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Pharmacological interventions for unilateral spatial neglect after stroke.
Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD010882.
DOI: [10.1002/14651858.CD010882.pub2](https://doi.org/10.1002/14651858.CD010882.pub2).

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[Intervention Review]

Pharmacological interventions for unilateral spatial neglect after stroke

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Editorial group: Cochrane Stroke Group.

Publication status and date: New, published in Issue 11, 2015.

Citation: Luvizutto GJ, Bazan R, Braga GP, Resende LADL, Bazan SGZ, El Dib R. Pharmacological interventions for unilateral spatial neglect after stroke. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD010882. DOI: [10.1002/14651858.CD010882.pub2](https://doi.org/10.1002/14651858.CD010882.pub2).

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ABSTRACT

Background

Unilateral spatial neglect (USN) is characterized by the inability to report or respond to people or objects presented on the side contralateral to the lesioned side of the brain and has been associated with poor functional outcomes and long stays in hospitals and rehabilitation centers. Pharmacological interventions (medical interventions only, use of drugs to improve the health condition), such as dopamine and noradrenergic agonists or pro-cholinergic treatment, have been used in people affected by USN after stroke, and effects of these treatments could provide new insights for health professionals and policy makers.

Objectives

To evaluate the effectiveness and safety of pharmacological interventions for USN after stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (April 2015), the Cochrane Central Register of Controlled Trials (April 2015), MEDLINE (1946 to April 2015), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to April 2015), EMBASE (1980 to April 2015), PsycINFO (1806 to April 2015) and Latin American Caribbean Health Sciences Literature (LILACS) (1982 to April 2015). We also searched trials and research registers, screened reference lists, and contacted study authors and pharmaceutical companies (April 2015).

Selection criteria

We included randomized controlled trials (RCTs) and quasi-randomized controlled trials (quasi-RCTs) of pharmacological interventions for USN after stroke.

Data collection and analysis

Two review authors independently assessed risk of bias in the included studies and extracted data.

Main results

We included in the review two studies with a total of 30 randomly assigned participants. We rated the quality of the evidence as very low as the result of study limitations, small numbers of events, and small sample sizes, with imprecision in the confidence interval (CI). We were not able to perform meta-analysis because of heterogeneity related to the different interventions evaluated between included studies. Very low-quality evidence from one trial (20 participants) comparing effects of rivastigmine plus rehabilitation versus rehabilitation on overall USN at discharge showed the following: Barrage (mean difference (MD) 0.30, 95% confidence interval (CI) -0.18 to 0.78); Letter Cancellation (MD 10.60, 95% CI 2.07 to 19.13); Sentence Reading (MD 0.20, 95% CI -0.69 to 1.09), and the Wundt-Jastrow Area Illusion Test (MD -4.40, 95%

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CI -8.28 to -0.52); no statistical significance was observed for the same outcomes at 30 days' follow-up. In another trial (10 participants), study authors showed statistically significant reduction in omissions in the three cancellation tasks under transdermal nicotine treatment (mean number of omissions 2.93 ± 0.5) compared with both baseline (4.95 ± 0.8) and placebo (5.14 ± 0.9) (main effect of treatment condition: $F(2,23) = 11.06$; P value < 0.0001). One major adverse event occurred in the transdermal nicotine treatment group, and treatment was discontinued in the affected participant. None of the included trials reported data on several of the prespecified outcomes (falls, balance, depression or anxiety, poststroke fatigue, and quality of life).

Authors' conclusions

The quality of the evidence from available RCTs was very low. The effectiveness and safety of pharmacological interventions for USN after stroke are therefore uncertain. Additional large RCTs are needed to evaluate these treatments.

PLAIN LANGUAGE SUMMARY

Using pharmacological medications for unilateral spatial neglect (USN) after stroke

Review question

Which pharmacological intervention (use of any type of medication) is more efficacious and safe for improving the ability of people with stroke to recognize their paralyzed limb after stroke, and what guidance can be provided to clinicians in their clinical practice?

Background

USN (difficulty recognizing the left or right side of the body and space) has been associated with poor independence and long stays in hospitals and rehabilitation centers, all of which predispose people with stroke to the risk of falls and to semi permanent or permanent wheelchair use, which can reduce their quality of life. Furthermore, this condition decreases the ability of people to return to work. Pharmacological medication for USN, such as dopamine and noradrenergic agonists or pro-cholinergic treatment, could have a positive effect in improving independence for people after stroke. This review aims to answer this question.

Study characteristics

Adults over 18 years of age, regardless of gender and ethnicity, with USN after stroke diagnosis measured by clinical examination or radiographically by computed tomography or magnetic resonance imaging, regardless of whether they were evaluated by any paper-and-pencil tests. We considered including people diagnosed with any type of stroke (ie, ischemic or hemorrhagic) from the acute phase (the first 24 to 72 hours) until one year after the stroke.

Key results

We identified two studies involving 30 participants up to April 2015. We are uncertain as to whether comparison of different pharmacological interventions (rivastigmine, transdermal nicotine) showed an important effect on (1) the ability of people to recognize their paralyzed limb, and (2) independence in daily life functions after stroke, because results were imprecise and included studies did not report most of the predefined outcomes (ie, falls, balance, depression or anxiety, poststroke fatigue, and quality of life).

Quality of the evidence

We considered the quality of included studies to be reasonable. Given the small sample size and methodological limitations (participants were assigned in a successive manner in one study), no conclusions can be drawn regarding the effectiveness of pharmacological medications in USN after stroke.

Conclusions and future research

The quality of the evidence obtained from available randomized controlled trials was very low. The effectiveness and safety of pharmacological interventions for USN after stroke are therefore uncertain. Additional large randomized controlled trials are needed to evaluate these treatments.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Pharmacological interventions for unilateral spatial neglect after stroke: rivastigmine + rehabilitation vs rehabilitation

Patient or population: unilateral spatial neglect after stroke

Settings: Italy

Intervention: rivastigmine 1.5 mg twice a day + physiotherapy and cognitive training

Comparison: physiotherapy and cognitive training

Outcomes	Mean difference (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
Overall USN at discharge Barrage; Letter Cancellation; Sentence Reading; Wundt-Jastrow Paolucci 2010 study Follow-up: last day of therapy (discharge)	Barrage 0.30 (-0.18 to 0.78) Letter Cancellation 10.60 (2.07 to 19.13) Sentence Reading 0.20 (-0.69 to 1.09) Wundt-Jastrow -4.40 (-8.28 to -0.52)	20 (1 study) ^{a,b,c,d,e}	⊕⊕⊕⊕ very low
Overall USN at follow-up Barrage; Letter Cancellation; Sentence Reading; Wundt-Jastrow Paolucci 2010 study Follow-up: 30 days after cessation of therapy	Barrage 0.10 (-0.30 to 0.50) Letter Cancellation 5.40 (-4.05 to 14.85) Sentence Reading 0.20 (-0.62 to 1.02) Wundt-Jastrow -3.10 (-6.99 to 0.79)	20 (1 study) ^{a,b,c,d,e}	⊕⊕⊕⊕ very low
Disabilities Rivermead Mobility Index Score Paolucci 2010 study Follow-up: last day of therapy (discharge)	Rivermead Mobility Index Score 0.10 (-2.62 to 2.82)	20 (1 study) ^{a,b,c,d,e}	⊕⊕⊕⊕ very low
Disabilities Rivermead Mobility Index Score Paolucci 2010 study Follow-up: 30 days after cessation of therapy	Rivermead Mobility Index Score 0.40 (-2.16 to 2.96)	20 (1 study) ^{a,b,c,d,e}	⊕⊕⊕⊕ very low
Daily life functions Barthel Index score Paolucci 2010 study Follow-up: last day of therapy (discharge)	Barthel Index score -3.30 (-18.02 to 11.42)	20 (1 study) ^{a,b,c,d,e}	⊕⊕⊕⊕ very low

Daily life functions

Barthel Index score

[Paolucci 2010](#) study

Follow-up: 30 days after cessation of therapy

Barthel Index score -2.10 (-16.06 to 11.86) 20 (1 study)^{a,b,c,d,e}

⊕⊕⊕⊕
very low

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

^aIt was not possible to perform meta-analysis; only 1 study could be represented graphically

^bQuality was downgraded by 1 level because of very serious imprecision (small number of events, small sample size, and wide confidence interval)

^cAlthough the confidence interval was narrow in some of the scales that evaluated the primary outcome, the magnitude of effect was controversial

^dQuality was downgraded by 1 level for uncertainty on both publication bias and heterogeneity, as included studies were insufficient to allow this analysis

^eRisk of bias in all domains was generally classified as low

Summary of findings 2.

Pharmacological interventions for unilateral spatial neglect after stroke: transdermal nicotine (Nicorette) vs placebo or control

Patient or population: unilateral spatial neglect after stroke

Settings: Switzerland

Intervention: pro-cholinergic agent (Nicorette, 10 mg) administered by patch

Comparison: placebo

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Overall USN Shape cancellation, letter cancellation, and Bells' cancellation Lucas 2013 study Follow-up period: days 1, 2, and 4	See comment	See comment	See comment	Outcome described only qualitatively
Disabilities Lucas 2013 study	See comment	See comment	See comment	Outcome not reported
Daily life functions Lucas 2013 study	See comment	See comment	See comment	Outcome not reported

*The basis for the **assumed risk** (eg, median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

BACKGROUND

Various non-pharmacological rehabilitation techniques have been explored for unilateral (restricted to one side of the body) spatial neglect (USN). The aim of these techniques has been to facilitate the recovery of perception and behavior. These techniques have included right half-field eye-patching (Tsang 2009), mirror therapy (Thieme 2013), prism adaptation (Mizuno 2011), left-hand somatosensory stimulation with visual scanning training (Polanowska 2009), contralateral transcutaneous electrical nerve stimulation and optokinetic stimulation (Schröder 2008), trunk rotation (Fong 2007), repetitive transcranial magnetic stimulation (Cazzoli 2012), galvanic vestibular stimulation (Nakamura 2015), and dressing practice (Walker 2011). These studies demonstrated a positive effect on visuospatial neglect after stroke, but their results do not support use of these techniques in isolation for improvement of secondary outcomes such as performance and sensorimotor functions, activities of daily living, or quality of life (Cazzoli 2012; Turton 2010; Thieme 2013).

