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REVIEW ARTICLE

SAFETY AND EFFICACY OF RECOVERY-PROMOTING DRUGS FOR MOTOR FUNCTION AFTER STROKE: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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Objective: **To investigate the efficacy and safety of drug interventions to promote motor recovery post-stroke.**

Data sources: **CENTRAL, CINAHL, Embase, MEDLINE, SCOPUS and Web of Science.**

Study selection: **Published human randomized controlled trials in which the primary intervention was a drug administered to promote motor recovery post-stroke, vs placebo.**

Data extraction: **Standardized pro forma used to extract safety and efficacy data; Cochrane Collaboration risk of bias assessment tool performed to assess risk of bias.**

Data synthesis: **Fifty randomized controlled trials from 4,779 citations were included. An overall trend of high risk of attrition (*n* = 27) and reporting bias (*n* = 36) was observed. Twenty-eight different drug interventions were investigated, 18 of which demonstrated statistically significant results favouring increased motor recovery compared with control intervention. Forty-four studies measured safety; no major safety concerns were reported.**

Conclusion: **Candidate drug interventions promoting motor recovery post-stroke were identified, specifically selective serotonin reuptake inhibitors and levodopa; however, the high risk of bias in many trials is concerning. Drugs to improve motor function remain an important area of enquiry. Future research must focus on establishing the right drug intervention to be administered at an optimal dose and time, combined with the most effective adjuvant physical therapy to drive stroke recovery.**

Key words: pharmaceutical preparations; stroke; rehabilitation.

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LAY ABSTRACT

Several drugs, administered in combination with rehabilitation, have been found to increase the amount of physical recovery achieved by a stroke survivor. This paper reviews the published literature to investigate which drugs have the best evidence of efficacy and safety to promote motor recovery after stroke. However, many studies investigating these drugs lack rigor and have little consistency between how trials were performed. Consequently, it is difficult to make a definitive judgement on how safe and effective these drugs are, or to compare drugs to determine superiority. To overcome this, a reporting standard must be developed for trials of these particular drugs. In addition, stricter adherence is necessary to already established reporting standards, including those that outline how parallel group randomized trials and physical interventions embedded within them are described (the Template for Intervention Description and Replication checklist and the Consolidated Standards of Reporting Trials statement, respectively).

Drug interventions are known to be effective for primary and secondary stroke prevention, and to promote reperfusion of penumbra within hours of stroke onset (1, 2). Neuroprotective drugs seem promising, but outcomes have failed to translate in human trials (2). As many people lack access to time-sensitive stroke interventions targeting prevention and reperfusion, drug interventions that mediate recovery beyond the window for effective reperfusion are important research targets. The treatment window for recovery-promoting drugs (RPD) ranges from days to years post-stroke, increasing the potential for survivors to be eligible, and benefit from treatment (3–5). Whilst rehabilitation has been proven to be of great benefit, RPDs may have a place in enhancing recovery in instances where stroke survivors receive little therapy and have low levels of physical activity (6).

Recovery-promoting drug interventions have been investigated for many years; however, there has been little consistency in clinical trials to allow for rigorous comparison or meta-analysis of outcomes across different drug classes. To date, systematic reviews of RPDs have been limited to specific classes of drugs. A Cochrane Review investigating the effect of amphetamine treatment (compared with placebo) in 10 trials ($n = 287$ patients) found no evidence to support routine use in stroke survivors to reduce death or

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disability when taking risk of harm into account (7). The number of patients included in the studies was too small to be able to draw firm conclusions regarding the effect of amphetamines on recovery from stroke (7). Conversely, another Cochrane Review ($n=52$ trials, 4,059 patients) provided "tantalizing evidence" that selective serotonin reuptake inhibitors (SSRIs) appear to improve dependence, disability, neurological impairment, and anxiety and depression after stroke (8). Both reviews recommended larger, well-designed trials be undertaken to clarify efficacy, and to overcome issues with heterogeneity and methodology seen in studies across both drug classes.

As both reviews targeted singular drug classes, neither could provide judgement comparing the outcomes of the drugs with each other. To address this gap, the aim of this systematic review was to investigate the efficacy and safety of drug interventions trialled to enhance motor recovery post-stroke (3, 4).

