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GUIDELINES

# European Academy of Neurology and European Federation of Neurorehabilitation Societies guideline on pharmacological support in early motor rehabilitation after acute ischaemic stroke

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## Abstract

**Background and purpose:** Early pharmacological support for post-stroke neurorehabilitation has seen an abundance of mixed results from clinical trials, leaving practitioners at a loss regarding the best options to improve patient outcomes. The objective of this evidence-based guideline is to support clinical decision-making of healthcare professionals involved in the recovery of stroke survivors.

**Methods:** This guideline was developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. PubMed, Cochrane Library and Embase were searched (from database inception to June 2018, inclusive) to identify studies on pharmacological interventions for stroke rehabilitation initiated in the first 7 days (inclusive) after stroke, which were delivered together with neurorehabilitation. A sensitivity analysis was conducted on identified interventions to address results from breaking studies (from end of search to February 2020).

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**Results:** Upon manually screening 17,969 unique database entries (of 57,001 original query results), interventions underwent meta-analysis. Cerebrolysin (30 ml/day, intravenous, minimum 10 days) and citalopram (20 mg/day, oral) are recommended for clinical use for early neurorehabilitation after acute ischaemic stroke. The remaining interventions identified by our systematic search are not recommended for clinical use: amphetamine (5, 10 mg/day, oral), citalopram (10 mg/day, oral), dextroamphetamine (10 mg/day, oral), Di-Huang-Yi-Zhi (2 × 18 g/day, oral), fluoxetine (20 mg/day, oral), lithium (2 × 300 mg/day, oral), MLC601(3 × 400 mg/day, oral), phosphodiesterase-5 inhibitor PF-03049423 (6 mg/day, oral). No recommendation 'for' or 'against' is provided for selegiline (5 mg/day, oral). Issues with safety and tolerability were identified for amphetamine, dextroamphetamine, fluoxetine and lithium.

**Conclusions:** This guideline provides information for clinicians regarding existing pharmacological support in interventions for neurorecovery after acute ischaemic stroke. Updates to this material will potentially elucidate existing conundrums, improve current recommendations, and hopefully expand therapeutic options for stroke survivors.

**KEYWORDS**
early motor rehabilitation, ischaemic stroke, neurorehabilitation

## INTRODUCTION

Stroke remains one of the most important causes of death and disability worldwide, leading to debilitating neurological deficits such as walking disability, the need for permanent care (in about one quarter of survivors) and other motor or sensory deficits which interfere with daily activities, even in mild cases [1–3]. Despite the fact that early neurorehabilitation has made tremendous progress in addressing motor function and abilities after stroke especially making use of motor learning and compensatory concepts, there are still very few strategies for improving motor impairment in the immediate, post-acute phase of stroke. To what extent pharmacological intervention may influence neurorecovery in stroke is a question which remains without a definitive answer. The field of neurorehabilitation is still often lacking backup from evidence-based medicine. Evidence-based recommendations for clinical practice are hence needed to deliver information in this field, providing insight about questions related to clinical decision-making for healthcare professionals working with stroke patients. Whilst early elements of neurorehabilitation should start in the hyper-acute phase, this guideline is constructed around initiation of pharmacological support in the acute phase (first 7 days after stroke), based on the new standards in stroke recovery research outlined by Bernhardt and colleagues in 2017 [1].

The objective of this guideline on pharmacological support in early motor rehabilitation after acute ischaemic stroke was to identify, summarize and appraise the wealth of existing information on the topic, using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [4] systematic approach and framework. This is an evidence-based guideline, developed jointly by representatives of the European Academy of Neurology (EAN) and the European Federation of Neurorehabilitation Societies (EFNR).

## METHODOLOGY

The systematic review was conducted using the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the *Cochrane Handbook for Systematic Reviews of Interventions*. Recommendations were drafted using the GRADE framework. Only interventions that fit the frame of the guideline's selected research questions (Table 1) were included in the analysis. The assumptions driving the selection of the inclusion and exclusion criteria for the reviewed studies were (1) that pharmacological intervention for early motor rehabilitation after acute

**TABLE 1** Guideline research questions

| ***Clinical question*** |
|---|
| In patients with early motor rehabilitation after acute ischaemic stroke, does a pharmacological treatment impact patient early motor performance (1 and 3 months after stroke), neurological function (1 and 3 months after stroke), global functional outcome (1 and 3 months after stroke), safety (serious adverse events), compared with standard/usual care? |
| *Patient/problem*: Acute ischaemic stroke |
| *Intervention*: Pharmacological intervention in the first 7 days after stroke |
| *Comparison*: Neurorehabilitation alone |
| *Outcomes (N = 4)*: early motor performance, neurological function, global functional outcome, safety |
| *Setting*: Early motor rehabilitation after acute ischaemic stroke |

ischaemic stroke should always be delivered only as an add-on (not in competition with) neurorehabilitation programmes and (2) that initiation of treatment should be performed within a 7-day post-stroke window to enhance endogenous plasticity, in agreement with the latest definitions and a shared vision for new standards in stroke recovery research [1]. Only randomized clinical trials and comparative observational studies were included in the analysis. Exclusion of interventions that fit these criteria is attributable only to missing or incomplete essential information that is required to compile data synthesis according to the above-mentioned scientific frameworks.

## Systematic literature search

PubMed, Cochrane Library and Embase were searched for papers reporting for prospective study designs, including randomized clinical trials, controlled studies and observational studies. The complete search strategy for each database is reported in Appendices S1–S14. The search was conducted from the beginning of database entries until 30 June 2018 and included entries with an English title and abstract. Embase was filtered for PubMed results. Search parameters were harmonized between databases (e.g., *All fields* was replaced with *All text* for Cochrane Library). To address new research on identified interventions that had surfaced after the original search cutoff data, a late research sensitivity analysis was conducted, spanning between 1 July 2018 and 29 February 2020.

## Guideline updates

This guideline is scheduled for updates as decided via consensus by a group composed of task force chairpersons, the chairperson of the EAN Neurorehabilitation Scientific Panel and a representative of the EFNR Scientific Committee. As new evidence that would fundamentally change the recommendations of the guideline emerges, a new production task force will be formed which may include members of the initial group, and the document is updated following the EAN's guidance [5]. The EAN Scientific Committee will regularly survey the validity of published guidelines and generally ask for revision every 5 years or less, if deemed necessary [6].