Most recently, pharmacological interventions, such as use of dopamine or noradrenergic agonists, have been shown to improve perception as measured by the Line Bisection task (Schenkenberg 1980) and the Line Cancellation task (Albert 1973) in people affected by USN, and they seem to represent a promising approach to treatment of patients with this condition (Bartolomeo 2012; Luauté 2006; Malhotra 2006).

Description of the condition

Stroke is the second leading cause of death worldwide and the primary cause of chronic disability in adults (Bonita 1992). In the United States, it is the fourth leading cause of death overall (Jauch 2013). Each year in the UK, 110,000 people suffer a stroke (Bray 2013), and in Asia the incidence is two to three times higher than in Europe (Hata 2013). In Brazil, stroke is the leading cause of death overall (Pontes-Neto 2008). Among people who survive a stroke, USN is the most frequent disorder for right hemisphere lesions (Gorgoraptis 2012). The incidence of USN varies widely from 10% to 82% (Chen 2012; Stone 1993; Vanier 1990).

USN is characterized by the inability to report or respond to people or objects presented on the side contralateral to the lesioned side of the brain, when this symptom cannot be accounted for by motor or sensory deficits (Plummer 2003; Tanaka 2010). Diagnoses are made by paper-and-pen tests, for example, cancellation and bisection tests (Agrell 1997) and, in subacute or chronic stages of neglect, after stroke diagnosis is made on the basis of behavioral measures derived from assessment of functional abilities in everyday life (Azouvi 2003). USN has been associated with poor functional outcomes and long stays in hospitals and rehabilitation centers, all of which predispose patients to the risk of falls and to semi permanent or permanent wheelchair use (Chen 2012; Gottesman 2008; Tanaka 2010), which can reduce their quality of life compared with that of other stroke patients who do not have USN (Harvey 2010). Furthermore, USN decreases a patient's work productivity, which has a socioeconomic impact, thus affecting a community's public health status (Brown 2006; Treger 2007).

Description of the intervention

Pharmacological intervention has been used in people affected by USN after stroke to enhance their performance on neglect tests and

assessment of daily life functions. Some studies aiming to explain the effects of dopamine and noradrenergic agonists, which have been shown to modulate cognitive function, have shown that they most likely act via postsynaptic α_2 receptors in the dorsolateral prefrontal cortex (a region of the brain responsible for working memory) (Malhotra 2006). Dopamine agonists have been shown to improve tests of visuospatial neglect such as line bisection, letter cancellation, and reading (Fleet 1987; Geminiani 1998; Hurford 1998; Mukand 2001), and to act in perceptual attentional systems and premotor components of visuospatial neglect (Mukand 2001). Noradrenergic agonists showed improvement on paper-and-pencil tasks as well as on visual exploration in participants who had a lesion that spared the dorsolateral prefrontal cortex (Malhotra 2006). Other pharmacological approaches for USN after stroke include pro-cholinergic drugs, which also work to modulate the activity of the attention system in the brain (Thiel 2005).

How the intervention might work

Dopamine is a biological amine synthesized in the hypothalamus, the basal ganglia, and many areas of the central and peripheral nervous system. Dopamine and its agonists play an important role in central nervous system regulation through stimulation of α - and β -adrenergic and dopaminergic receptors. Dopaminergic agonists, which cross the blood-brain barrier, have neurological and endocrine central effects and act directly at postsynaptic receptors within the basal ganglia, increasing the availability of dopamine in the synaptic cleft (Velasco 1998). Dopamine-selective D1 agonists are one type of pharmacological intervention that have been used for USN. Dopamine D1 receptors can have an effect on visual areas of attention and could provide a possible mechanism for facilitating spatial attention and working memory (Castner 2000; Funahashi 1994). Noradrenergic agonists have been associated with increased output from the locus coeruleus (a part of the brainstem) to both inferior parietal and frontal lobes of the cortex (the outer covering of the brain) via the thalamus (portion of the diencephalon), which may be involved in USN (Singh-Curry 2011). Cholinergic drugs work to increase levels of acetylcholine and subsequently enhance the function of neural cells; they can modulate activity in the frontoparietal attention system of the brain and working memory tasks (Thiel 2005), and may increase selective attention during spatial exploration (Witte 1997).

Why it is important to do this review

Stroke is a prevalent disease that has high morbidity and mortality worldwide; it is characterized as a serious public health problem. People who develop USN after stroke have major functional disabilities, as well as decreased rates of adherence to rehabilitation programs (Paolucci 2001; Wee 2008). Understanding the effects of a pharmacological intervention, given alone or in combination with non-pharmacological strategies for rehabilitation, could provide new insights for health professionals and policy makers.

OBJECTIVES

To evaluate the effectiveness and safety of pharmacological interventions for unilateral spatial neglect (USN) after stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) and quasi-randomized controlled trials (quasi-RCTs).

Types of participants

Adults over 18 years of age, regardless of gender and ethnicity, with USN after stroke diagnosis measured by clinical examination or radiographically by computed tomography (CT) or magnetic resonance imaging (MRI), regardless of whether they were included after evaluation by a paper-and-pencil test. We included people diagnosed with any type of stroke (ie, ischemic or hemorrhagic) from the acute phase (the first 24 to 72 hours ([Furlan 2012](#))) until one year after the stroke.

Types of interventions

We included trials that compared:

- drug A versus placebo or control;
- drug A + rehabilitation versus rehabilitation; and
- drug A versus drug B (with or without rehabilitation).

We considered any non-pharmacological therapy provided with the aim of improving USN as rehabilitation therapy, such as right half-field eye-patching, mirror therapy, prism adaptation, left-hand somatosensory stimulation, visual scanning training, contralateral transcutaneous electrical nerve stimulation, optokinetic stimulation, trunk rotation, repetitive transcranial magnetic stimulation, galvanic vestibular stimulation, and dressing practice.

Types of outcome measures

Primary outcomes

Test of neglect

- Overall USN measured by any paper-and-pencil tests, such as the Line Cancellation task ([Albert 1973](#)), the Line Bisection test ([Schenkenberg 1980](#)), or the Star Cancellation Test ([Halligan 1992](#)); and by any validated specific instrument, such as the Catherine Bergego Scale ([Azouvi 2003](#)) and the Behavioural Inattention Test ([Wilson 1987](#)).

Secondary outcomes

- Disability in neurological and functional abilities as measured by any validated specific instrument, such as the National Institutes of Health Stroke Scale and the Modified Rankin Scale ([Cincura 2009](#)), the Box and Block Test ([Mathiowetz 1985](#)), or the Fugl-Meyer Assessment ([Sanford 1993](#)) after treatment and over the long term.
- Daily life functions as measured by any validated measurement scale, such as the Barthel Index ([Cincura 2009](#)).
- Number of reported falls as measured by diaries of falls, by the Morse Fall Scale ([Morse 1989](#)), or by the Hendrich II Fall Risk Model ([Hendrich 2003](#)) after treatment and over the long term.
- Balance as measured by the Berg Balance Scale, the balance subscale of the Fugl-Meyer test, and the Postural Assessment

Scale for Stroke Patients ([Mao 2002](#)) after treatment and over the long term.

- Depression or anxiety as measured by the Beck Depression Inventory, the Hospital Anxiety and Depression Scale, Symptom Checklist-90 (SCL-90), and the Hamilton Depression Rating Scale ([Aben 2002](#)) after treatment and over the long term.
- Evaluation of poststroke fatigue by the Fatigue Severity Scale ([Lerdal 2011](#)) after treatment and over the long term.
- Quality of life (however defined by the study authors) after treatment and over the long term.
- Adverse events (eg, euphoria, hallucinations, orthostatic hypotension, nausea, insomnia, dizziness, syncope) after treatment and over the long term.
- Death.

Search methods for identification of studies

See the "Specialized register" section of the [Cochrane Stroke Group](#) module. We searched for trials in all languages and when possible arranged for translation of relevant articles.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (April 2015) and the following electronic databases and trials registers.

- Cochrane Central Register of Controlled Trials (CENTRAL) (2015, April issue) ([Appendix 1](#)).
- MEDLINE (Ovid) (1948 to April 2015) ([Appendix 2](#)).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (Ebsco) (1982 to April 2015) ([Appendix 3](#)).
- EMBASE (Ovid) (1980 to April 2015) ([Appendix 4](#)).
- PsycINFO (Ovid) (1806 to April 2015) ([Appendix 5](#)).
- Latin American and Caribbean Health Sciences Literature (LILACS) (1982 to April 2015) ([Appendix 6](#)).
- ClinicalTrials.gov (April 2015) (www.clinicaltrials.gov/).
- Stroke Trials Registry (April 2015) (www.strokecenter.org/trials/).
- International Standardized Randomized Controlled Trial Number (ISRCTN) Registry (June 2015) (<http://www.isrctn.com/>).
- European Union (EU) Clinical Trials Register (June 2015) (www.clinicaltrialsregister.eu).
- World Health Organization (WHO) International Clinical Trials Registry Platform (June 2015) (<http://www.who.int/ictpr/en/>).
- Australian-New Zealand Clinical Trials Registry (June 2015) (www.anzctr.org.au/).

We developed search strategies for CENTRAL, MEDLINE, CINAHL, EMBASE and PsycINFO with the help of the Cochrane Stroke Group Trials Search Co-ordinator, and we adapted the MEDLINE strategy for LILACS and the trials registers.

Searching other resources

In an effort to identify additional published, unpublished and ongoing trials, we:

- screened the reference lists of identified studies;

- contacted the following pharmaceutical companies: Aché, Boehringer Ingelheim, Novartis, Sanofi-Aventis, GlaxoWellcome, and Pfizer (July 2015);
- contacted study authors and experts; and
- used Science Citation Index Cited Reference Search for forward tracking of important articles.