METHODS

Protocol and registration

This systematic review was registered on PROSPERO (reference number: CRD42016048035). Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement provided the framework for the article (9).

Data sources and searches

Six electronic databases (Cochrane CENTRAL, CINAHL, Embase, MEDLINE, SCOPUS and Web of Science) were searched from database inception to 2 May 2017. Reference lists of included studies were entered into the Web of Science to identify relevant studies from forward citations.

The search term "recovery-promoting drug" was not widely recognized. Relevant drug studies identified through a scoping search were mined for terminology describing the concept of "promoting neurorecovery". The resulting search strategy was curated carefully, containing key words and MeSH terms associated with target pathways, anatomy and processes (e.g. "efferent pathways", "motor cortex" and "neurogenesis"), and molecules involved in neural plasticity and neural repair (e.g. more broadly: "nerve growth factors", "psychotropic drugs"; specifically "biogenic amines" and "dopamine") with the intention of selecting motor recovery-specific studies from the broader pool of neurorecovery trials (Figs S1–S7).

Study selection

Study inclusion criteria were: (*i*) randomized placebo-controlled trial design; (*ii*) commencement of 1 or more RPD intervention/s >24 h post-stroke (10); and (*iii*) a measure of motor outcome of components of the motor system within the domains of body functions and structures and activity, as defined by the International Classification of Functioning, Disability and Health (ICF) (11). Non-English publications and aphasia trials were excluded, the latter being a language disorder, not attributable to motor function.

Titles and abstracts were reviewed and shortlisted by author NF, and by author JB if inclusion was unclear. Eligibility was determined through independent assessments of full-text versions of shortlisted articles by authors NF and KH, while author JB confirmed eligibility when necessary.

Data extraction and analysis, and risk of bias assessment

Study details (sample size, time post-stroke, age, sex, stroke severity), experimental design descriptors (drug and control intervention details, adjuvant physical therapy, treatment/follow-up endpoints), outcome measures and corresponding measures of central tendency were extracted by author NF and corroborated by author KH utilizing standardized pro forma (12). Authors of included studies were emailed for missing data.

Physical rehabilitation interventions within each trial were recorded as "adjuvant therapies". The endpoint was defined as final assessment of outcome; whether occurring at final dose of drug intervention or end of follow-up was noted, along with whether primary outcome measures were designated. The extent of safety monitoring and adverse events were recorded, and whether they were pre-specified outcomes or general observations. Safety assessment was based on mortality and severe adverse events (SAEs) associated with drug intervention, e.g. haemorrhage, neurological deterioration. Risk of bias was assessed by NF and KH using the Cochrane risk of bias assessment tool (13). Between-group endpoint estimates and change scores were extracted for motor outcomes. When statistically significant *p*-values were noted, effect sizes were calculated (NF) from raw data using Cohen's d method, where possible (14).

RESULTS

Database searching yielded 1,548 results, with 29 studies eligible for inclusion. These studies contained 3,231 references, used to identify further studies, which led to the inclusion of a further 21 studies (Fig. 1). Therefore, a total of 50 studies ($n=5,643$ participants) were included. Duplicate citation (25%) or not RCT (40%) were the most common reasons for exclusion.

Included studies were published between 1973 and 2017 (Table SI). Methodologies varied, including crossover trials ($n=10$) (15–24) and short-term studies with outcomes measured ≤24 h post-RPD administration ($n=11$) (16–26). Sample sizes ranged from 8 to 1,099 participants (median: 40, IQR: 18.5–83), mean age spanned 53 (25) to 78 years (27). Participants were predominantly male (range 32–100%); only 12 (24%) studies had ≥50% females.

Twenty-eight different RPDs were investigated (Table I). Four studies compared 2 drug intervention arms with placebo (28–31). Four studies evaluated MLC 601 (NeuroAid™) and involved the largest proportion of participants ($n=2,099$, 37.2%) (32–36). The most frequently studied pharmacological interventions were