## Selecting, extracting and synthesizing the evidence

Three reviewers were involved in a two-step study screening process. In the first round, two reviewers independently reviewed the titles and abstracts identified through the literature search and discarded the entries that did not meet the inclusion criteria. If it was unclear whether a study met the inclusion criteria, the full text of the related article was assessed. Any discrepancies at this stage were resolved by consensus. In the second round, full-text review of the selected studies for pertinence to the clinical question and adherence to the inclusion criteria was performed independently by the two reviewers. Only studies in which the double intervention (rehabilitation and pharmacological) was initiated within the acute phase (the first 7 days, inclusive [1]) after stroke were included, excluding any 'subacute' or later initiation. Post-stroke rehabilitation was defined in accordance with the International Classification of Functioning, Disability and Health as any procedure formally included in the analysed study that aimed to facilitate optimal functioning of individuals experiencing or likely to experience post-stroke disability in their interaction with the environment. Any discrepancies between the two reviewers were resolved by consensus. Where consensus was not possible, a third reviewer adjudicated the process. Reasons for exclusion and a detailed PRISMA flow diagram and checklist are available for consultation in Appendices S1–S14. A tailored spreadsheet was used for data extraction. Data were assessed for suitability of meta-analysis development. All identified interventions within papers were associated with the Anatomical Therapeutic Chemical Classification System (ATCC), including Herbal ATCC drug class codes. A single case that involved an intervention not classifiable by this method was labelled with its therapeutic denomination.

Alternative assessment scales, describing the same outcomes of interest, were integrated by using standardized mean differences (SMD), rendering data available for pooling from different rating scales within a predefined domain.

In line with the GRADE approach, when several outcomes were possible for each clinical question, explicit judgements were made about the importance of each outcome for making a recommendation accompanied by ranking outcomes by their relative importance. Early motor performance at 1 and 3 months was defined as primary and secondary critical outcomes, respectively, when formulating recommendations for this guideline on pharmacological support in early motor rehabilitation. Findings for neurological function, global functional outcome at 1 and 3 months, and safety outcomes are also reported and considered when making recommendations. For comparability across all patient/population, intervention, comparison and outcomes (PICOs) and identified studies, outcome scales were grouped based on the subdomains of the efficacy clinical question (early motor performance, neurological function, global functional outcome). The allocation of studies and classification of evaluation scales per guideline PICOs was performed via an Excel form, where all information required for data analysis was extracted and documented from primary sources. Scales were also ordered with respect to their importance within PICOs, based on task force consultations prior to systematic statistical outcome evaluation.

After this stage, studies were validated using cross-tabulation and recomputation of results, along with other standards and tests. An important challenge with validation was that effect sizes, relative risks or odds ratios reported in papers were in some cases not reproducible. In these cases, the results were reconstructed using available supplemental data. If no resolution was possible, the studies were excluded from this step of the protocol. The process continued with synthesis procedures, according to the approved protocol. Any disagreements regarding inclusion of individual articles were resolved by consensus; if agreement was not obtained on inclusion

of a study, the full-text study was sent to the third independent reviewer for adjudication. The flow of the paper selection process for each question and the reason(s) for exclusion was fully documented for maximum traceability. Data from each included article were extracted by two task force members (reviewers), working independently and using an extraction form which was devised for the study. Each included study (except for qualitative research reports, see below) was assessed for selection, performance, detection, attrition and reporting bias, and other bias that might have been detected during the review process [7]. Disagreement regarding the extracted elements, classification of evidence or assessment of effect size was resolved by consensus; if consensus was not obtained, another task force member was involved. For each research question, the core panel constructed evidence profiles, including details of the quality assessment as well as summary (pooled) or unpooled outcome data, an absolute measure of intervention effect when appropriate, and the summary of quality of evidence for each outcome. Evidence profiles were reviewed and approved by all task force members.

### Summarizing the quality of the evidence for each outcome

The task force graded the overall quality of the evidence separately addressing each outcome across studies [4,5]. The relevant evidence was collated in a summary of findings table, including each relevant outcome, using the Revman software (version 5.3, The Cochrane Collaboration) for detailed descriptions and the GRADEpro software (version 3.6, GRADE Working Group) for condensed overview purposes.

### Formulating recommendations

The last step was going from evidence to recommendations. The determination of the direction and strength of recommendations was based on task force interpretation of the available evidence: the balance between desirable and undesirable critical outcomes determined the direction of the recommendation.

A two-round approach was used [5]. In the first round, the direction of each recommendation was considered (the goal was to achieve the greatest benefit with the lowest harm), which implies a judgement of the balance between desirable and undesirable effects. In the second round, the strength of each recommendation was defined (i.e., the degree of confidence that the desirable effects outweigh the undesirable ones, taking into account four determinants: quality of the evidence, balance between desirable and undesirable effects, patient values and preferences). Consensus on each recommendation was achieved by using the Delphi method, in order to minimize biases that can be introduced by group dynamics or dominant personalities [8]. The Delphi method involves anonymous voting, facilitated discussions, group feedback, and statistical analysis of the responses. For ensuring full anonymity throughout the whole voting process, a computerized system with coded server upload was developed, preventing any individual disclosure during the production process. At each round, task force members independently uploaded an anonymously completed questionnaire. The EAN Register of Interest Form, capturing relevant financial activities, and an additionally implemented Register of Study Involvement Form, capturing potential intellectual conflicts, determined the voting rights for each intervention. Only members free of conflicts of interest voted for specific interventions. At each round, a facilitator provided an anonymous summary of the task force opinions from the previous round, and areas of disagreement were identified. Voting members were invited to—anonymously—review their earlier answers in the light of the replies from other members of the task force. Once consensus was reached assumptions and rationale for all decisions were explicitly discussed. If disagreement still existed, its nature and extent were accounted for and explained in the guideline report.

## RESULTS

Our systematic search process yielded 57,001 cumulative query results across all databases, out of which 17,969 unique entries were manually screened for inclusion. The following interventions were eligible for formal meta-analysis: amphetamine (5, 10 mg/day, oral), cerebrolysin (30 ml/day, intravenous, minimum 10 days), citalopram (10, 20 mg/day, oral), dextroamphetamine (10 mg/day, oral), Di-Huang-Yi-Zhi (2 × 18 g/day, oral), fluoxetine (20 mg/day, oral), lithium (2 × 300 mg/day, oral), MLC601(3 × 400 mg/day, oral), phosphodiesterase-5 inhibitor PF-03049423 (6 mg/day, oral), selegiline (5 mg/day, oral). Results are synthesized in Table 2.

### Amphetamine

#### Early motor performance (month 1, month 3)

One trial ($N$ = 33) compared amphetamine with standard/usual care using the Fugl-Meyer (FM) upper limb scale at 1 month after stroke [9]. Low-quality evidence from a single randomized trial indicated little difference between groups. The FM upper limb score in the amphetamine group was 2.4 higher (95% confidence interval [CI] −16.27 to 21.07), with SMD 0.09 (95% CI −0.60 to 0.77). At 3 months, two randomized trials [9,10] ($N$ = 69) compared amphetamine with standard/usual care on motor performance using different FM scales, with no difference between groups (low-quality evidence from meta-analysis; SMD −0.01, 95% CI −0.49 to 0.46).