Data collection and analysis

Selection of studies

Two review authors (GJL and RB) independently screened titles and abstracts of records obtained through electronic database searches and excluded obviously irrelevant reports. We retrieved full-text articles for the references that remained; two review authors (GJL and RB) independently screened the articles to identify studies for inclusion, and identified and recorded the reasons for exclusion of ineligible studies. We resolved disagreements through discussion, or, if required, we consulted a third person (RED). We collated multiple reports on the same study, so that each study, not each reference, was the unit of interest in the review. We recorded the selection process and completed a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Data extraction and management

Two review authors (GJL and GPB) independently extracted data from the included studies. We resolved discrepancies by discussion and used a standard data extraction form based on the one recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to extract the following information: characteristics of the study (design, methods of randomization); participants; interventions; and outcomes (types of outcome measures, adverse events). We contacted the authors of the included studies for clarification about missing data, or for further information.

Assessment of risk of bias in included studies

Two review authors (GJL and RB) independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or by consultation with another review author (RED). We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded the risk of bias for each domain as high, low, or unclear and provided information from the study report, together with justification for our judgment, in the "Risk of bias" tables.

Measures of treatment effect

Binary outcomes

For dichotomous data, we planned to use risk ratio (RR) as the effect measure, along with the 95% confidence interval (CI).

Continuous outcomes

For continuous data, we presented the results as mean differences (MDs) with 95% CIs. We planned to use the standardized mean difference (SMD) to combine trials that measured the same outcome but used different measures.

Unit of analysis issues

The unit of analysis was each participant recruited into the trial.

Dealing with missing data

An intention-to-treat analysis (ITT) is one in which all participants in a trial are analyzed according to the intervention to which they were allocated, whether or not they received the intervention. We assumed that participants who dropped out were non-responders. For each trial, we reported whether investigators stated if the analysis was performed according to the ITT principle. If participants were excluded after allocation, we reported in full any details provided. Therefore, we planned to perform the analysis on an ITT basis (Newell 1992) when possible. Otherwise, we planned to adopt the per-protocol analysis.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. We classified heterogeneity by using the following I^2 values.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: shows considerable heterogeneity.

If considerable heterogeneity existed (ie, $> 75\%$), we did not combine the studies but provided a descriptive summary of results.

Assessment of reporting biases

Apart from assessing the risk of selective outcome reporting, considered under the assessment of risk of bias in included studies, we planned to assess the likelihood of potential publication bias by using funnel plots if we identified at least eight trials. If small studies in a meta-analysis appear to show larger treatment effects, we considered other possible causes, including selection bias, poor methodological quality, heterogeneity, artifact, and chance.

Data synthesis

When we considered studies to be sufficiently similar, we conducted a meta-analysis by pooling appropriate data using RevMan 5.3 (RevMan 2014). We used the fixed-effect model to analyze data. In future updates of this review, when we identify substantial heterogeneity (eg, $I^2 > 50\%$), we will compute pooled estimates of the treatment effect for each outcome by using a random-effects model (with two or more studies).

Subgroup analysis and investigation of heterogeneity

We did not perform the subgroup analysis because clinical heterogeneity was excessive ($I^2 > 50\%$), and we used subgroup analysis to pool the results. Subgroup analyses are secondary analyses in which participants are divided into groups according to shared characteristics, and outcome analyses are conducted to determine whether any significant treatment effect occurs in

response to that characteristic. We plan to carry out the following subgroup analyses in a future update of the review.

- Different ages: younger adults (18 years to 65 years) versus older adults (over 65 years).
- Different combinations of pharmacological drugs and rehabilitation, for example, dopamine plus mirror therapy versus noradrenaline versus prism adaptation.
- Different co-morbidities (ie, hypertension, cardiovascular disease, diabetes, smoking, etc - the presence of at least two co-morbidities versus no co-morbidities).

We planned to perform the Chi² test for subgroup differences set at a P value of 0.05.

Sensitivity analysis

As we identified an inadequate number of studies, we did not perform a sensitivity analysis for the primary outcome (ie, disability and test of neglect) to evaluate the effect on results of studies with high risk of bias, nor on data from ITT versus per-protocol analyses.

"Summary of findings" tables

In our review, we used the principles of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes (overall USN, disability, and daily life functions at both discharge and follow-up) and constructed a "Summary of findings" (SoF) table by using GRADE software. The GRADE approach appraises the quality of a body of evidence according to the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Assessment of the quality of a body of evidence considers within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias. The quality of the evidence for a specific outcome was altered by one level according to the performance of studies against these five factors.

- High-quality evidence: Findings are consistent among at least 75% of RCTs with low risk of bias; data are consistent, direct, and precise, and no publication biases are known or suspected. Further research is unlikely to change the estimate or our confidence in the results.
- Moderate-quality evidence: One of the domains is not met. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low-quality evidence: Two of the domains are not met. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low-quality evidence: Three of the domains are not met. We are very uncertain about the results.
- No evidence: We identified no RCTs that addressed this outcome.

RESULTS

Description of studies

See the [Characteristics of included studies](#) table.

Results of the search

We identified a total of 1617 citations through database searches (see [Figure 1](#) for search results). After screening by title and then by abstract, we obtained full-paper copies for 24 citations that were potentially eligible for inclusion in the review. We excluded 22 studies for the reasons described in the [Characteristics of excluded studies](#) table (Buxbaum 2007; Cho 2009; Damulin 2008; Geminiani 1998; Gorgoraptis 2012; Grujic 1998; Kakuda 2011; Kettunen 2012a; Kettunen 2012b; Krivonos 2010; Laihosalo 2011; Lehmann 2001; Losoi 2012; Mukand 2001; Nolte 2009; Pokryszko-Dragan 2008; Sato 2006; Spalletta 2003; Tobinick 2012; Toyoda 2004; Troisi 2002; Xu 2007). The remaining two studies, with a total of 30 participants, met the minimum methodological requirements, and we included them in this review (Lucas 2013; Paolucci 2010). We also found one ongoing study (EudraCT 200400050717).

Figure 1. Study flow diagram.

Included studies

We included two studies with a total of 30 randomly assigned participants ([Lucas 2013](#); [Paolucci 2010](#)).

[Lucas 2013](#) assessed transdermal nicotine compared with placebo in an elderly stroke population with a single focal lesion to the right hemisphere involving the middle cerebral artery and partial or full visual hemifield cuts. The methodological quality of this study revealed high risk of bias for random sequence generation and other bias, and low risk of bias for blinding of participants and personnel, incomplete outcome data, and selective reporting. The outcome used in this study - USN - was measured by shape, letter, and Bells' cancellation, and subsidiary analysis showed no systematic influence of hemifield defects on performance or treatment response. The number of participants per group was uncertain.

[Paolucci 2010](#) evaluated rivastigmine plus rehabilitation versus rehabilitation, also in an elderly population with a single focal lesion to the right hemisphere involving the middle cerebral artery. The overall risk of bias of this study was low, as all domains were adequately performed except allocation concealment, which we classified as having unclear risk of bias. The outcome used in this study - USN - was measured by the Barrage Test, the Letter Cancellation Test, a Sentence Reading Test, and the Wundt-Jastrow Area Illusion Test.

It was possible to present some of the data from [Paolucci 2010](#) graphically (meta-analysis representation), but it was not possible to combine the results of both included studies because of the diversity of the outcomes reported and the interventions used.

Design of the studies

[Lucas 2013](#) was a quasi-randomized trial; [Paolucci 2010](#) was an RCT.

Type of intervention and follow-up

[Lucas 2013](#) allocated participants to a pro-cholinergic agent (Nicorette, 10 mg) administered by patch or placebo (patch). Follow-up occurred four days after the intervention.

[Paolucci 2010](#) randomly assigned participants to physiotherapy, cognitive training and rivastigmine 1.5 mg twice a day versus physiotherapy and cognitive training. Follow-up occurred one month after therapy was completed.

Type of study participants

Participants in [Lucas 2013](#) were right-handed (except one), hemodynamically stable, conscious, and sufficiently co-operative to undergo a testing session of 45 minutes, and showed stable symptoms of neglect. The study excluded current smokers who smoked one or more cigarettes per day, and investigators systematically quantified and registered any past history of smoking.

[Paolucci 2010](#) assessed right-hemisphere stroke. We excluded people with stroke due to hemorrhagic lesions, the presence of sequelae of previous cerebrovascular accidents and/or of other chronic disabling pathologies, and a score under the established cutoff of 22 on the Mini Mental State Examination.

Type of outcomes measures

[Lucas 2013](#) evaluated USN by Shape Cancellation, Letter Cancellation, and Bells' Cancellation, and by brain lesion analysis.

[Paolucci 2010](#) measured USN by Letter Cancellation, Barrage Test, Sentence Reading Test, Wundt-Jastrow Area Illusion Test, and functional evaluation (length of stay in rehabilitation, independence in daily living, mobility status, Barthel Index, Rivermead Mobility Index).

Excluded studies

We excluded 22 studies for the reasons described in the [Characteristics of excluded studies](#) table ([Buxbaum 2007](#); [Cho 2009](#); [Damulin 2008](#); [Geminiani 1998](#); [Gorgoraptis 2012](#); [Grujic 1998](#); [Kakuda 2011](#); [Kettunen 2012a](#); [Kettunen 2012b](#); [Krivonos 2010](#); [Laihosalo 2011](#); [Lehmann 2001](#); [Losoi 2012](#); [Mukand 2001](#); [Nolte 2009](#); [Pokryszko-Dragan 2008](#); [Sato 2006](#); [Spalletta 2003](#); [Tobinick 2012](#); [Toyoda 2004](#); [Troisi 2002](#); [Xu 2007](#)).

Studies awaiting assessment

Five studies are awaiting assessment, as they were published in languages other than English or Portuguese ([Bruckner 1979](#); [Ibadullaev 2004](#); [Itoh 1998](#); [Pilkowska 2002](#); [Zhou 2004](#)).

Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lucas 2013
Paolucci 2010

Allocation

In [Paolucci 2010](#), randomization was performed using an electronically produced randomization list. Therefore, we classified this domain as having low risk of bias. With regard to allocation concealment, [Paolucci 2010](#) did not report this, and so we classified it as unclear.

[Lucas 2013](#) is a quasi-randomized trial, as study authors assigned participants in a successive manner; therefore, we classified it as having high risk of bias for this domain. With regards to allocation concealment, no description regarding allocation concealment was provided, so we ranked the study as having unclear risk of bias.

Blinding

In [Paolucci 2010](#), blinding was provided with regard to outcome assessors and the investigator; therefore, we ranked this study as having low risk of bias. However, with regard to blinding of participants, researchers provided no information, so we ranked this study as having unclear risk of bias.

In [Lucas 2013](#), blinding with regard to participants and personnel was provided; therefore, we ranked this study as having low risk of bias. However, with regard to outcome assessors, investigators provided no information, so we ranked this study as having unclear risk of bias.

Incomplete outcome data

The two studies performed intention-to-treat analysis.

[Paolucci 2010](#) reported no withdrawals or dropouts, so we classified this study as having low risk of bias.

In [Lucas 2013](#), only one participant was lost (10%), so we classified this study as having low risk of bias.

Selective reporting

We noted no evidence of selective reporting in either of the included studies ([Lucas 2013](#); [Paolucci 2010](#)); therefore, we ranked both studies as having low risk of bias for this domain.

Other potential sources of bias

We found no evidence of other biases in [Paolucci 2010](#); therefore, we ranked this study as having low risk of bias for this domain. However, in [Lucas 2013](#), a pharmaceutical company provided the intervention drugs; therefore, we ranked this study as having high risk of bias for this domain. The two studies included in this review did not report the sample size calculation.

Effects of interventions

See: [Summary of findings for the main comparison; Summary of findings 2](#)

See [Summary of findings for the main comparison](#).

Transdermal nicotine treatment (Nicorette) versus placebo or control

[Lucas 2013](#) reported this comparison; however, it was not clear how many participants were evaluated in each group. Therefore, we could provide no additional data.

Overall USN

[Lucas 2013](#) reported on this outcome. The number of omissions (number of targets identified by the participant) in the three cancellation tasks (shape, letter, and Bells' cancellation) showed statistical significance that was reduced under transdermal nicotine treatment (mean number of omissions 2.93 ± 0.5) compared with both baseline (4.95 ± 0.8) and placebo (5.14 ± 0.9) (main effect of treatment condition: $F(2,23) = 11.06$; P value < 0.0001). Investigators did not assess the following outcomes in this trial: disabilities, daily life functions, number of reported falls, balance, depression or anxiety, poststroke fatigue, quality of life, and death.

Adverse events

[Lucas 2013](#) reported on this outcome. Only two participants had a positive score for one item (diarrhea) on the negative symptom checklist. For one participant with a score of 2 on this scale (major symptom), treatment was interrupted, and the participant was not included in the study. The second participant presented a score of 1 (minor symptom) in the first few hours after treatment, but the symptom soon resolved, and the participant continued in the study with no other problems. The two participants were included in the intervention arm of this study.

Rivastigmine + rehabilitation versus rehabilitation

[Paolucci 2010](#) reported on this comparison.

Overall USN

[Paolucci 2010](#) reported on this outcome. A statistically significant difference favored rivastigmine plus rehabilitation regarding outcomes in the subcategory of letter cancellation (left side) at discharge (MD 10.60, 95% CI 2.07 to 19.13) and effectiveness of letter cancellation at discharge (MD 29.62, 95% CI 10.87 to 48.37). However, researchers reported no statistically significant differences between treatment groups regarding outcomes in the subcategories of barrage (left side) at discharge (MD 0.30, 95% CI -0.18 to 0.78), effectiveness of barrage at discharge (MD 11.46, 95% CI -27.29 to 50.21), sentence reading at discharge (MD 0.20, 95% CI -0.69 to 1.09), and effectiveness of sentence reading at discharge (MD -20.30, 95% CI -56.67 to 16.07). A statistically significant difference favored rehabilitation (control) in terms of outcomes in the subcategories of Wundt-Jastrow (left side) at discharge (MD -4.40, 95% CI -8.28 to -0.52) and effectiveness of Wundt-Jastrow at discharge (MD -25.98, 95% CI -47.78 to -4.18) ([Analysis 1.1](#)).

Investigators reported no statistically significant differences between treatment groups regarding outcomes at follow-up in the subcategories of barrage (left side) (MD 0.10, 95% CI -0.30 to 0.50), letter cancellation (left side) (MD 5.40, 95% CI -4.05 to 14.85), sentence reading (MD 0.20, 95% CI -0.62 to 1.02), and Wundt-Jastrow (MD -3.10, 95% CI -6.99 to 0.79) ([Analysis 1.2](#)).

Disabilities

In terms of this outcome, [Paolucci 2010](#) reported no statistically significant differences between rivastigmine plus rehabilitation and rehabilitation alone regarding disability in both of the subcategories Rivermead Mobility Index Score at discharge (MD 0.10, 95% CI -2.62 to 2.82) and Rivermead Mobility Index Score at follow-up (MD 0.40, 95% CI -2.16 to 2.96) ([Analysis 1.3](#)).

Daily life functions

[Paolucci 2010](#) reported on this outcome and described no statistically significant differences between rivastigmine plus rehabilitation and rehabilitation in terms of daily life functions in both subcategories of Barthel Index Score at discharge (MD -3.3, 95% CI -18.02 to 11.42) and Barthel Index Score at follow-up (MD -2.10, 95% CI -16.06 to 11.86) ([Analysis 1.4](#)).

Investigators did not assess the following outcomes in this trial: number of reported falls, balance, depression or anxiety, poststroke fatigue, quality of life, death, and adverse events.

DISCUSSION

Summary of main results

This systematic review offers up-to-date but limited evidence supported by only two randomized controlled trials on the effectiveness and safety of pharmacological interventions for unilateral spatial neglect (USN) after stroke ([Lucas 2013](#); [Paolucci 2010](#)).

We presented the results of overall USN from [Paolucci 2010](#) in a forest plot, which showed a statistically significant difference between the intervention and rehabilitation alone in the Letter Cancellation Test at discharge. The study also showed a non-significant difference between the intervention and rehabilitation alone on the Barrage Test and on a Sentence Reading Test. The Wundt-Jastrow Area Illusion Test showed a statistically significant difference favoring rehabilitation (control).

Several pharmacological approaches have been explored to determine whether some drugs, such as acetylcholinesterase inhibitors (AChEIs), might be useful in promoting recovery from USN. AChEIs have been used in treating patients with mild to moderate Alzheimer's disease ([Birks 2009](#)). They may help improve rehabilitation outcomes by enhancing cognitive functioning and reducing apathy, thereby increasing participation and enhancing the ability to learn during rehabilitation ([Paolucci 2010](#)). In [Paolucci 2010](#), AChEIs were responsible for enhancing performance in only one test of neglect, but improvement in some USN measures was not replicated in functional outcome measures in either group. The effectiveness of rehabilitation strategies for reducing the disabling effects of neglect and increasing independence remains unproven.

The pro-cholinergic treatment was reasonably well tolerated in this setting and was associated with significantly reduced neglect in visual tasks, which tended to be more pronounced in people with severe neglect and to persist in chronic stages ([Lucas 2013](#)). Effects of pro-cholinergic treatment of USN after stroke by a single administration of transdermal nicotine induced consistent improvement in target detection and exploration behavior on visual tasks and would be mediated by increased nicotine activity in cortical arousal and facilitated processing of task-relevant information. However, nicotine activity may increase sustained attention or the general motivation factor ([Knott 1999](#); [Lucas 2013](#)). Neuroimaging studies after pro-cholinergic treatment have demonstrated consistent modulation of parietal and frontal activity and activation in attention-related networks into more posterior parietal regions, which are the main regions involved in USN after stroke ([Ernst 2001](#); [Thiel 2005](#); [Vossel 2008](#)). Results of the studies included in this review demonstrate improvement at the USN level

but show no impact on functional abilities nor on the capacity of individuals for daily life functions.

[Lucas 2013](#) reported improved performance on USN tests among participants receiving transdermal nicotine treatment, and investigators concluded that this intervention may be one rehabilitation approach that can be used to improve patient care over the long term, while enhancing functionality. In [Paolucci 2010](#), a statistically significant difference favoring rivastigmine plus rehabilitation was observed with one of the USN tests applied at discharge, but not at follow-up. Results of this study show improved performance on USN tests in the initial phase of treatment (rivastigmine plus rehabilitation). The same results were found over the long term, showing that improvements in spatial performance were not fixed by the participant.

Overall completeness and applicability of evidence

In the two included studies, patient groups, interventions, and relevant outcomes have been addressed to prove the effectiveness of drug therapy, but the authors of this review propose use of a specific instrument, such as the Catherine Bergego Scale ([Azouvi 2003](#)) or the Behavioural Inattention Test ([Wilson 1987](#)), to clarify the effects of unilateral spatial neglect on disabilities. None of the included trials reported data on several of the prespecified outcomes (falls, balance, depression or anxiety, poststroke fatigue and quality of life).

Quality of the evidence

We included only two studies in this review; the overall sample size of these studies was very small, although most of the domains assessed were classified as showing low risk of bias regarding methodological quality. This would be reflected in any conclusions drawn from this review. Quality of the evidence for outcomes assessed in the two trials was very low; we downgraded quality from high to very low because of the presence of a serious risk of selection bias and imprecision (due to few events and small sample sizes). The magnitude of effect in [Paolucci 2010](#) favored the control group in one outcome (Wundt-Jastrow Area Illusion Test), and favored the intervention group in another outcome (letter cancellation test) ([Analysis 1.1](#)). We could not assess publication bias and could not investigate heterogeneity, as included studies were insufficient to allow these analyses.

