of physiotherapy a critical factor in deciding patterns of recovery from stroke: a pragmatic randomized controlled trial. Physiother Res Int 2000;5:230–40. http://dx.doi.org/10.1002/pri.203.
[59] Rodgers H, Mackintosh J, Price C, Wood R, McNamee P, Fearon T, et al. Does an early increased-intensity interdisciplinary upper limb therapy programme following acute stroke improve outcome? Clin Rehabil 2003;17:579–89. http://dx.doi.org/10.1191/0269215503cr652oa.
[60] Sivenius J, Pyörälä K, Heinonen O, Salonen JT, Riekkinen P. The significance of intensity of rehabilitation of stroke–a controlled trial. Stroke 1985;16:928–31. http://dx.doi.org/10.1161/01.str.16.6.928.