#### Neurological function (month 1, month 3)

One randomized trial ($N$ = 33) compared amphetamine with standard/usual care using the Scandinavian Stroke Scale (SSS) at

**TABLE 2** Summary of recommendations

| Pharmacological intervention | Daily dose | Recommendation |
|---|---|---|
| Amphetamine | 5 mg, 10 mg | Against use |
| Cerebrolysin | 30 ml | For use |
| Citalopram | 10 mg | Against use |
| | 20 mg | For use |
| Dextroamphetamine | 10 mg | Against use |
| Di-Huang-Yi-Zhi | 36 g | Against use |
| Fluoxetine | 20 mg | Against use |
| Lithium | 600 mg | Against use |
| MLC601 | 1200 mg | Against use |
| Phosphodiesterase-5 inhibitor | 6 mg | Against use |
| Selegiline | 5 mg | No recommendation |

1 month after stroke [9]. Low-quality evidence indicated little difference between groups with SSS in the amphetamine group 1.1 lower (95% CI −10.25 to 8.05), SMD −0.08 (95% CI −0.76 to 0.60). At 3 months the SSS in the same trial was 1.8 higher (95% CI −6.99 to 10.59; low-quality evidence), with SMD 0.14 (95% CI −0.55 to 0.82).

### Global functional outcome (month 1, month 3)

One randomized trial (*N* = 33) compared amphetamine with standard/usual care using the Barthel Index (BI) at 1 month after stroke [9]. Low-quality evidence indicated little difference between groups with BI in the amphetamine group 1.0 higher (95% CI −3.52 to 5.52) and with SMD 0.15 (95% CI −0.54 to 0.83). At 3 months two trials (*N* = 69) compared amphetamine with standard/usual care on BI. Low-quality evidence from meta-analysis indicated a marginal group difference with BI 0.58 higher (95% CI −4.22 to 5.37) and SMD −0.08 (95% CI −0.55 to 0.40).

### Serious adverse events (SAEs)

Low-quality evidence from two randomized trials [9,10] (*N* = 69) indicated no difference between the groups regarding the number of patients with SAEs (control group 4/35; amphetamine group 3/34; odds ratio [OR] 0.65, 95% CI 0.13–3.38).

### Clinical guide

Minimal effects. The evidence indicates no issues with intervention safety. Additional information derived from the evidence which was not subject to this guideline signals cautionary use of amphetamine [11], due to weak or ambiguous safety and tolerability profiles.

### Recommendation

Based on low quality of evidence and the observed inferiority for the secondary critical outcome, a weak recommendation against amphetamine for patients in early motor neurorehabilitation is given. In view of the low total sample size (*N* = 69), future studies may change this recommendation.

## Cerebrolysin

### Early motor performance (month 1, month 3)

One randomized trial (*N* = 203) compared cerebrolysin with standard/usual care at 1 month after stroke using the Action Research Arm Test (ARAT) [12]. The mean baseline ARAT in the control group was 10.7 (16.5). High-quality evidence from a single trial indicated beneficial (statistically significant) effects with ARAT improvement 0.5 SD larger (SMD 0.5, 95% CI 0.20–0.80) and OR 2.35 (95% CI 1.43–4.04). At 3 months a low-quality evidence meta-analysis of two trials (*N* = 442) showed beneficial (statistically non-significant) effects with ARAT improvement 0.44 SD larger (SMD 0.44, 95% CI −0.22 to 1.11) and OR 2.12 (95% CI 0.68–6.59) [13].

### Neurological function (month 1, month 3)

Four randomized trials (*N* = 542) compared cerebrolysin with standard/usual care at 1 month after stroke using the National Institutes of Health Stroke Scale (NIHSS) [12–15]. The mean baseline NIHSS in the control groups was 9.6 (SD 3.6). A high-quality evidence meta-analysis of the four trials indicated beneficial (statistically significant) effects with NIHSS improvement (decrease) 0.40 SD larger in the cerebrolysin group than in the control group (SMD −0.40, 95% CI −0.62 to −0.18) and OR 1.94 (95% CI 1.35–2.77). At 3 months a high-quality evidence meta-analysis of two randomized trials (*N* = 248, NIHSS baseline mean 10.0, SD 3.2) showed beneficial (statistically significant) effects with NIHSS improvement 0.77 SD larger in the

cerebrolysin group compared to control (SMD −0.77, 95% CI −1.15 to −0.38) and OR 3.67 (95% CI 1.89–7.13) [12,14].

### Global functional outcome (month 1, month 3)

One randomized trial (*N* = 59) compared cerebrolysin with standard/usual care at 1 month after stroke using the modified Rankin Scale (mRS) [15]. Moderate-quality evidence indicated a beneficial (statistically significant) effect on global functional outcome. The improvement (decrease) of the mRS score in the cerebrolysin group was on average 0.88 SD larger (SMD −0.88, −1.46, −0.31) than in the control group; the OR was 4.52 (95% CI 1.88–14.93). At 3 months high-quality evidence from a single trial (*N* = 205) showed beneficial (statistically significant) effects with mRS improvement 0.88 SD larger in the cerebrolysin group compared to control (SMD −0.88, 95% CI −1.20 to 0.57) and OR 4.52 (95% CI 2.72–8.23) [12]

### Serious adverse events

Moderate-quality evidence from four randomized trials [12,13,15,16] (*N* = 578) indicated no difference between the groups regarding the number of patients with SAEs (control group 13/289; cerebrolysin group 12/289; OR 0.92, 95% CI 0.41–2.05).

### Late research sensitivity analysis

A post hoc sensitivity analysis with exclusion of one randomized trial [13] due to identification of missing primary publication (the trial was published only as part of a meta-analysis) changed the level of evidence for PICO 1a (Early Motor Performance) at month 3 from *low* to *high*. At 3 months high-quality evidence from a single trial (*N* = 205) showed beneficial (statistically significant) effects with ARAT improvement 0.79 SD larger (SMD 0.79, 95% CI 0.45–1.13) and OR 3.85 (95% CI 2.23–7.28). The exclusion of this trial did not change the level of evidence for other PICOs.

### Clinical guide

Evidence identified in this guideline indicates no issues with intervention safety. Additional information derived from evidence which was not subject to this guideline signals stronger effects of cerebrolysin in moderate–severe cases [17]. In view of the agent's route of administration, cerebrolysin add-on treatment should be prioritized in moderate–severe stroke cases (NIHSS ≥8).