The methodological quality of the two studies was reasonable, even though risk of selection bias was substantial (participants were assigned in a successive manner) and potential conflicts of interest were revealed (support from the pharmaceutical company Pfizer) in [Lucas 2013](#).

Potential biases in the review process

We developed a comprehensive search strategy; we handsearched the reference lists of identified studies for additional citations and contacted experts in the field. Therefore, we are confident that we have identified most clinical trials conducted to compare pharmacological interventions for USN after stroke.

Agreements and disagreements with other studies or reviews

The study conducted by [Gorgoraptis 2012](#) was not included in our review because it is not a properly randomized study,

all participants received the intervention and control in the same order, and the sequences are too similar. Study authors used rotigotine transdermal patches (dopamine agonist) in 16 participants with hemispatial neglect following right-hemisphere stroke. People were excluded if they presented with a pre-existing neurological condition (eg, dementia, Parkinson's disease, multiple sclerosis); an acute concomitant illness (eg, infection, unstable angina, myocardial infarction, or heart, respiratory, renal, or liver failure); systolic blood pressure < 120 mmHg and/or diastolic < 70 mmHg; exposure to any other investigational drug within 30 days of enrollment in the study; presence of clinically significant drug or alcohol abuse within the previous six months; pregnancy; and breast-feeding. Results of this study showed that treatment with rotigotine was associated with a significant increase in the number of targets identified on the left side (12.8% increase in the number of targets found on the left side). No serious adverse events were noted during treatment with rotigotine. Mild adverse effects included fatigue, mild skin irritation at the site of the patch, and gastrointestinal disturbance, including nausea, vomiting, and diarrhea, which are known potential side effects of rotigotine. The study author concluded that rotigotine was reasonably well tolerated in this setting and was associated with significant improvement in one visual search task, but this trial was limited by the design and by the small sample size. This study shows agreement with findings of the studies included in our review, in that use of dopamine agonists reduced USN after stroke and improved spatial perception during early stages of treatment, but investigators did not present long-term results.

In a systematic review of non-pharmacological interventions based on a cognitive approach (Bowen 2013), review authors concluded that evidence was still insufficient to show the effects of cognitive rehabilitation interventions on functional ability in

daily life function and on standardized neglect assessments. As the effectiveness of cognitive rehabilitation for reducing disabling effects of neglect and increasing independence remains unproven, no rehabilitation approach can be supported or refuted by current randomized controlled trials. Therefore, Bowen 2013 agrees with the data presented in our review that show no favorable effects of pharmacological interventions for improving disabilities and daily life functions.

AUTHORS' CONCLUSIONS

Implications for practice

The quality of the evidence from available randomized controlled trials was very low; therefore, we can draw no definitive conclusions on the effectiveness and safety of pharmacological interventions for unilateral spatial neglect after stroke. The applicability of these findings might be compromised, as most of the results described in this review were obtained from trials with very small sample sizes.

Implications for research

This review underlines the need to conduct well-designed trials in this field. Future trials must be adequately powered and should include standardized outcome measures, such as overall USN and disability and functional abilities measured by both validated and non-validated instruments, daily life function, quality of life, and death.

ACKNOWLEDGEMENTS

We would like to thank Hazel Fraser and Brenda Thomas for help provided during preparation of this review.

REFERENCES

References to studies included in this review

Lucas 2013 {published data only}

Lucas N, Saj A, Schwartz S, Ptak R, Thomas C, Conne P, et al. Effects of pro-cholinergic treatment in patients suffering from spatial neglect. *Frontiers in Human Neuroscience* 2013;**12**(7):574.

Paolucci 2010 {published data only}

Paolucci S, Bureca I, Multari M, Nocentini U, Matano A. An open-label pilot study of the use of rivastigmine to promote functional recovery in patients with unilateral spatial neglect due to first ischemic stroke. *Functional Neurology* 2010;**25**(4):195-200.

References to studies excluded from this review

Buxbaum 2007 {published data only}

Buxbaum LJ, Ferraro M, Whyte J, Gershkoff A, Coslett HB. Amantadine treatment of hemispatial neglect: a double-blind, placebo-controlled study. *American Journal of Physical Medicine and Rehabilitation* 2007;**86**(7):527-37.

Cho 2009 {published data only}

Cho HJ, Kim YJ. Efficacy and safety of oral citicoline in acute ischemic stroke: drug surveillance study in 4,191 cases. *Methods and Findings in Experimental and Clinical Pharmacology* 2009;**31**(3):171-6.

Damulin 2008 {published data only}

Damulin IV, Koberskaya NN, Mkhitarayan EA. Effects of cerebrolisin on moderate cognitive impairments in cerebral vascular insufficiency (a clinical-electrophysiological study). *Neuroscience and Behavioral Physiology* 2008;**38**(6):639-45.

Geminiani 1998 {published data only}

Geminiani G, Bottini G, Sterzi R. Dopaminergic stimulation in unilateral neglect. *Journal of Neurology, Neurosurgery, and Psychiatry* 1998;**65**(3):344-7.

Gorgoraptis 2012 {published data only}

Gorgoraptis N, Mah YH, Machner B, Singh-Curry V, Malhotra P, Hadji-Michael M, et al. The effects of the dopamine agonist rotigotine on hemispatial neglect following stroke. *Brain* 2012;**135**:2478-91.

Grujic 1998 {published data only}

Grujic Z, Mapstone M, Gitelman DR, Johnson N, Weintraub S, Hays A, et al. Dopamine agonists reorient visual exploration away from the neglected hemispace. *Neurology* 1998;**51**(5):1395-8.

Kakuda 2011 {published data only}

Kakuda W, Abo M, Kobayashi K, Momosaki R, Yokoi A, Fukuda A, et al. Combination treatment of low-frequency rTMS and occupational therapy with levodopa administration: an intensive neurorehabilitative approach for upper limb hemiparesis after stroke. *International Journal of Neuroscience* 2011;**121**(7):373-8.

Kettunen 2012a {published data only}

Kettunen JE, Laihosalo M, Ollikainen J, Dastidar P, Nurmi L, Koivisto AM, et al. Rightward bias in right hemisphere infarct patients with or without thrombolytic treatment and in healthy controls. *Neurocase* 2012;**18**(5):359-65.

Kettunen 2012b {published data only}

Kettunen JE, Nurmi M, Koivisto AM, Dastidar P, Jehkonen M. The presence of visual neglect after thrombolytic treatment in patients with right hemisphere stroke. *Scientific World Journal* 2012;**2012**:434120.

Krivosos 2010 {published data only}

Krivosos OV, Amosova NA, Smolentseva IG. Use of the glutamate NMDA receptor antagonist PK-Merz in acute stroke. *Neuroscience and Behavioral Physiology* 2010;**40**(5):529-32.

Laihosalo 2011 {published data only}

Laihosalo M, Kettunen JE, Koivisto AM, Dastidar P, Ollikainen J, Jehkonen M. Thrombolytic therapy and visuoperceptual functions in right hemisphere infarct patients. *Journal of Neurology* 2011;**258**(6):1021-5.

Lehmann 2001 {published data only}

Lehmann V, Hildebrandt H, Olthaus O, Sachsenheimer W. Drug influence on visuospatial attention deficit in patients with right hemisphere media infarction. *Aktuelle Neurologie* 2001;**28**:176-81.

Losoi 2012 {published data only}

Losoi H, Kettunen JE, Laihosalo M, Ruuskanen EI, Dastidar P, Koivisto AM, et al. Predictors of functional outcome after right hemisphere stroke in patients with or without thrombolytic treatment. *Neurocase* 2012;**18**(5):377-85.

Mukand 2001 {published data only}

Mukand JA, Guilmette TJ, Allen DG, Brown LK, Brown SL, Tober KL, et al. Dopaminergic therapy with carbidopa L-dopa for left neglect after stroke: a case series. *Archives of Physical Medicine and Rehabilitation* 2001;**82**(9):1279-82.

Nolte 2009 {published data only}

Nolte CH, Jungehulsing GJ, Rosnagel K, Roll S, Haeusler KG, Reich A, et al. Vascular risk factor awareness before and pharmacological treatment before and after stroke and TIA. *European Journal of Neurology* 2009;**16**(6):678-83.

Pokryszko-Dragan 2008 {published data only}

Pokryszko-Dragan A, Slotwinski K, Budrewicz SP, Podemski R, Zagrajek M, Bilinska M. Attention level and event-related evoked potentials in patients with cerebrovascular disease treated with amantadine sulfate - a pilot study. *Advances in Clinical and Experimental Medicine* 2008;**17**(5):553-8.

Sato 2006 {published data only}

Sato S, Yamakawa Y, Terashima Y, Ohta H, Asada T. Efficacy of milnacipran on cognitive dysfunction with post-stroke depression: preliminary open-label study. *Psychiatry and Clinical Neurosciences* 2006;**60**(5):584-9.

Spalletta 2003 {published data only}

Spalletta G, Guida G, Caltagirone C. Is left stroke a risk-factor for selective serotonin reuptake inhibitor antidepressant treatment resistance?. *Journal of Neurology* 2003;**250**(4):449-55.

Tobinick 2012 {published data only}

Tobinick E, Kim NM, Reyzin G, Rodriguez-Romanacce H, Depuy V. Selective TNF inhibition for chronic stroke and traumatic brain injury: an observational study involving 629 consecutive patients treated with perispinal etanercept. *CNS Drugs* 2012;**26**(12):1051-70.

Toyoda 2004 {published data only}

Toyoda K, Fujii K, Kamouchi M, Nakane H, Arihiro S, Okada Y, et al. Free radical scavenger, edaravone, in stroke with internal carotid artery occlusion. *Journal of the Neurological Sciences* 2004;**221**(1-2):11-7.

Troisi 2002 {published data only}

Troisi E, Paolucci S, Silvestrini M, Matteis M, Vernieri F, Grasso MG, et al. Prognostic factors in stroke rehabilitation: the possible role of pharmacological treatment. *Acta Neurologica Scandinavica* 2002;**105**(2):100-6.