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2536

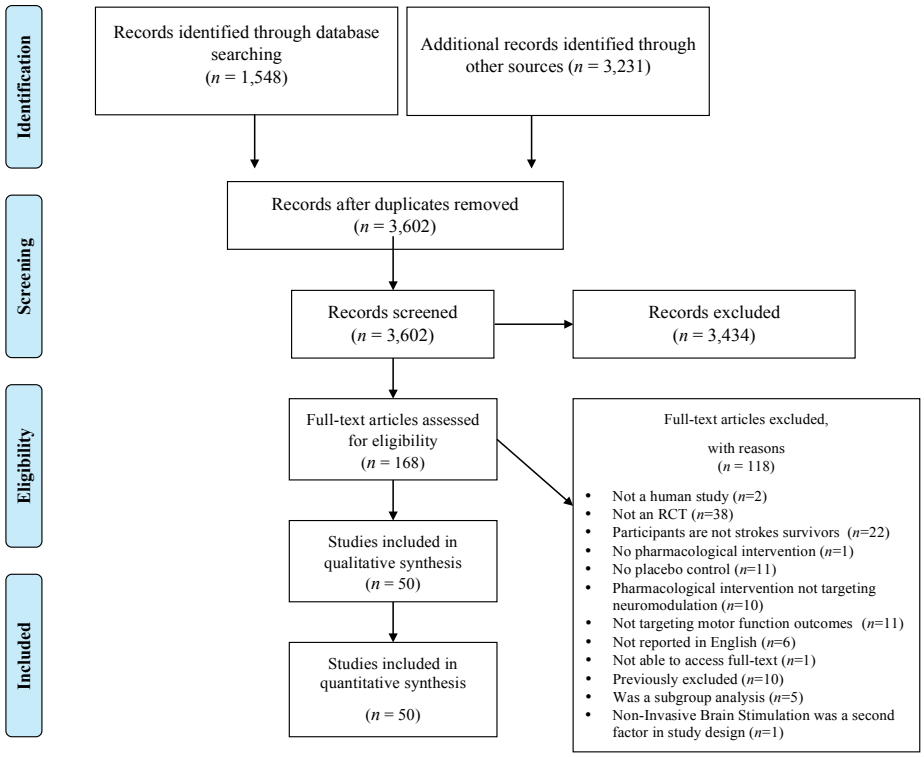

Fig. 1. PRISMA 2009 study selection flow diagram.

dexamphetamine (6 trials) (37–42) and levodopa (6 trials) (15, 16, 19, 20, 29, 43).

Bias scores were mixed across studies (Table SII). Only 4 studies had a low risk of bias across all 6 criteria, each study focused on a different RPD intervention (36, 44–46). High risk of bias was observed most commonly in attrition bias (27 studies, 54%) (15, 21, 27–30, 32, 33, 37–41, 43, 47–59) and reporting bias (36 studies, 72%) (15–19, 21–33, 37–43, 47, 49–52, 56, 59–63) domains.

Study endpoints ranged between 60 min (16, 22) and 2 years (57) after the final RPD dose. Trial endpoints were split evenly between day of final RPD dose (15–26, 28, 44, 45, 47–49, 52–54, 56, 59, 60, 63) and beyond dosing completion (27, 29–43, 46, 50, 51, 55, 57, 58, 61, 62, 64).

Fifty-six different efficacy outcome measures were used, with primary efficacy outcome measures designated in 23 studies (16, 20, 32, 35–40, 42–46, 48, 50, 51, 53–56, 61, 62). Fourteen studies were described as safety and efficacy studies (31, 34–36, 40, 44, 46, 50, 51, 58, 59, 61, 62, 64), but only 4 had designated primary safety outcome measures (31, 61, 62, 64). In 22 studies safety was measured using outcome(s) specified in methods and reported in results (21, 29, 31, 33–36, 40, 44, 46, 49–52, 56–59, 61–64), while mortality and adverse events were observed and reported in another 22 studies (15, 17, 20, 22–28, 30, 37–39, 41, 43, 45, 47, 48, 53, 55, 60). In 6 studies, no safety considerations were reported (16, 18, 19, 32, 42, 54). No authors reported higher mortality or adverse events in drug intervention groups compared with placebo (Table SIII).