### Recommendation

Based on low and high quality of evidence across primary and secondary critical outcomes, a weak recommendation for cerebrolysin (30 ml, intravenous, minimum 10 days) is given for early motor neurorehabilitation after moderate–severe ischaemic stroke.

## Citalopram 10 mg

### Early motor performance (month 1, month 3)

One small randomized trial (*N* = 20) compared citalopram 10 mg with standard/usual care at 1 month after stroke using the Lindmark scale (LS) [18]. The mean baseline LS in the control group was 54. Low-quality evidence from a single trial indicated a beneficial (but non-statistically significant) effect. The LS motor score in the citalopram 10 mg group was 4.0 higher (95% CI −4.77 to 12.77), with SMD 0.38 (95% CI −0.50 to 1.27). No estimates were available for the 3-month outcome.

### Neurological function (month 1, month 3)

One small randomized trial (*N* = 20) compared citalopram 10 mg with standard/usual care at 1 month after stroke using the NIHSS [18]. The mean baseline NIHSS in the control group was 5.3 [18]. Low-quality evidence from a single trial indicated a beneficial (but non-statistically significant) effect (the NIHSS in the citalopram 10 mg group was 1.2 lower [95% CI −2.68 to 0.28], with SMD −0.68 [95% CI −1.59 to 0.23]). For the 3-month outcome, no estimates were available.

### Global functional outcome (month 1, month 3)

One small randomized trial (*N* = 20) compared citalopram 10 mg with standard/usual care at 3 months after stroke using the BI [18]. The mean baseline BI in the control group was 60. Low-quality evidence from a single trial indicated a non-beneficial (non-statistically significant) effect (the BI in the citalopram 10 mg group was 7.0 higher [95% CI −16.27 to 30.27], with SMD 0.25 [95% CI −0.63 to 1.13]). For the 1-month outcome, no estimates were available.

### Serious adverse events

No estimates on patients with SAEs were available. No 'major' adverse events were reported in either group (one small trial with *N* = 20).

### Clinical guide

Minimal to more than small effects. Evidence indicates no issues with intervention safety.

### Recommendation

Based on low quality of evidence and missing estimates on patients with SAEs, a weak recommendation against citalopram 10 mg is given for early motor neurorehabilitation after acute ischaemic stroke. In view of the low total sample size and one single trial only (*N* = 20), future studies may change this recommendation.

## Citalopram 20 mg

### Early motor performance (month 1, month 3)

One randomized trial (*N* = 123) compared citalopram 20 mg with standard/usual care using the NIHSS motor arm subscale at 1 month after stroke [19]. The mean baseline NIHSS motor arm subscore in the control group was 2.21. Moderate-quality evidence from a single trial indicated a more than small difference between groups with the motor arm subscore in the citalopram 20 mg group 0.37 lower compared to control (95% CI −0.71 to −0.03), with SMD −0.38 (95% CI −0.74 to −0.03). At 3 months the group difference in the same trial was −0.57 (95% CI −0.86 to −0.28), with SMD −0.69 (95% CI −1.06 to −0.33). The (statistically significant) results at 1 month and at 3 months should be interpreted with an appropriate level of caution due to imprecision of the NIHSS motor arm subscale, existing baseline differences favouring intervention, and unclear handling of dropouts (15%).

### Neurological function (month 1, month 3)

One randomized trial (*N* = 123) compared citalopram 20 mg with standard/usual care at 3 months after stroke using the rate of patients with at least 50% improvement of NIHSS [19]. Moderate-quality evidence from a single trial indicated a beneficial effect with 79% favourable outcomes in the citalopram 20 mg group compared to 54% in the control group (risk difference [RD] 0.25, 95% CI 0.10–0.40; relative risk [RR] 1.46, 95% CI 1.15–1.86).

### Global functional outcome (month 1, month 3)

One randomized trial (*N* = 123) compared citalopram 20 mg with standard/usual care at 1 month after stroke using the rate of patients with favourable mRS score (0–2) [19]. Moderate-quality evidence from a single trial indicated a beneficial effect with 58% favourable outcomes in the citalopram 20 mg group compared to 32% in the control group (RD 0.26, 95% CI 0.08–0.43; RR 1.80, 95% CI 1.15–2.81). At 3 months the group difference was 22.93 (95% CI 11.13–34.73), with SMD 0.97 (95% CI 0.43–1.51).

### Serious adverse events

No estimates on SAEs were available (no SAE information from two trials with *N* = 786).

### Late research sensitivity analysis

*Early motor performance (month 3)*

One randomized trial (*N* = 60) compared citalopram 20 mg with standard/usual care at 3 months after stroke using the FM motor score [20]. There was indication for beneficial effects (statistically significant) with FM motor score being 22.93 higher (95% CI 11.13–34.73), with SMD 0.97 (95% CI 0.43–1.51). Moderate-quality evidence from post hoc meta-analysis of two available trials [19,20] on motor performance at 3 months, including the late research inclusion, indicated relevant (statistically significant) group differences with SMD 0.78 (95% CI 0.48–1.08). The level of evidence was rated down by 1 point due to imprecision of the motor subscale, existing baseline differences and unclear handling of dropouts (15%) in one of the two studies.

*Global functional outcome (month 1)*

One late research randomized trial in patients with mild stroke (*N* = 642) compared citalopram 20 mg with standard/usual care at 1 month after stroke using the rate of patients with favourable mRS score (0–2) [20]. There was no indication for beneficial effects with 67% favourable outcomes in the citalopram 20 mg group compared to 78% in the control group (RD −0.11, 95% CI −0.18 to −0.04; RR 0.86, 95% CI 0.78–0.95). Low-quality evidence from post hoc meta-analysis of two available trials [19,20] on favourable mRS score (0–2), including the late research trial, indicated marginal group differences with RD −0.06, 95% CI −0.12 to 0.01; RR 0.92, 95% CI 0.84–1.02. There was serious heterogeneity of the two trials with $I^2$ = 93%. The level of evidence was rated down by 2 points due to imprecision and severe heterogeneity ($I^2$ = 93%).

### Clinical guide

No reliable information on SAEs. Overall safety profile suggests good tolerability.

### Recommendation

Based on moderate quality of evidence for beneficial effects in the critical outcomes, a weak recommendation for citalopram 20 mg is given for early motor neurorehabilitation after acute ischaemic stroke.