Xu 2007 {published data only}

Xu J. Effect of post-stroke sensory disorders on the recovery processes of motor function and activity of daily living: a non-randomized synchronical controlled trial. *Neural Regeneration Research* 2007;**2**(12):744-6.

References to ongoing studies
EudraCT 200400050717 {published data only}

Effectiveness of rivastigmine treatment in post-stroke patients with right brain damage and unilateral spatial neglect. www.clinicaltrialsregister.eu/ctr-search/trial/2004-000507-17/IT (accessed June 2015).

Additional references
Aben 2002

Aben I, Verhey F, Lousberg R, Lodder J, Honig A. Validity of the Beck Depression Inventory, Hospital Anxiety and Depression Scale, SCL-90, and Hamilton Depression Rating Scale as screening instruments for depression in stroke patients. *Psychosomatics* 2002;**43**:386-93.

Agrell 1997

Agrell BM, Dehlin OI, Dahlgren CJ. Neglect in elderly stroke patients: a comparison of five tests. *Psychiatry and Clinical Neurosciences* 1997;**51**:295-300.

Albert 1973

Albert ML. A simple test of visual neglect. *Neurology* 1973;**23**:658-64.

Azouvi 2003

Azouvi P, Olivier S, de Montety G, Samuel C, Louis-Dreyfus A, Tesio L. Behavioral assessment of unilateral neglect: study of

the psychometric properties of the Catherine Bergego Scale. *Archives of Physical Medicine and Rehabilitation* 2003;**84**:51-7.

Bartolomeo 2012

Bartolomeo P, Thiebaut de Schotten M, Chica AB. Brain networks of visuospatial attention and their disruption in visual neglect. *Frontiers in Human Neuroscience* 2012;**6**:110.

Birks 2009

Birks J, Grimley Evans J, Iakovidou V, Tsolaki M, Holt FE. Rivastigmine for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: [10.1002/14651858.CD001191](https://doi.org/10.1002/14651858.CD001191)]

Bonita 1992

Bonita R. Epidemiology of stroke. *Lancet* 1992;**339**:342-4.

Bowen 2013

Bowen A, Hazelton C, Pollock A, Lincoln NB. Cognitive rehabilitation for spatial neglect following stroke. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: [10.1002/14651858.CD003586.pub3](https://doi.org/10.1002/14651858.CD003586.pub3)]

Bray 2013

Bray BD, Ayis S, Campbell J, Hoffman A, Roughton M, Tyrrell PJ, et al. Associations between the organisation of stroke services, process of care, and mortality in England: prospective cohort study. *BMJ* 2013;**346**:1-12.

Brown 2006

Brown DL, Boden-Albala B, Langa KM, Lisabeth LD, Fair M, Smith MA, et al. Projected costs of ischemic stroke in the United States. *Neurology* 2006;**67**:1390-5.

Castner 2000

Castner SA, Williams GV, Goldman-Rakic PS. Reversal of antipsychotic induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science* 2000;**287**:2020-2.

Cazzoli 2012

Cazzoli D, Müri RM, Schumacher R, von Arx S, Chaves S, Gutbrod K, et al. Theta burst stimulation reduces disability during the activities of daily living in spatial neglect. *Brain* 2012;**135**:3426-39.

Chen 2012

Chen P, Hreha K, Fortis P, Goedert KM, Barrett AM. Functional assessment of spatial neglect: a review of the Catherine Bergego Scale and an introduction of the Kessler Foundation Neglect Assessment Process. *Topics in Stroke Rehabilitation* 2012;**19**:423-35.

Cincura 2009

Cincura C, Pontes-Neto OM, Neville IS, Mendes HF, Menezes DF, Mariano DC, et al. Validation of the National Institutes of Health Stroke Scale, modified Rankin Scale and Barthel Index in Brazil: the role of cultural adaptation and structured interviewing. *Cerebrovascular Diseases* 2009;**27**:119-22.

Ernst 2001

Ernst M, Heishman SJ, Spurgeon L, London ED. Smoking history and nicotine effects on cognitive performance. *Neuropsychopharmacology* 2001;**25**:313-9.

Fleet 1987

Fleet WS, Valenstein E, Watson RT, Heilman KM. Dopamine agonist therapy for neglect in humans. *Neurology* 1987;**37**:1765-70.

Fong 2007

Fong KN, Chan MK, Ng PP, Tsang MH, Chow KK, Lau CW, et al. The effect of voluntary trunk rotation and half-field eye-patching for patients with unilateral neglect in stroke: a randomized controlled trial. *Clinical Rehabilitation* 2007;**21**:729-41.

Funahashi 1994

Funahashi S, Kubota K. Working memory and prefrontal cortex. *Neuroscience Research* 1994;**21**:1-11.

Furlan 2012

Furlan AJ. Challenges in acute ischemic stroke clinical trials. *Current Cardiology Reports* 2012;**14**:761-6.

Gottesman 2008

Gottesman RF, Kleinman JT, Davis C, Heidler-Gary J, Newhart M, Kannan V, et al. Unilateral neglect is more severe and common in older patients with right hemispheric stroke. *Neurology* 2008;**71**:1439-44.

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians. *BMJ* 2008;**336**:995-8.

Halligan 1992

Halligan PW, Burn JP, Marshall JC, Wade DT. Visuo-spatial neglect: qualitative differences and laterality of cerebral lesion. *Journal of Neurology, Neurosurgery, and Psychiatry* 1992;**55**:1060-8.

Harvey 2010

Harvey M, Muir K, Reeves I, Duncan G, Birschel P, Roberts M, et al. Long term improvements in activities of daily living in patients with hemispatial neglect. *Behavioural Neurology* 2010;**23**:237-9.

Hata 2013

Hata J, Kiyohara Y. Epidemiology of stroke and coronary artery disease in Asia. *Circulation Journal* 2013;**77**:1923-32.

Hendrich 2003

Hendrich AL, Bender PS, Nyhuis A. Validation of the Hendrich II Fall Risk Model: a large concurrent case/control study of hospitalized patients. *Applied Nursing Research* 2003;**16**:9-21.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated

March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Hurford 1998

Hurford P, Stringer AY, Jann B. Neuropharmacologic treatment of hemineglect: a case report comparing bromocriptine and methylphenidate. *Archives of Physical Medicine and Rehabilitation* 1998;**79**:346-9.

Jauch 2013

Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;**44**:870-947.

Knott 1999

Knott V, Bosman M, Mahoney C, Ilivitsky V, Quirt K. Transdermal nicotine: single dose effects on mood, EEG, performance, and event-related potentials. *Pharmacology Biochemistry and Behavior* 1999;**63**:253-61.

Lerdal 2011

Lerdal A, Kottorp A. Psychometric properties of the Fatigue Severity Scale-Rasch analyses of individual responses in a Norwegian stroke cohort. *International Journal of Nursing Studies* 2011;**48**:1258-65.

Luauté 2006

Luauté J, Halligan P, Rode G, Rossetti Y, Boisson D. Visuo-spatial neglect: a systematic review of current interventions and their effectiveness. *Neuroscience and Biobehavioral Reviews* 2006;**30**:961-82.

Malhotra 2006

Malhotra PA, Parton AD, Greenwood R, Husain M. Noradrenergic modulation of space exploration in visual neglect. *Annals of Neurology* 2006;**59**:186-90.

Mao 2002

Mao HF, Hsueh IP, Tang PF, Sheu CF, Hsieh CL. Analysis and comparison of the psychometric properties of three balance measures for stroke patients. *Stroke* 2002;**33**:1022-7.

Mathiowetz 1985

Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block Test of manual dexterity. *American Journal of Occupational Therapy* 1985;**39**:386-91.

Mizuno 2011

Mizuno K, Tsuji T, Takebayashi T, Fujiwara T, Hase K, Liu M. Prism adaptation therapy enhances rehabilitation of stroke patients with unilateral spatial neglect: a randomized, controlled trial. *Neurorehabilitation and Neural Repair* 2011;**25**:711-20.

Morse 1989

Morse JM, Black C, Oberle K, Donahue P. A prospective study to identify the fall-prone patient. *Social Science & Medicine* 1989;**28**:81-6.

Nakamura 2015

Nakamura J, Kita Y, Ikuno K, Kojima K, Okada Y, Shomoto K. Influence of the stimulus parameters of galvanic vestibular stimulation on unilateral spatial neglect. *NeuroReport* 2015;**26**:462-6.

Newell 1992

Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837-41.

Paolucci 2001

Paolucci S, Antonucci G, Grasso MG, Pizzamiglio L. The role of unilateral spatial neglect in rehabilitation of right brain-damaged ischemic stroke patients: a matched comparison. *Archives of Physical Medicine and Rehabilitation* 2001;**82**:743-9.

Plummer 2003

Plummer P, Morris ME, Dunai J. Assessment of unilateral neglect. *Physical Therapy* 2003;**83**:732-40.

Polanowska 2009

Polanowska K, Seniów J, Paprot E, Leśniak M, Członkowska A. Left-hand somatosensory stimulation combined with visual scanning training in rehabilitation for post-stroke hemineglect: a randomised, double-blind study. *Neuropsychological Rehabilitation* 2009;**19**:364-82.

Pontes-Neto 2008

Pontes-Neto OM, Silva GS, Feitosa MR, de Figueiredo NL, Fiorot JA Jr, Rocha TN, et al. Stroke awareness in Brazil: alarming results in a community-based study. *Stroke* 2008;**39**:292-6.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sanford 1993

Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Physical Therapy* 1993;**73**:447-54.

Schenkenberg 1980

Schenkenberg T, Bradford DC, Ajax ET. Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology* 1980;**30**:509-17.

Schröder 2008

Schröder A, Wist ER, Hömberg V. TENS and optokinetic stimulation in neglect therapy after cerebrovascular accident: a randomized controlled study. *European Journal of Neurology* 2008;**15**:922-7.