Of the 28 RPDs identified, 18 (from 25 trials) showed recovery-promoting potential (Table I) (15–18, 20, 22–24, 26, 29, 30, 32, 36, 42, 43, 45, 48, 52–54, 56, 59, 60, 62, 63). Seventeen RPDs were single-drug interventions, and the final RPD was a combination of methylphenidate and levodopa (29). For 13 RPDs, favourable results were reported from a single trial only (17, 23, 26, 29, 30, 42, 48, 52–54, 56, 59, 62). Neutral or unfavourable results were reported in ≥1 other trial for 4 (of these 13) drug interventions (amphetamine, dexamphetamine, MLC 601 and selegiline) (27, 37–41, 44, 47, 51, 57). Favourable effects on motor function were reported in ≥2 trials for Cerebrolysin®, citalopram, fluoxetine, levodopa (+carbidopa) and methylphenidate (15, 16, 18, 20, 22, 24, 30, 32, 36, 43, 45, 60, 63). However, a beneficial effect on *the same outcome* was not replicated for any given drug intervention. For example, in 6 studies investigating levodopa, 19 different efficacy outcome measures were used (15, 16, 19, 20, 29, 43), with only 2 (9-Hold Peg Test; 9HPT (15, 19), Rivermead Motor Assessment scale (RMA) (15, 43)) utilized in >1 study. Use of multiple outcome measures in any 1 trial, and variation between trials is shown in Table I (and Table SI).

Table I. Summary of pharmacological interventions and outcomes investigated in the studies, clustered by drug class[a]

Pharmacological intervention	Sample size: Analysed (recruited)	Author	Efficacy outcome measures (Primary OM - specified)		Safety outcome measures (SOM): Serious adverse events, death		
			$p < 0.05$	$p > 0.05$	SOM measured (*primary)	Safety observed	No safety data
CNS stimulant (75)							
amphetamine	47 (48)	**Crisostomo et al (1988) (26)**	**Fugl-Meyer Assessment (UL+LL)**	-		✔	
		Sonde et al (2001) (27)	-	Fugl-Meyer Assessment Barthel Index		✔	
dexamphetamine	173 (185)	Gladstone et al (2006) (37)	-	Fugl-Meyer Assessment Functional Independence Measure Chedoke-McMaster Disability Inventory Clinical Outcome Variable Scale Chedoke-McMaster Arm and Hand Activity Inventory		✔	
		Platz et al (2005) (38)	-	TEMPA unilateral TEMPA all Tapping time Aiming test 10-metre Walk Test		✔	
		Schuster et al (2011) (39)	-	Chedoke–McMaster Stroke Assessment (CMSA) - ADL CMSA – impairment CMSA – arm CMSA – hand CMSA – leg CMSA – foot CMSA – postural control		✔	
		Sprigg et al (2007) (40)	-	Fugl-Meyer Assessment (UL) Motricity Index (UL) Scandinavian Stroke Scale Barthel Index modified Rankin Scale extended Activity of Daily Living	✔		
		Treig et al (2006) (41)	-	Barthel Index Rivermead Assessment Scale (RMA) – gross function RMA – leg and trunk RMA – arm		✔	
		Walker-Batson et al (1995) (42)	**Fugl-Meyer Assessment**	-			✔
methylphenidate	106 (129)	**Grade et al (1998) (63)**	**modified Functional Independence Measure**	Fugl-Meyer Assessment	✔		
		Lokk et al (2011) (29)[b]	-	Fugl-Meyer Assessment Barthel Index National Institute of Health Stroke Scale	✔		
		Tardy et al (2006) (22)	**Finger tapping test**	Handgrip force Target pursuit task		✔	
CNS stimulant (67, 75)/Inert metabolic dopamine precursor (75) (+ peripheral dopa decarboxylase inhibitor) (75)							
methylphenidate/levodopa (+ carbidopa)	39 (50)	**Lokk et al (2011) (29)[b]**	**Barthel Index** **National Institute of Health Stroke Scale**	Fugl-Meyer Assessment	✔		
Dopamine agonist (75)							
ropinirole	33 (33)	Cramer et al (2009) (46)	-	Timed 50-Foot Walk Test 6-Minute Walk Test Fugl-Meyer Assessment Stroke Impact Scale-16 Barthel Index	✔		

Table I. *Cont.*[a]