## Dextroamphetamine

### Early motor performance (month 1, month 3)

One randomized trial (*N* = 67) compared dextroamphetamine with standard/usual care at 1 month after stroke using the FM scale [21]. The mean baseline FM score in the control group was 30.0. Low-quality evidence from a single trial indicated a marginal difference between groups with FM score in the dextroamphetamine group 1.0 higher (95% CI −6.43 to 8.43), with SMD 0.06 (95% CI −0.42 to 0.54). At 3 months the same trial indicated no difference between groups with FM score 0.4 lower in the dextroamphetamine group (95% CI −8.35 to 7.55), with SMD −0.02 (95% CI −0.50 to 0.46).

### Neurological function (month 1, month 3)

One randomized trial (*N* = 67) compared dextroamphetamine with standard/usual care at 1 month after stroke using the Chedoke Arm and Hand Activity Inventory Score (CAHAI) [21]. Low-quality evidence from a single trial indicated no beneficial effect, with CAHAI in the dextroamphetamine group 6.2 lower (95% CI −18.84 to 6.44), and with SMD −0.23 (95% CI −0.71 to 0.25). At 3 months the FM balance score of the same trial indicated little difference between groups with 0.2 higher FM balance score in the dextroamphetamine group (95% CI −1.05 to 1.45), and with SMD 0.08 (95% CI −0.40 to 0.56).

### Global functional outcome (month 1, month 3)

One randomized trial (*N* = 67) compared dextroamphetamine with standard/usual care at 1 month after stroke using the Functional Independence Measure (FIM) [21]. The mean baseline FIM was 67.3. Low-quality evidence from a single trial indicated a small difference between groups with FIM in the dextroamphetamine group 3.7 lower (95% CI −11.78 to 4.38), and with SMD −0.22 (95% CI −0.70 to 0.26). At 3 months the FIM of the same trial indicated little difference between groups with FIM balance score 1.3 lower in the dextroamphetamine group (95% CI −8.87 to 6.27), with SMD −0.08 (95% CI −0.56 to 0.40).

### Serious adverse events

No estimates on SAEs were available. The study drug was reported as being 'well tolerated'.

### Clinical guide

Minimal effects, including harm. Additional information derived from evidence which was not subject to this guideline signals cautionary use of dextroamphetamine, due to weak or ambiguous safety and tolerability profiles [22].

### Recommendation

Based on low quality of evidence and no effect on critical outcomes, a weak recommendation against dextroamphetamine is given for early motor neurorehabilitation after acute ischaemic stroke.

## Di-Huang-Yi-Zhi (DHYZ)

### Early motor performance (month 1, month 3)

One randomized trial (*N* = 87) compared DHYZ with standard/usual care at 1 month after stroke using the FM scale [23]. The mean baseline FM score in the control group was 51.0. Low-quality evidence from a single trial indicated little difference between groups, with FM scores in the DHYZ group 1.2 lower (95% CI −6.42 to 4.02), and with SMD −0.10 (95% CI −0.52 to 0.32). At 3 months, moderate-quality evidence in the same trial indicated beneficial effects with 6.50 higher FM scores in the DHYZ group (95% CI 0.73–12.27), and with SMD 0.47 (95% CI 0.04–0.90).

### Neurological function (month 1, month 3)

No estimates were available for the neurological function of DHYZ in patients with acute ischaemic stroke.

### Global functional outcome (month 1, month 3)

One randomized trial (*N* = 87) compared DHYZ with standard/usual care at 1 month after stroke using the BI [23] The mean baseline BI in the control group was 51.0. Low-quality evidence from a single trial indicated a BI decrease in the DHYZ group compared to control (the BI in the DHYZ group was 3.7 lower [95% CI −8.38 to 0.98], with SMD −0.33 [95% CI −0.75 to 0.10]). Moderate-quality (statistically significant) evidence at 3 months indicated beneficial effects with BI 4.5 higher in the DHYZ group compared to control (95% CI 0.24–8.76), and with SMD 0.44 (95% CI 0.01–0.87).

### Serious adverse events

Low-quality evidence from one randomized trial [23] (*N* = 100) indicated no difference between the groups with 0/50 events in the control group and 0/50 events in the DHYZ group (odds ratio not estimable).

### Clinical guide

Minimal to moderate effects, including harm. Evidence indicates no issues with intervention safety.

### Recommendation

Based on low-quality evidence for negative effects on the primary critical outcome and moderate quality of evidence for beneficial effects on the secondary critical outcome, a weak recommendation against DHYZ is given for early motor neurorehabilitation after acute ischaemic stroke. In view of the low total sample size (*N* = 87) more studies in the future may change this recommendation.

## Fluoxetine

### Early motor performance (month 1, month 3)

One randomized trial (*N* = 113) compared fluoxetine with standard/usual care at 3 months after stroke using the FM scale [24]. The mean baseline FM score in the control group was 13.4. High-quality evidence from a single trial indicated a beneficial (statistically significant) effect on motor performance, as FM change from baseline in the fluoxetine group was 9.7 higher (95% CI 3.68–15.72), with SMD 0.59 (95% CI 0.21–0.97).

### Neurological function (month 1, month 3)

One randomized trial (*N* = 113) compared fluoxetine with standard/usual care at 3 months after stroke using NIHSS (mean baseline NIHSS in the control group 13.1) [24]. Low-quality evidence from a single trial indicated a beneficial (but non-statistically significant) effect on neurological function, with NIHSS in the fluoxetine group 1.1 lower (95% CI −2.61 to 0.41) than in the control group, with SMD −0.27 (95% CI −0.64 to 0.10).

### Global functional outcome (month 1, month 3)

One randomized trial (*N* = 113) compared fluoxetine with standard/usual care at 3 months after stroke using the mRS [24]. Low-quality evidence from a single trial indicated a beneficial (but non-statistically significant) effect on global functional outcome. The mRS score in the fluoxetine group was on average 0.21 SD lower (−0.56, 0.14) than in the control group; OR 1.43 (95% CI 0.79–2.66).

### Serious adverse events

Whilst two SAEs were reported for fluoxetine, the number of patients with SAEs was not provided.

### Late research sensitivity analysis

*Early motor performance (month 3)*

One randomized late research trial (*N* = 60) [25] compared fluoxetine 20 mg with standard/usual care at 3 months after stroke using the FM motor score. There was indication for beneficial effects (statistically significant) with the FM motor score being 24.46 higher (95% CI 12.93–35.99), with SMD 1.06 (95% CI 0.52–1.60). High-quality evidence from a post hoc meta-analysis of two available randomized trials [26,27] on motor performance at 3 months, including the late research trial, indicated relevant (statistically significant) group differences with the FM motor score being 20.89 higher (95% CI 13.68–28.10), and SMD 0.84 (95% CI 0.53–1.16).