Singh-Curry 2011

Singh-Curry V, Malhotra P, Farmer SF, Husain M. Attention deficits following ADEM ameliorated by guanfacine. *Journal of Neurology, Neurosurgery and Psychiatry* 2011;**82**:688-90.

Stone 1993

Stone SP, Halligan PW, Greenwood RJ. The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age and Ageing* 1993;**22**:46-52.

Tanaka 2010

Tanaka T, Ifukube T, Sugihara S, Izumi T. A case study of new assessment and training of unilateral spatial neglect in stroke patients: effect of visual image transformation and visual stimulation by using a Head Mounted Display system (HMD). *Journal of Neuroengineering and Rehabilitation* 2010;**7**:20.

Thiel 2005

Thiel CM, Zilles K, Fink GR. Nicotine modulates reorienting of visuospatial attention and neural activity in human parietal cortex. *Neuropsychopharmacology* 2005;**30**:810-20.

Thieme 2013

Thieme H, Bayn M, Wurg M, Zange C, Pohl M, Behrens J. Mirror therapy for patients with severe arm paresis after stroke: a randomized controlled trial. *Clinical Rehabilitation* 2013;**27**:314-24.

Treger 2007

Treger I, Shames J, Giaquinto S, Ring H. Return to work in stroke patients. *Disability and Rehabilitation* 2007;**29**:1397-403.

Tsang 2009

Tsang MH, Sze KH, Fong KN. Occupational therapy treatment with right half-field eye-patching for patients with subacute stroke and unilateral neglect: a randomised controlled trial. *Disability and Rehabilitation* 2009;**31**:630-7.

Turton 2010

Turton AJ, O'Leary K, Gabb J, Woodward R, Gilchrist ID. A single blinded randomised controlled pilot trial of prism adaptation for improving self-care in stroke patients with neglect. *Neuropsychological Rehabilitation* 2010;**20**:180-96.

Vanier 1990

Vanier M, Gauthier L, Lambert J, Pepin EP, Robillard A, Dubouloz CJ, et al. Evaluation of left visuospatial neglect: norms and discrimination power of two tests. *Neuropsychology* 1990;**4**:87-96.

Velasco 1998

Velasco M, Luchsinger A. Dopamine: pharmacologic and therapeutic aspects. *American Journal of Therapeutics* 1998;**5**:37-43.

Vossel 2008

Vossel S, Thiel CM, Fink GR. Behavioral and neural effects of nicotine on visuospatial attention reorienting in non-smoking subjects. *Neuropsychopharmacology* 2008;**33**:731-8.

Walker 2011

Walker MF, Sunderland A, Fletcher-Smith J, Drummond A, Logan P, Edmans JA, et al. The DRESS trial: a feasibility randomized controlled trial of a neuropsychological approach to dressing therapy for stroke inpatients. *Clinical Rehabilitation* 2011;**26**:675-85.

Wee 2008

Wee JY, Hopman WM. Comparing consequences of right and left unilateral neglect in a stroke rehabilitation population. *American Journal of Physical Medicine and Rehabilitation* 2008;**87**:910-20.

Wilson 1987

Wilson B, Cockburn J, Halligan P. Development of a behavioral test of visuospatial neglect. *Archives of Physical Medicine and Rehabilitation* 1987;**68**:98-102.

Witte 1997

Witte EA, Davidson MC, Marrocco RT. Effects of altering brain cholinergic activity on covert orienting of attention: comparison of monkey and human performance. *Psychopharmacology* 1997;**132**:324-34.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Lucas 2013

Methods	Design: double-blind placebo-controlled within-subject design Multicenter Justification for the sample size: not reported Setting: Geneva University Hospital and Plein Soleil Foundation of Lausanne, Switzerland Follow-up period: days 1, 2, and 4
Participants	10 participants randomly assigned and 9 analyzed Mean age: 69.1 years Sex: 2 men, 8 women Inclusion criteria: right-handed (except 1), stable vigilance and sufficient co-operation to undergo a testing session of 45 minutes, and signs of stable symptoms of neglect Exclusion criteria: currently smoking ≥ 1 cigarette per day, with any past history of smoking systematically quantified and registered
Interventions	Experimental group: pro-cholinergic agent (Nicorette, 10 mg) administered by patch. Each participant was treated once (on day 2 or on day 4). The patch was applied in the morning between 7 am and 8 am and was removed around 6 pm to 7 pm Control group: placebo (patch)
Outcomes	Primary outcomes: USN (shape cancellation, letter cancellation, and Bells' cancellation) Secondary outcomes: brain lesion analysis
Notes	We contacted study authors on 24 April 2015 to request further information on both methodological and statistical data. We are awaiting their reply Topography: All participants (except 1) were right-handed and showed clinical and radiological evidence of a single focal lesion in the right hemisphere due to stroke, involving the middle cerebral artery territory in all cases Clinical status: Participants had partial (5 quadrantanopia) or full (3 hemianopia) visual hemifield cuts, as determined by clinical examination that includes confrontation Initial neglect severity: 5 participants presented with high initial neglect severity and 5 with low initial neglect severity

Lucas 2013 (Continued)

Transdermal nicotine side effects (demographic data): 1 participant presented with mild diarrhea in the morning

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This is a quasi-randomized trial, as study authors assigned participants in a successive manner
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded to treatment allocation, as they used active and placebo patches that were visually identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant had treatment interrupted and was not included in the study
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	High risk	The intervention drug was provided by Pfizer

Paolucci 2010

Methods	<p>Design: double-blind randomized controlled trial</p> <p>Single center</p> <p>Justification for the sample size: not reported</p> <p>Setting: Santa Lucia Foundation, Rome, Italy</p> <p>Follow-up period: 1 month after cessation of therapy</p>
Participants	<p>20 participants randomly assigned and 20 analyzed</p> <p>Mean age: drugs and rehabilitation 64.10 years; only rehabilitation 67.7 years</p> <p>Sex: drugs and rehabilitation: 6 men, 4 women; only rehabilitation: 4 men, 6 women</p> <p>Inclusion criteria: right-hemisphere stroke</p> <p>Exclusion criteria: stroke in left hemisphere, stroke due to hemorrhagic lesions, subarachnoid hemorrhage, presence of sequelae of previous cerebrovascular accidents and/or of other chronic disabling pathologies (eg. severe Parkinson's disease; polyneuropathy; severe cardiac, liver, or renal failure; cancer; and limb amputation), score lower than the established cutoff of 22 on the Mini Mental State Examination</p>

Paolucci 2010 (Continued)

Interventions	<p>Experimental group: physiotherapy, cognitive training, and rivastigmine 1.5 mg twice a day. After the first week, the dose was increased to 3 mg twice a day for 8 weeks</p> <p>Control group: physiotherapy and cognitive training</p>
Outcomes	<p>Primary outcomes: USN (Letter Cancellation Test, Barrage Test, Sentence Reading Test, Wundt-Jastrow Area Illusion Test)</p> <p>Secondary outcomes: functional evaluation (length of stay in rehabilitation; independence in daily living; mobility status; Barthel Index; Rivermead Mobility index)</p>
Notes	<p>We contacted study authors on 24 April 2015 to request further information on both methodological and statistical data. We are awaiting their reply</p> <p>Topography: In the rivastigmine plus rehabilitation group, 70% of participants had total anterior circulation infarcts and 30% had partial anterior circulation infarcts; in the rehabilitation only group (control), 80% of participants had total anterior circulation infarcts and 20% had partial anterior circulation infarcts</p> <p>Clinical status: At admission, the 2 subgroups had similar clinical, cognitive, and functional characteristics</p> <p>Initial neglect severity: no statistically significant differences in neglect severity between the 2 groups</p> <p>Rivastigmine side effects: 1 participant had nausea, probably due to the progressive titration of medication, but rivastigmine treatment as provided in this study was safe and feasible and did not increase the risk of adverse events</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed using an electronically produced randomization list"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Personnel: "The neuropsychologist, not being involved in the study, did not know which group the patients had been assigned to"</p> <p>Participants: not reported</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The rating scales were assessed independently by two ward physicians who were blind to the purpose of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

USN: unilateral spatial neglect.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Buxbaum 2007	Non-RCT
Cho 2009	Cohort study
Damulin 2008	Case series
Geminiani 1998	Case series
Gorgoraptis 2012	Non-RCT
Grujic 1998	Case series
Kakuda 2011	Case series
Kettunen 2012a	Cohort study
Kettunen 2012b	Cohort study
Krivonos 2010	Cohort study
Laihosalo 2011	Case series
Lehmann 2001	Non-RCT
Losoi 2012	Cohort study
Mukand 2001	Case series
Nolte 2009	Case series
Pokryszko-Dragan 2008	Cohort study
Sato 2006	Cohort study
Spalletta 2003	Case series
Tobinick 2012	Case series
Toyoda 2004	Cohort study
Troisi 2002	Case series
Xu 2007	Non-RCT

RCT: randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

[EudraCT 200400050717](#)

Trial name or title	Effectiveness of rivastigmine treatment in poststroke patients with right brain damage and unilateral spatial neglect
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EudraCT 200400050717 (Continued)

Methods

Participants	Elderly adults
Interventions	Rivastigmine
Outcomes	Improvement USN and functional status in right brain damaged participants
Starting date	10 June 2004
Contact information	Fondazione Santa Lucia
Notes	

USN: unilateral spatial neglect.

DATA AND ANALYSES
Comparison 1. Drug A + rehabilitation versus rehabilitation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall USN at discharge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Barrage (left side)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Effectiveness on Barrage	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Letter Cancellation (left side)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Effectiveness on Letter Cancellation	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Sentence Reading	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Effectiveness on Sentence Reading	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 Wundt-Jastrow (left side)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.8 Effectiveness on Wundt-Jastrow	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Overall USN at follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Barrage (left side)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Letter Cancellation (left side)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Sentence Reading	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Wundt-Jastrow (left side)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Disabilities	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Rivermead Mobility Index Score at discharge	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Rivermead Mobility Index Score at follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Daily life functions	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Barthel Index score at discharge	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Barthel Index score at follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Drug A + rehabilitation versus rehabilitation, Outcome 1 Overall USN at discharge.