Pharmacological intervention	Sample size: Analysed (recruited)	Author	Efficacy outcome measures (Primary OM - specified) $p < 0.05$	Efficacy outcome measures (Primary OM - specified) $p > 0.05$	Safety outcome measures (SOM): Serious adverse events, death: SOM measured (*primary)	Safety observed	No safety data
Erythropoietin agonists (75)							
erythropoietin	40 (40)	**Ehrenreich et al (2002) (62)**	**Barthel Index** **Δ Scandinavian Stroke Scale** **S100β (serum marker of brain injury)**	National Institute of Health Stroke Scale Scandinavian Stroke Scale modified Rankin Scale Δ National Institute of Health Stroke Scale	✔*		
Gonadotrophin (67, 75)/erythropoietin agonist (67)							
human choriogonadotropin alfa/ erythropoietin	89 (96)	Cramer et al (2014) (61)	-	Δ National Institute of Health Stroke Scale National Institute of Health Stroke Scale % modified Rankin Scale ≤2 Barthel Index	✔*		
Granulocyte colony–stimulating factor (75)							
Filgrastim (G-CSF)	290 (372)	Ringelstein et al (2013) (55)	-	modified Rankin Scale National Institute of Health Stroke Scale		✔	
		Schaebitz et al (2010) (64)	-	modified Rankin Scale National Institute of Health Stroke Scale Barthel Index infarct evolution	✔*		
Humanized monoclonal antibody (50)							
GSK249320	64 (133)	Cramer et al (2017) (50)	-	Δ 10-metre Walk Test Δ 10-metre Walk Test (day 180) modified Rankin Scale National Institute of Health Stroke Scale Box and Block test	✔		
Hydrogenated Ergot Alkaloid (67)							
hydergine	21 (39)	Bochner et al (1973) (49)	-	Limb strength Handgrip strength # handgrip in 30sec 12-foot Walk Test Timed sit-to-stand Feeding ability assessment	✔		
Inert metabolic dopamine precursor + peripheral dopa decarboxylase inhibitor (75)							
levodopa + carbidopa	172 (202)	**Acler et al (2009a) (15)**	**Nine-Hole Peg Test (affected hand)** **10-metre Walk Test**	Rivermead Assessment Scale Transcranial magnetic stimulation		✔	
		Floel et al (2005) (16)	**%TMS-evoked thumb movement in Training Target Zone**	Motor Threshold (agonist) Motor Threshold (antagonist) Motor Evoked Potential (agonist) Motor Evoked Potential (antagonist)			✔
		Lokk et al (2011) (29)[b]	-	Fugl-Meyer Assessment Barthel Index National Institute of Health Stroke Scale	✔		
		Restemeyer et al (2007) (19)	-	Nine-Hole Peg Test Action Research Arm Test Transcranial magnetic stimulation			✔
		Rosser et al (2008) (20)	**Δ in reaction times** **Number of errors**	Reaction times to random elements		✔	
		Scheidtmann et al (2001) (43)	**Rivermead Assessment Scale**	-		✔	

Table I. *Cont.*[a]

Pharmacological intervention	Sample size: Analysed (recruited)	Author	Efficacy outcome measures (Primary OM - specified) $p < 0.05$	Efficacy outcome measures (Primary OM - specified) $p > 0.05$	Safety outcome measures (SOM): Serious adverse events, death: SOM measured (*primary)	Safety observed	No safety data
Irreversible MAO-B inhibitor (75)							
selegiline	59 (71)	Bartolo et al (2015) (47)	-	National Institute of Health Stroke Scale Functional Independence Measure		✔	
		Sivenius et al (2001) (56)	**Scandinavian Stroke Scale**	Barthel Index Fugl-Meyer Assessment	✔		
Methylxanthine drug (21)							
theophylline	18 (20)	Schambra et al (2016) (21)	-	Pinch force dynamometry – both hands Nine-Hole Peg Test (time) – both hands Nine-Hole Peg Test (# errors) – both hands Resting motor threshold – both hemispheres Short-interval intracortical inhibition (ISI: 1ms) – both hemispheres Short-interval intracortical inhibition (ISI: 2ms) – both hemispheres Long-interval intracortical inhibition – both hemispheres Interhemispheric inhibition – both hemispheres	✔		
Mood-stabiliser/antimanic (76)							
lithium carbonate	66 (80)	**Mohammadianinejad et al (2014) (53)**	**↑≥25% Fugl-Meyer Assessment**	Δ modified National Institute of Health Stroke Scale Δ Fugl-Meyer Assessment - hand assessment		✔	
Neuropeptide, porcine brain extract (67)							
Cerebrolysin®	1,308 (1,513)	**Amiri-Nikpour et al (2014) (32)**	**National Institute of Health Stroke Scale** **Pulsatility index - right middle cerebral artery**	Δ Mean flow velocity - right middle cerebral artery Δ Mean flow velocity - left middle cerebral artery Δ Mean flow velocity - basilar artery Pulsatility index - left middle cerebral artery Pulsatility index - basilar artery			✔
		Chang et al (2016) (33)	-	Fugl-Meyer Assessment (total, UL, LL) Diffusion tensor imaging – axial diffusivity – affected hemisphere Diffusion tensor imaging – radial diffusivity – affected hemisphere Diffusion tensor imaging – fractional anisotropy – affected hemisphere rsfMRI	✔		
		Heiss et al (2012) (34)	-	Global directional test: (Δ Barthel Index + modified Rankin Scale + ΔNational Institute of Health Stroke Scale)	✔		