### Clinical guide

Results from our systematic search yielded high-quality evidence for beneficial effects of fluoxetine on motor performance and low-quality evidence for neurological function and global functional outcome. There are no reliable data on SAEs. Information derived from evidence which was not subject to this guideline signals cautionary use of fluoxetine [26–28], due to weak or ambiguous safety and tolerability profiles, including potential increased risk for bone fractures, hyponatraemia and epileptic seizures.

### Recommendation

Cumulative evidence highlighted by our systematic search (beneficial effects on motor function at 1 and 3 months) and critical findings of studies outside predefined PICOs (global functional outcome at 6 months, pointing toward no effect of fluoxetine for neurorehabilitation after acute ischaemic stroke, as well as issues of safety [26–28]) have informed a weak recommendation against fluoxetine for early motor neurorehabilitation after acute ischaemic stroke.

## Lithium

### Early motor performance (month 1, month 3)

One randomized trial (*N* = 66) compared lithium with standard/usual care at 1 month after stroke using the FM motor scale—hand subsection (hFM) [29]. The mean baseline hFM in the control group was 0.76. Low-quality evidence from a single trial indicated a more than small beneficial (but non-statistically significant) effect. The hFM in the lithium group was 0.84 higher (95% CI −0.17 to 1.85), with SMD 0.40 (95% CI −0.09 to 0.89). For the 3-month outcome no estimates were available.

### Neurological function (month 1, month 3)

One randomized trial (*N* = 66) compared lithium with standard/usual care at 1 month after stroke using the modified NIHSS scale (mNIHSS) [29]. The mean baseline mNIHSS in the control group was 6.82. Low-quality evidence from a single trial indicated a more than small beneficial (but non-statistically significant) effect with mNIHSS reduction in the lithium group 0.7 larger (95% CI −1.55 to 0.15), with SMD −0.40 (95% CI −0.89 to 0.09). No estimates were available for the 3-month outcome.

### Global functional outcome (month 1, month 3)

No estimates were available for global functional outcome.

### Serious adverse events

Low-quality evidence from one randomized trial [29] (*N* = 66) indicated no difference between the groups with 0/34 events in the control group and 0/32 events in the lithium group (odds ratio not estimable).

### Clinical guide

More than small effects in early motor performance and neurological function after month 1. No estimates for month 3. Additional information derived from evidence which was not subject to this guideline signals cautionary use of lithium [30], due to weak or ambiguous safety and tolerability profiles.

### Recommendation

Based on low-quality evidence for beneficial effects, a weak recommendation against lithium is given for patients in early motor neurorehabilitation.

## MLC601

### Early motor performance (month 1, month 3)

One randomized trial (*N* = 1061) compared MLC601 with standard/usual care at 3 months after stroke using the NIHSS motor score [31]. Low-quality evidence from a single trial indicated little difference between groups. The mean change of the NIHSS motor score in the MLC601 group was 0.17 larger (95% CI −0.55 to 0.21).

### Neurological function (month 1, month 3)

One randomized trial (*N* = 1061) compared MLC601 with standard/usual care at 3 months after stroke using NIHSS [31]. The mean baseline NIHSS in the control group was 8.6. Low-quality evidence from a single trial indicated little difference between groups. The mean NIHSS decrease in the MLC601 group was on average 0.46 larger (95% CI −1.26 to 0.34).

### Global functional outcome (month 1, month 3)

One randomized trial (*N* = 1061) compared MLC601 with standard/usual care at 3 months after stroke using the mRS [31]. Low-quality evidence from a single trial indicated no beneficial effect on global functional outcome. The mRS score in the MLC601 group was on average 0.04 SD lower (95% CI −1.74 to 1.02) than in the control group; OR 1.06 (0.87–1.38).

### Serious adverse events

Moderate-quality evidence from one randomized trial [31] (*N* = 1087) indicated no difference between the groups with 74/545 events in the control group and 60/542 events in the MLC601 group (OR 0.79, 95% CI 0.55–1.14).

### Clinical guide

Minimal effects. Evidence indicates no issues with intervention safety.

### Recommendation

Based on low quality of evidence, negligible intervention effect and lack of evidence for the primary critical outcome, a weak recommendation against MLC601 is given for early motor neurorehabilitation in patients after acute ischaemic stroke.

## Phosphodiesterase-5 inhibitor PF-03049423

### Early motor performance (month 1, month 3)

No estimates were available for early motor performance.

### Neurological function (month 1, month 3)

One randomized trial (*N* = 137) compared PF-03049432 with standard/usual care at 3 months after stroke using the rate of patients

with NIHSS score 0 or 1 [32]. Low-quality evidence from a single trial indicated no group differences (RD −0.01, 95% CI −0.16 to 0.14; RR 0.96, 95% CI 0.54–1.71).

### Global functional outcome (month 1, month 3)

One randomized trial (*N* = 1061) compared PF-03049432 with standard/usual care at 3 months after stroke using the mRS [32]. Low-quality evidence from a single trial indicated little beneficial (non-statistically significant) effect on global functional outcome. The mRS score in the PF-03049432 group was on average 0.11 SD lower (−0.45, 0.23) than in the control group, with OR 1.20 (95% CI 0.67–2.17).

### Serious adverse events

Moderate-quality evidence from one randomized trial [32] (*N* = 137) indicated no difference between the groups with 18/67 events in the control group and 15/70 events in the PF-03049432 group (OR 0.74, 95% CI 0.34–1.62).

### Clinical guide

No or only little beneficial effect. Evidence indicates no issues with intervention safety.

### Recommendation

Based on low-quality evidence, a weak recommendation against PF-03049432 is given for patients in early motor neurorehabilitation. In view of the low total sample size (*N* = 137) more studies in the future may change this recommendation.

## Selegiline

### Early motor performance (month 1, month 3)

One small randomized trial (*N* = 19) compared selegiline with standard/usual care at 1 month after stroke using the FM scale [33]. The mean baseline in the control group was 55.3. Low-quality evidence from a single trial indicated no beneficial effect. FM motor performance in the selegiline group was 12.8 lower (95% CI −37.26 to 11.66), with SMD −0.46 (95% CI −1.38 to 0.45). At 3 months there was only marginal difference between groups (low-quality evidence with FM 2.0 higher [95% CI −17.21 to 21.21], SMD 0.10 [95% CI −0.92 to 1.11]).

### Neurological function (month 1, month 3)

One small randomized trial (*N* = 19) compared selegiline with standard/usual care at 1 month after stroke using the SSS [33]. The mean baseline in the control group was 38.9. Low-quality evidence from a single trial indicated no beneficial effect. The SSS in the selegiline group was 3.3 lower (95% CI −10.94 to 4.34), with SMD −0.38 (95% CI −1.29 to 0.53). At 3 months there was a more than small beneficial (non-statistically significant) effect (low-quality evidence) with SSS 2.6 higher (95% CI −1.8 to 7.0), SMD 0.55 (95% CI −0.49 to 1.59).

