

Table 1. 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 OJM - specified)	Safety outcome measures (SOM): Serious adverse events, death
			$p < 0.05$	$p > 0.05$
CNS stimulant (75) amphetamine	47 (48)	Crisostomo et al (1988) (26) Sonde et al (2001) (27)	Fugl-Meyer Assessment (UL+LL)	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
methylphenidate	106 (129)	Walker-Batson et al (1995) (42) Grade et al (1998) (63)	Fugl-Meyer Assessment 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)		Lokk et al (2011) (29)^b	Finger tapping test	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

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			$p < 0.05$	SOM measured (*primary) No safety observed data
Erythropoietin agonists (75)	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 chorionadotropin alfa/ erythropoietin	89 (96)	Cramer et al (2014) (61)	-	Δ National Institute of Health Stroke Scale % modified Rankin Scale s2 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 ✓*
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) hydroergine	21 (39)	Bochner et al (1973) (49)	-	Limb strength Handgrip strength # handgrip in 30sec 1.2-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 %TMS-evoked thumb movement in Training Target Zone	Rivermead Assessment Scale Transcranial magnetic stimulation ✓
		Floel et al (2005) (16)		Motor Threshold (agonist) Motor Threshold (antagonist) Motor Evoked Potential (agonist) Motor Evoked Potential (antagonist) Fugl-Meyer Assessment Barthel Index ✓
		Lokk et al (2011) (29) ^b	-	National Institute of Health Stroke Scale Barthel Index ✓
		Restemeyer et al (2007) (19)	-	Nine-Hole Peg Test Action Research Arm Test Transcranial magnetic stimulation Reaction times to random elements ✓
		Rosser et al (2008) (20)	Δ in reaction times Number of errors	✓
		Scheidtmann et al (2001) (43)	Rivermead Assessment Scale	✓

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Pharmacological intervention	Sample size: Analysed (recruited)	Author	Efficacy outcome measures (Primary OM – specified)	Safety outcome measures (SOM): Serious adverse events, death
Irreversible MAO-B inhibitor (75)	59 (71)	Bartolo et al (2015) (47)	$p < 0.05$	SOM measured (*primary) ✓ No safety observed data
selegiline			National Institute of Health Stroke Scale Functional Independence Measure Barthel Index Fugl-Meyer Assessment	✓
Methylxanthine drug (21)	18 (20)	Schambra et al (2016) (21)	Scandinavian Stroke Scale	✓
theophylline			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)	66 (80)	Mohammadianinejad et al (2014) (53)	$\uparrow \geq 25\%$ Fugl-Meyer Assessment	Δ modified National Institute of Health Stroke Scale Δ Fugl-Meyer Assessment – hand assessment
lithium carbonate				✓
Neuropeptide, porcine brain extract (67)	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
Cerebrolysin®				✓
		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) + Δ National Institute of Health Stroke Scale

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		Lang et al (2013) (35)	$p < 0.05$	SOM measured (*primary) ✓ No safety observed data
		Muresanu et al (2016) (36)	<ul style="list-style-type: none"> Δ National Institute of Health Stroke Scale Δ Barthel Index Δ modified Rankin Scale Δ Short Form 36 Items Health Survey - physical component 	<ul style="list-style-type: none"> modified Rankin Scale Δ National Institute of Health Stroke Scale Barthel Index Δ gait velocity Δ Nine-Hole Peg Test
Noradrenaline reuptake inhibitor (75)	10 (10)	Zittel et al (2007) (23)	Handgrip force	Nine-Hole Peg Test ✓
reboxetine	74 (83)	Li et al (2004) (52)	Finger tapping test (# taps)	Motor evoked potential (TMS)
Peripheral chemoreceptor agonist + alkaloid/ vasodilator (67)	9 (12)	Ward et al (2017) (58)	Barthel Index	✓
almitrine bismesylate + raubasine	9 (12)	Ward et al (2017) (58)	Neurological Functional Deficit Score	✓
Selective norepinephrine reuptake inhibitor (75)	28 (28)	Adler et al (2009b) (60)	-	Fugl-Meyer Assessment Action Research Arm Test Wolf Motor Function Test
atomoxetine	28 (28)	Adler et al (2009b) (60)	-	Fugl-Meyer Assessment Action Research Arm Test Wolf Motor Function Test
Selective serotonin reuptake inhibitor (75)	10 (11)	Zittel et al (2008) (24)	National Institute of Health Stroke Scale	Barthel Index ✓
citalopram	10 (11)	Gourab et al (2015) (17)	<ul style="list-style-type: none"> Motor threshold - unaffected hemisphere (TMS) Intracortical Inhibition - unaffected hemisphere (TMS) 	<ul style="list-style-type: none"> 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)
escitalopram	10 (11)	Zittel et al (2008) (24)	Nine-Hole Peg Test	Handgrip strength ✓
	10 (11)	Gourab et al (2015) (17)	<ul style="list-style-type: none"> Velocity-dependent plantarflexion stretch reflexes - under passive conditions, at 90°/sec 	<ul style="list-style-type: none"> Maximal ankle isometric strength Maximal knee isometric strength Velocity-dependent plantarflexion stretch reflexes: <ul style="list-style-type: none"> - under passive conditions, at: <ul style="list-style-type: none"> 30°/sec, 60°/sec; 120°/sec - during superimposed maximal volitional drive, at: <ul style="list-style-type: none"> 30°/sec, 60°/sec; 90°/sec; 120°/sec - after after superimposed maximal volitional drive, at: <ul style="list-style-type: none"> 30°/sec, 60°/sec; 90°/sec; 120°/sec Fugl-Meyer Assessment – LL 6-minute Walk Test 10-metre Walk Test

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fluoxetine	228 (261)	Chollet et al (2011) (45)	$p < 0.05$ Fugl-Meyer Assessment (FMA) – total FMA – UL FMA – LL National Institute of Health Stroke Scale (motor scores) modified Rankin Scale	$p > 0.05$ 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)	57 (60)	Urfer et al (2014) (31) ^b	-	Δ National Institute of Health Stroke Scale modified Rankin Scale Barthel Index 10-metre Walk Test
cutamesine	20 (20)	Cherry et al (2014) (25)	-	Stability platform task Simulated feeding trial Untrained balance task
Suspected partial NMDA agonist (25)	20 (20)			
d-cycloserine	20 (20)			
Traditional Chinese medicine (44, 48, 59)	87 (100)	Yu et al (2015) (59)	Fugl-Meyer Assessment Barthel Index	-
Di-Huang-Yin-Zi (DHYZ)	87 (100)			
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
		Venketasubramanian et al (2015) (57)	-	National Institute of Health Stroke Scale modified Rankin Scale modified Rankin Scale ≤ 1 Barthel Index ≥ 95
Tetracyclic antidepressant (67)	46 (52)	Dam et al (1996) (28) ^b	-	Hemiplegic Stroke Scale Barthel Index
maprotiline	46 (52)			
Tricyclic antidepressant (67)	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