Table I. *Cont.*[a]

Pharmacological intervention	Sample size: Analysed (recruited)	Author	Efficacy outcome measures (Primary OM - specified) $p < 0.05$	Efficacy outcome measures (Primary OM - specified) $p > 0.05$	Safety outcome measures (SOM): Serious adverse events, death: SOM measured (*primary)	Safety observed	No safety data
		Lang et al (2013) (35)	-	modified Rankin Scale Δ National Institute of Health Stroke Scale Barthel Index	✔		
		Muresanu et al (2016) (36)	**Δ Action Research Arm Test** **Δ National Institute of Health Stroke Scale** **Δ Barthel Index** **Δ modified Rankin Scale** **Δ Short Form 36 items Health Survey** **- physical component**	Δ gait velocity Δ Nine-Hole Peg Test	✔		
Noradrenaline reuptake inhibitor (75)							
reboxetine	10 (10)	**Zittel et al (2007) (23)**	**Handgrip force** **Finger tapping test (# taps)**	Nine-Hole Peg Test Motor evoked potential (TMS)		✔	
Peripheral chemoreceptor agonist + alkaloid/ vasodilator (67)							
almitrine bismesylate + raubasine	74 (83)	**Li et al (2004) (52)**	**Barthel Index** **Neurological Functional Deficit Score**	-	✔		
Selective norepinephrine reuptake inhibitor (75)							
atomoxetine	9 (12)	Ward et al (2017) (58)	-	Fugl-Meyer Assessment Action Research Arm Test Wolf Motor Function Test	✔		
Selective serotonin reuptake inhibitor (75)							
citalopram	28 (28)	**Acler et al (2009b) (60)**	**National Institute of Health Stroke Scale** **Motor threshold** **– unaffected hemisphere (TMS)** **Intracortical Inhibition** **– unaffected hemisphere (TMS)**	Barthel Index Lindmark Scale Motor threshold – affected hemisphere (TMS) Intracortical Inhibition – affected hemisphere (TMS) Motor Evoked Potential – affected hemisphere (TMS) Motor Evoked Potential – unaffected hemisphere (TMS)		✔	
		Zittel et al (2008) (24)	**Nine-Hole Peg Test**	Handgrip strength		✔	
escitalopram	10 (11)	**Gourab et al (2015) (17)**	**Velocity-dependent plantarflexion stretch reflexes** **- under passive conditions, at 90°/sec**	Maximal ankle isometric strength Maximal knee isometric strength Velocity-dependent plantarflexion stretch reflexes: - under passive conditions, at: 30°/sec, 60°/sec; 120°/sec - during superimposed maximal volitional drive, at: 30°/sec, 60°/sec; 90°/sec; 120°/sec - after after superimposed maximal volitional drive, at: 30°/sec, 60°/sec; 90°/sec; 120°/sec Fugl-Meyer Assessment – LL 6-minute Walk Test 10-metre Walk Test		✔	

Table I. *Cont.*[a]