### Global functional outcome (month 1, month 3)

One small randomized trial (*N* = 19) compared selegiline with standard/usual care at 1 month after stroke using the BI [33] The mean baseline in the control group was 43.5. Low-quality evidence from a single trial indicated no beneficial effect. The BI in the selegiline group was 3.3 lower (95% CI −33.0 to 26.4), with SMD −0.10 (95% CI −1.00 to 0.81). At 3 months there was a small beneficial (but non-statistically significant) effect (low-quality evidence) with BI 5.4 higher (95% CI −16.82 to 27.62), SMD 0.23 (95% CI −0.79 to 1.25).

### Serious adverse events

Whilst five SAEs were reported for selegiline and 10 for placebo, the number of patients with SAEs in the two treatment groups was not reported.

### Clinical guide

Unclear effects (medium-sized superiority to medium-sized inferiority) resulting from low-quality evidence. There are no reliable data on SAEs.

### Recommendation

Based on low confidence in effect estimates and otherwise inconclusive results, no recommendation is made for or against selegiline for neurorehabilitation after acute ischaemic stroke, as this would be speculative given current available evidence.

# DISCUSSION

Neurorecovery is a dynamic and multifactorial process and is most prominent in the first 30 days after stroke onset [2,34].

Neuroplasticity is the biological support of brain recovery, comprising all mechanisms of neuronal reorganization, including synaptogenesis, dendrite growth, axonal sprouting, recruitment of new anatomical pathways with similar functions to those injured, activation of functional but silent synapses, and cell genesis [35]. These metabolic, inflammatory and genetic processes occur in a specific temporal sequence, dependent on the time elapsed since stroke onset. The thorough knowledge of this sequence and of the interconnections between these processes is vital because various pharmacological or non-pharmacological therapies have the potential to reduce disability only if they are applied at the right time. Pharmacological intervention can overcome inhibitory mechanisms and stimulate neuroplasticity in many ways, ranging from behaviour to gene expression [24,36]. Neural plasticity represents the central core of functional recovery after a stroke and it is important to develop strength strategies able to facilitate these processes in order to offer the best treatment for stroke patients.

Recent clinical studies showed that pharmacological intervention is able to stimulate endogenous neuroplasticity and combined with early motor rehabilitation can significantly reduce disability after stroke. Selective serotonin reuptake inhibitors (SSRIs), neurotrophic factors, monoclonal antibodies, levodopa, methylphenidate and amphetamine are only a few of the drugs studied in early rehabilitation after stroke. Many questions regarding translation of results from these studies to clinical practice were raised (i.e., related to drug selection, dosage, duration, initiation timing). Despite identifying and processing over 57,000 database entries, the strict GRADE approach employed by this guideline warrants exclusion of papers that do not meet all inclusion criteria, even if they broadly fit the topic of study. Some interventions (e.g., levodopa—see methodological Appendices S1–S14), did not make it to the end due to missing information in the reported trials.

This guideline found sufficient evidence to recommend use of cerebrolysin in moderate–severe cases, as an add-on therapy to standard rehabilitation, when initiated in the first 7 days after acute ischaemic stroke. A weak recommendation for citalopram 20 mg was given due to one included negative late breaking trial [20] which enrolled very mild cases only; thus the option may be considered for moderate–severe patients.

Cerebrolysin is a pharmacological agent that contains active fragments of various neurotrophic factors, obtained using a standardized biological method of controlled breakdown of highly purified lipid-free brain proteins [37]. Active neurotrophic factor fragments (peptides) and amino acids quickly cross the blood–brain barrier and bind to specific receptors on different membranes of the nervous system. Each fragment specifically initiates an intracellular signalling pathway via the phosphorylation of the involved protein kinases, which ultimately leads to the activation of transcription factors and the production of proteins involved in processes such as the maintenance of cellular neurotrophicity, neuroprotection, neuroplasticity and neurogenesis. Cerebrolysin has a pharmacologically multimodal mechanism of action, influencing the brain's endogenous defence activity in the post-lesional brain via pleiotropic therapeutic effects by simultaneously modulating several components of the pathological cascade in stroke, traumatic brain injury and neurodegenerative diseases [38–40].

Several studies on stroke patients have tested whether antidepressants such as fluoxetine and citalopram may have a role in neurorehabilitation. SSRIs in particular are recognized to elicit a neuroprotective effect through their anti-inflammatory action. By heightening the amount of serotonin, a valuable cerebral monoamine, these drugs may influence both short-term and long-term facilitation processes involved in motor and cognitive rehabilitation [41]. The systematic review and meta-analysis performed by McCann et al. in 2014 suggests that SSRIs improve infarct volume and neurobehavioural outcome in animal models of ischaemic stroke [42]. In animal studies, various beneficial mechanisms whereby SSRIs may improve structural and functional recovery from ischaemic brain damage have been identified, including enhancement of neuroplasticity, anti-inflammation mediated neuroprotection (inhibiting late stages of post-ischaemic inflammation), improvement of cerebral blood flow autoregulation, and modulation of the adrenergic neurohormonal system [43]. It is reemphasized that any clinical decision based on evidence drawn from studies which are close but do not meet the inclusion criteria and the scope of this guideline (e.g., the FOCUS trial [26], studying the effect of 20 mg fluoxetine initiated between 2 and 15 days after ischaemic stroke, as measured by mRS at 6 months, excluded from this guideline due to missing neurorehabilitation programme and unavailability of outcome results for month 1 or month 3, as well as a Cochrane review for cerebrolysin excluded due to different study inclusion criteria, e.g., initiation of therapy in the first 48 h after stroke, comparison with placebo or no treatment, no mention of neuorehabilitation) [44] should be appraised with caution in conjunction with the guideline research question and findings, to identify the best options for patient care. It is also noted that, after first submission of this paper, two trials on fluoxetine (EFFECTS and AFFINITY) were published with negative results on the primary outcome (mRS) after a 6-month follow-up. Fluoxetine did reduce the occurrence of depression, whilst increasing the risk of bone fractures and hyponatraemia [27,28].