Pharmacological intervention	Sample size: Analysed (recruited)	Author	Efficacy outcome measures (Primary OM - specified) $p<0.05$	Efficacy outcome measures (Primary OM - specified) $p>0.05$	Safety outcome measures (SOM): Serious adverse events, death: SOM measured (*primary)	Safety observed	No safety data
fluoxetine	228 (261)	**Chollet et all (2011) (45)**	**Fugl-Meyer Assessment (FMA) - total** **FMA – UL** **FMA – LL** **National Institute of Health Stroke Scale (motor scores)** **modified Rankin Scale**	National Institute of Health Stroke Scale (score 0-5)		✔	
		Dam et al (1996) (28)[b]	-	Hemispheric. Stroke Scale Barthel Index		✔	
		Mikami et al (2013) (30)[b]	**modified Rankin Scale**	Functional Independence Measure		✔	
		Pariente et al (2001) (18)	**Handgrip strength** **Finger tapping** **Motor activation – active task (fMRI)**	Nine-Hole Peg Test Motor activation – passive task (fMRI)			✔
Sigma-1 Receptor Agonist (31)							
cutamesine	57 (60)	Urfer et al (2014) (31)[b]	-	Δ National Institute of Health Stroke Scale modified Rankin Scale Barthel Index 10-metre Walk Test	✔*		
Suspected partial NMDA agonist (25)							
d-cycloserine	20 (20)	Cherry et al (2014) (25)	-	Stability platform task Simulated feeding trial Untrained balance task		✔	
Traditional Chinese medicine (44, 48, 59)							
Di-Huang-Yin-Zi (DHYZ)	87 (100)	**Yu et al (2015) (59)**	**Fugl-Meyer Assessment** **Barthel Index**	-	✔		
Ginkgo biloba	57 (102)	**Oskouei et al (2013) (54)**	**Δ National Institute of Health Stroke Scale ≥ 50%**	Δ National Institute of Health Stroke Scale			✔
MLC 601 (NeuroAid™)	1803 (2288)	**Bavarsad et al (2011) (48)**	**Δ Mean flow velocity** **Barthel Index**	modified Rankin Scale		✔	
		Chen et al (2013) (44)	-	Δ modified Rankin Scale (mRS) mRS 0-1 mRS 0-2 Δ National Institute of Health Stroke Scale (NIHSS) ≥5 points Δ NIHSS (total score –motor score) Barthel Index	✔		
		Kong et al (2009) (51)	-	Fugl-Meyer Assessment Functional Independence Measure National Institute of Health Stroke Scale	✔		
		Venketasubramanian et al (2015) (57)	-	modified Rankin Scale modified Rankin Scale ≤1 Barthel Index ≥ 95	✔		
Tetracyclic antidepressant (67)							
maprotiline	46 (52)	Dam et al (1996) (28)[b]	-	Hemiplegic Stroke Scale Barthel Index		✔	
Tricyclic antidepressant (67)							
nortiptyline	61 (83)	**Mikami et al (2013) (30)[b]**	**modified Rankin Scale**	Functional Independence Measure		✔	

[a]Bold font: statistically significant finding in favour of RPD.
[b]This study contained more than 1 intervention arm, as well as a placebo arm.Δ: change; ADL: activities of daily living; fMRI: functional magnetic resonance imaging; ISI: interstimulus interval; LL: lower limb; rsfMRI: resting-state functional magnetic resonance imaging; TEMPA: Upper Extremity Performance Test for the Elderly; UL: upper limb

Adjuvant physical therapy was inconsistently reported and insufficient to allow for replication. There was extreme variation between therapy amount, type (i.e. Bobath vs Arm Ability training; physiotherapy vs occupational therapy, etc.) and duration. In 15 studies, no adjuvant therapy was reported (15, 17, 18, 21, 34, 35, 48, 49, 51, 52, 54, 55, 61, 62, 64), while in another 13 studies dose of adjuvant therapy was not reported (25, 30–32, 40, 42, 44, 45, 50, 53, 56, 57, 63). In 3 studies, a total of ≤60 min of adjuvant therapy was provided over the duration of the trial (16, 22, 26).

It was deemed impossible to perform data syntheses (meta-analyses) to compare RPDs regardless of drug class, due to the large variability in design, duration and outcome measures.

DISCUSSION

Eighteen of 28 drug interventions identified in this review demonstrated recovery-promoting potential without associated increased rates of mortality or SAEs. Yet, there were high attrition rates and bias, and variable outcomes used, which prevented meta-analysis. These issues are not isolated to RPD; the Stroke Recovery and Rehabilitation Roundtable group highlighted this as common in stroke rehabilitation trials (10, 65, 66). Nevertheless, several classes of RPDs should be discussed in more detail.