Based on findings summarized by this guideline, it is concluded that further efforts are required to provide more precise recommendations and insight into practical aspects to be considered when approaching supportive therapies for early motor rehabilitation after ischaemic stroke. Researchers must address some epistemological uncertainties, such as consensus on the agreed types of rehabilitation protocols to be studied. At the level of our research questions, pairing pharmacological intervention with some motor rehabilitation is recommended. However, due to the heterogeneity of approaches and limited reported information on rehabilitation protocols, more specific questions regarding frequency, type or setting for this intervention cannot be answered. Accounting for these therapeutic nuances is essential to reduce noise and draw conclusions on the add-on effect of post-stroke pharmacological intervention. Secondly, future appraisal efforts may consider a broader spectrum of intervention timelines and outcomes, as informed by our

systematic mapping of evidence that has identified a trend toward broader therapeutic windows and longer patient follow-up. A propensity for transitioning patient-oriented outcomes is also a matter to be methodologically accounted for when comparing broad types of study outcomes. Finally, a layer that must be accounted for in all future research is economic evaluation. In the context of pressured health systems due to the ongoing pandemic and morbidity trends, cost-effectiveness analyses inform policymakers on how to provide the highest level of access to target populations. A secondary advantage of reporting on this type of outcome is that information regarding patients' quality of life is highlighted, complementing efficacy and effectiveness data from clinical trials. By interweaving these aspects, interested stakeholders are provided with a multidimensional snapshot on therapeutic options, most often required for clinical and policy decision-making, particularly in a high-burden disease such as stroke.

Promising advances in basic science also bring new opportunities to study the pharmacological enhancement of post-stroke neurorehabilitation [45]. As new research emerges, this guideline aims to inform clinicians regarding existing pharmacological support in interventions for neurorecovery after acute ischaemic stroke. Updates to this material will potentially elucidate existing conundrums, improve current recommendations, and hopefully expand therapeutic options for stroke survivors.

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## CONFLICT OF INTEREST

E.B. discloses minor financial activities (board membership, payment for lectures including service on speakers' bureau) with UCB Pharma and Viropharma and major grants from UCB Pharma and EISAI Italia, not related to this guideline. E.B. has voted on all interventions. H.B. discloses no financial or intellectual conflict of interest. H.B. has voted on all interventions. C.B. discloses being a subinvestigator in the CARS 1 trial (Cerebrolysin and Recovery After Stroke), funded by EVER Neuro Pharma—the producer of cerebrolysin, and a subinvestigator in the CAPTAIN II trial (safety of cerebrolysin in neurorecovery after moderate–severe traumatic brain injury), funded academically as part of doctoral studies. C.B. has abstained from voting on evidence for cerebrolysin in this guideline. N.B. discloses being a principal investigator in the CASTA trial (Cerebrolysin in patients with acute ischaemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial), funded by EVER Neuro Pharma—the producer of cerebrolysin, and the first author of the paper 'Safety and efficacy of cerebrolysin in early post-stroke recovery: a meta-analysis of nine randomized clinical trials' (*Stroke*, 2017, 10.1007/s10072-017–3214–0). N.B. has abstained from voting on evidence for cerebrolysin in this guideline. K.D. discloses no financial or intellectual conflict of interest. K.D. has voted on all interventions. S.G. discloses no financial or intellectual conflict of interest. S.G. has voted on all interventions. V.H. discloses minor financial activities (royalties) not related to this guideline, as well as being a principal investigator in the CAPTAIN I trial, funded by EVER Neuro Pharma—the producer of cerebrolysin. V.H. has abstained from voting on evidence for cerebrolysin in this guideline. V.L. discloses no financial or intellectual conflict of interest. V.L. has voted on all interventions. D.F.M. discloses major financial activities (travel/accommodation/meeting expenses) with the Foundation for the Study of Nanoneuroscience and Neuroregeneration, not related to this guideline, as well as being a principal investigator in the Cerebrolysin REGistry Study in Stroke (CREGS 2) and the CARS I trial, funded by EVER Neuro Pharma—the producer of cerebrolysin, and a principal investigator in the CAPTAIN II and CAPTAIN rTMS trials, funded academically as part of doctoral studies. D.F.M. has abstained from voting on evidence for cerebrolysin in this guideline. M.P. discloses minor financial activities (consultancy, payment for lectures including service on speakers' bureau, travel/accommodation/meeting expenses) not related to this guideline. M.P. has voted on all interventions. G.R. discloses no financial or intellectual conflict of interest. G.R. is a technical expert providing voluntary support and has not participated in grading evidence. L.S. discloses minor financial activities (consultancy, travel/accommodation/meeting expenses) not related to this guideline. L.S. has voted on all interventions. S.S. discloses no financial or intellectual conflict of interest. S.S. is a technical expert providing voluntary support and has not participated in grading evidence. J.C.V. discloses minor financial activities (consultancy, payment for lectures including service on speakers' bureau) not related to this guideline, as well as being on the Advisory Board of Ever Pharma (2013–2015), performing technical support for the CARS 1 and 2 trials and the CREGS 2 study, funded by EVER Neuro Pharma—the producer of cerebrolysin. J.C.V. has abstained from voting on evidence for cerebrolysin in this guideline.

## AUTHOR CONTRIBUTIONS

**Ettore Beghi**: Conceptualization (equal); investigation (equal); methodology (equal); supervision (equal); validation (equal); writing—original draft (equal); writing—review and editing (equal). **Heinrich Binder**: Conceptualization (equal); investigation (equal); validation (equal); writing—review and editing (equal). **Codruta Birle**: Data curation (equal); investigation (equal); validation (equal); writing—review and editing (equal). **Natan Bornstein**: Conceptualization (equal); investigation (equal); validation (equal); writing—review and editing (equal). **Karin Diserens**: Conceptualization (equal); investigation (equal); validation (equal); writing—review and editing (equal). **Stanislav Alexandru Groppa**: Conceptualization (equal); investigation (equal); validation (equal); writing—review and editing (equal). **Volker Hoemberg**: Conceptualization (equal); investigation (equal); validation (equal); writing—review and editing (equal). **Vitalie Lisnic**: Conceptualization (equal); investigation (equal); validation (equal); writing—review and editing (equal). **Maura Pugliatti**: Conceptualization (equal); investigation (equal); methodology (equal); supervision (equal); validation (equal); writing—review and

editing (equal). **Gary Randall**: Methodology (supporting); validation (equal); writing—original draft (supporting); writing—review and editing (supporting). **Leopold Saltuari**: Conceptualization (equal); investigation (equal); validation (equal); writing—review and editing (equal). **Stefan Strilciuc**: Data curation (equal); methodology (equal); project administration (supporting); supervision (supporting); validation (supporting); writing—original draft (equal); writing—review and editing (equal). **Johannes Vester**: Conceptualization (lead); data curation (equal); formal analysis (lead); investigation (equal); methodology (equal); software (lead); validation (equal); visualization (lead); writing—original draft (equal); writing—review and editing (equal). **Dafin Muresanu**: Conceptualization (lead); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (lead); resources (lead); supervision (equal); validation (equal); writing—original draft (equal); writing—review and editing (equal).

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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