Three SSRIs were found to have some evidence of efficacy and safety: citalopram, escitalopram and fluoxetine (17, 18, 24, 30, 45, 60). Typically used as antidepressants, SSRIs inhibit serotonin reuptake into presynaptic neurones thereby enhancing nerve transmission. Motor excitability over the unaffected hemisphere is thought to be decreased, whilst neuroprotective capacity and hippocampal neurogenesis is promoted (67). Of all SSRIs reviewed, fluoxetine was most extensively studied (4/7 SSRI trials with largest cohorts $n = 8$–118) (18, 28, 30, 45). It is therefore unsurprising that fluoxetine is involved in 3 current international trials (FOCUS, AFFINITY, EFFECTS, combined $n = 5{,}045$ at May 2018), the results of which will provide reliable estimates of effect (68, 69).

Levodopa (as single-drug intervention) was the subject of 5 studies in this review, 4 of which were favourable (15, 16, 19, 20, 43). Replenishing depleted striatal dopamine, levodopa stimulates dopamine pathways to increase motor activity (67). Trials administered immediate-release levodopa preparations just prior to motor retraining, in order to favourably exploit levodopa's short duration of action, theoretically priming the brain and maximizing remodulation of neural pathways with minimal side-effects or potential dose tolerance (67). Timing of dose administration relative to physical rehabilitation is an important consideration. Current trials provide insufficient evidence to guide these decisions. Nevertheless, further exploration of levodopa as an RPD appears worthwhile.

Safety measurement was inconsistent. When assessed, mortality and AE were predominantly not different to placebo. Assessment of safety may have been overlooked, in part, due to dosages tested being consistent with dosages used for other indications, with previously established safety profiles. Implementation of standardized guidelines for measurement of safety e.g. International Council for Harmonisation Harmonised Tripartite Guideline S7a – Safety Pharmacology Studies For Human Pharmaceuticals, would improve trial rigour and increase potential for meta-analyses in future (70).

This review demonstrates the challenge of comprehensively and easily identifying all RPD studies, even with a robust systematic approach. While 1,548 articles were identified for screening from the comprehensive database search, yielding 29 studies for inclusion in this review, a further 3,231 citations were identified from the references and forward citations of these included studies. This probably highlights the inconsistent categorization of RPD studies within research databases, which relies on several variables, including limitations of current non-specific MeSH and key terms to adequately tag publications, and the personal preferences and perspectives of the submitting authors when ascribing MeSH and key terms to their submissions (71). If RPD research is to continue to gain momentum as an important field of study, developing a dedicated MeSH term, such as "recovery-promoting drug", is worth consideration.

Personalization of RPD intervention for stroke survivors based on individual recovery needs, medical profile, personal preferences and character traits is an exciting prospect. With several RPDs demonstrating potential efficacy, how and for whom they are prescribed requires careful consideration. Coupling a more detailed understanding of RPD pharmacology and biological processes responsible for motor recovery may aid the development of a more ordered classification system for RPDs based on their biological targets.

Differing mechanisms of action and varied indications for use of the drugs in this review offer future possibilities of combining RPDs to exploit synergistic effects. Pilot testing of combination therapy would be necessary to establish safety. Based on this review, combined daily dosing of an SSRI, i.e. fluoxetine, and levodopa, administered 60–90 min prior to a clinician-led rehabilitation regimen of evidence-based adjuvant physical therapy, has potential to maximize therapeutic value by capitalizing on different mechanisms of action. The results of the fluoxetine mega-trials are awaited with interest.

In conclusion, RPDs are an important area for future study. Greater collaboration between pre-clinical and clinical recovery scientists would increase the rate of translation in this field (72). Development of reporting standards for current trials and adherence to recommendations from the stroke recovery research community would significantly improve trial quality (65). Increased methodological rigor is imperative to allow comparison between recovery promoting drugs in future, and will be achieved through stricter adherence to the Template for Intervention Description and Replication (TIDieR) checklist and Consolidated Standards of Reporting Trials (CONSORT) statement, to adequately describe adjuvant rehabilitation interventions and parallel group randomized trials, respectively (73, 74). Considered attention to the limitations of past RPD research may ultimately lead to discoveries with the potential to impact the global disability burden of stroke.

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