Study or subgroup	Rivastigmine+rehab.		Rehabilitation		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
1.1.1 Barrage (left side)						
Paolucci 2010	10	10.9 (0.3)	10	10.6 (0.7)		0.3[-0.18,0.78]
1.1.2 Effectiveness on Barrage						
Paolucci 2010	10	78.3 (41.6)	10	66.9 (46.7)		11.46[-27.29,50.21]
1.1.3 Letter Cancellation (left side)						
Paolucci 2010	10	50.5 (3.2)	10	39.9 (13.4)		10.6[2.07,19.13]
1.1.4 Effectiveness on Letter Cancellation						
Paolucci 2010	10	92.7 (10.7)	10	63 (28.3)		29.62[10.87,48.37]
1.1.5 Sentence Reading						
Paolucci 2010	10	5.7 (0.7)	10	5.5 (1.3)		0.2[-0.69,1.09]
1.1.6 Effectiveness on Sentence Reading						
Paolucci 2010	10	63.3 (46.4)	10	83.6 (36)		-20.3[-56.67,16.07]
1.1.7 Wundt-Jastrow (left side)						
Paolucci 2010	10	1.5 (2.6)	10	5.9 (5.7)		-4.4[-8.28,-0.52]
1.1.8 Effectiveness on Wundt-Jastrow						
Paolucci 2010	10	62.3 (28.2)	10	88.3 (21.1)		-25.98[-47.78,-4.18]
					Rehabilitation -100 -50 0 50 100 Rivastigmine+rehab.	

Analysis 1.2. Comparison 1 Drug A + rehabilitation versus rehabilitation, Outcome 2 Overall USN at follow-up.

Analysis 1.3. Comparison 1 Drug A + rehabilitation versus rehabilitation, Outcome 3 Disabilities.

Analysis 1.4. Comparison 1 Drug A + rehabilitation versus rehabilitation, Outcome 4 Daily life functions.

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 [mh ^"cerebrovascular disorders"] or [mh "basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh "carotid artery diseases"] or [mh "intracranial arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh "intracranial hemorrhages"] or [mh ^stroke] or [mh "brain infarction"] or [mh ^"stroke, lacunar"] or [mh ^"vasospasm, intracranial"] or [mh ^"vertebral artery dissection"]

- #2 (stroke or poststroke or "post-stroke" or cerebrovasc* or brain next vasc* or cerebral next vasc* or cva* or apoplexy* or SAH):ti,ab
- #3 ((brain* or cerebral* or cerebell* or intracran* or intracerebral) near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus*)):ti,ab
- #4 ((brain* or cerebral* or cerebell* or intracerebral or intracranial or subarachnoid) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)):ti,ab
- #5 [mh ^hemiplegia] or [mh paresis]
- #6 (hemipleg* or hemipar* or paresis or paretic):ti,ab
- #7 #1 or #2 or #3 or #4 or #5 or #6
- #8 [mh ^"perceptual disorders"] or [mh ^perception] or [mh "visual perception"] or [mh ^"space perception"] or [mh ^attention] or [mh ^"functional laterality"] or [mh ^"extinction, psychological"]
- #9 (hemineglect or hemi-neglect):ti,ab
- #10 ((unilateral or spatial or hemispatial or hemi-spatial or visual) near/5 neglect):ti,ab
- #11 (inattention or hemi-inattention or extinction):ti,ab
- #12 ((perceptual or perception or visuospatial or visuo-spatial or visuoperceptual or visuo-perceptual or attention*) near/5 (disorder* or deficit* or impairment* or abilit* or problem*)):ti,ab
- #13 #8 or #9 or #10 or #11 or #12
- #14 [mh /DT,DE,PD]
- #15 [mh "dopamine agents"]
- #16 [mh "dopamine agonists"]
- #17 (dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine):ti,ab,kw
- #18 [mh "adrenergic alpha-agonists"]
- #19 [mh "adrenergic alpha-1 receptor agonists"] or [mh "adrenergic alpha-2 receptor agonists"]
- #20 ((adrenergic or noradrenergic) near/5 agonist*):ti,ab
- #21 (norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyl dopa or xylazine):ti,ab,kw
- #22 [mh "adrenergic beta-agonists"] or [mh "adrenergic beta-1 receptor agonists"] or [mh "adrenergic beta-2 receptor agonists"] or [mh "adrenergic beta-3 receptor agonists"]
- #23 (clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine):ti,ab,kw
- #24 [mh "Drug Therapy"]
- #25 ((drug or pharmacol*) near/5 (therap* or treat* or effect*)):ti,ab
- #26 pharmacotherap*:ti,ab
- #27 {or #14-#26}
- #28 #7 and #13 and #27

Appendix 2. MEDLINE search strategy

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.
3. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. perceptual disorders/ or perception/ or exp visual perception/ or space perception/ or attention/ or functional laterality/ or extinction, psychological/
9. (hemineglect or hemi-neglect).tw.
10. ((unilateral or spatial or hemispatial or visual) adj5 neglect).tw.
11. (perception or inattention or hemi-inattention or extinction).tw.
12. ((perceptual or visuo?spatial or visuo?perceptual or attention\$) adj5 (disorder\$ or deficit\$ or impairment\$ or abilit\$ or problem\$)).tw.
13. 8 or 9 or 10 or 11 or 12
14. (drug effects or drug therapy or pharmacology).fs.
15. dopamine agents/ or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine/ or amantadine/ or amphetamine/ or benserazide/ or benzphetamine/ or carbidopa/ or dihydroxyphenylalanine/ or dopamine/ or fusaric acid/ or levodopa/ or memantine/ or methamphetamine/
16. dopamine agonists/ or 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1h-3-benzazepine/ or apomorphine/ or bromocriptine/ or dihydroergocornine/ or dihydroergocryptine/ or dihydroergotamine/ or dihydroergotoxine/ or fenoldopam/ or lisuride/ or metergoline/ or pergolide/ or piribedil/ or quinpirole/
17. (dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine).tw,nm.
18. adrenergic alpha-agonists/ or epinephrine/ or etilefrine/ or naphazoline/ or norepinephrine/ or octopamine/ or oxymetazoline/ or phenylpropanolamine/ or synephrine/
19. adrenergic alpha-1 receptor agonists/ or ergotamine/ or mephentermine/ or metaraminol/ or methoxamine/ or midodrine/ or phenylephrine/ or adrenergic alpha-2 receptor agonists/ or clonidine/ or dexmedetomidine/ or guanabenz/ or guanfacine/ or medetomidine/ or methyl dopa/ or xylazine/
20. ((adrenergic or noradrenergic) adj5 agonist\$).tw.
21. (norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyl dopa or xylazine).tw,nm.
22. adrenergic beta-agonists/ or clenbuterol/ or epinephrine/ or isoproterenol/ or isoxsuprine/ or nylidrin/ or oxyfedrine/ or tretoquinol/ or adrenergic beta-1 receptor agonists/ or dobutamine/ or etilefrine/ or prenalterol/ or xamoterol/ or adrenergic beta-2 receptor agonists/ or albuterol/ or fenoterol/ or hexoprenaline/ or isoetharine/ or metaproterenol/ or procaterol/ or ritodrine/ or terbutaline/ or adrenergic beta-3 receptor agonists/
23. (clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline).tw,nm.
24. exp Drug Therapy/
25. ((drug or pharmacol\$) adj5 (therap\$ or treat\$ or effect\$)).tw.
26. (pharmacotherapy\$ or fluoxetine or rivastigmine).tw.
27. or/14-26
28. Randomized Controlled Trials as Topic/
29. random allocation/
30. Controlled Clinical Trials as Topic/
31. control groups/
32. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
33. double-blind method/
34. single-blind method/
35. Placebos/
36. placebo effect/
37. cross-over studies/
38. Therapies, Investigational/

39. Drug Evaluation/
40. Research Design/
41. randomized controlled trial.pt.
42. controlled clinical trial.pt.
43. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
44. (random\$ or RCT or RCTs).tw.
45. (controlled adj5 (trial\$ or stud\$)).tw.
46. (clinical\$ adj5 trial\$).tw.
47. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
48. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
49. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
50. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
51. (cross-over or cross over or crossover).tw.
52. (placebo\$ or sham).tw.
53. trial.ti.
54. (assign\$ or allocat\$).tw.
55. controls.tw.
56. or/28-55
57. 7 and 13 and 27 and 56
58. exp animals/ not humans.sh.
59. 57 not 58

Appendix 3. CINAHL search strategy

- S1 .(MH "Cerebrovascular Disorders") OR (MH "Basal Ganglia Cerebrovascular Disease+") OR (MH "Carotid Artery Diseases+") OR (MH "Cerebral Ischemia+") OR (MH "Cerebral Vasospasm") OR (MH "Intracranial Arterial Diseases+") OR (MH "Intracranial Embolism and Thrombosis") OR (MH "Intracranial Hemorrhage+") OR (MH "Stroke") OR (MH "Vertebral Artery Dissections")
- S2 .(MH "Stroke Patients") OR (MH "Stroke Units")
- S3 .TI (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH) or AB (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH)
- S4 .TI (brain* or cerebr* or cerebell* or intracran* or intracerebral) or AB (brain* or cerebr* or cerebell* or intracran* or intracerebral)
- S5 .TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*)
- S6 .S4 and S5
- S7 .TI (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) or AB (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid)
- S8 .TI (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) or AB (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)
- S9 .S7 and S8
- S10 .(MH "Hemiplegia")
- S11 .TI (hemipleg* or hemipar* or paresis or paretic) or AB (hemipleg* or hemipar* or paresis or paretic)
- S12 .S1 or S2 or S3 or S6 or S9 or S10 or S11
- S13 .(MH "Unilateral Neglect") OR (MH "Unilateral Neglect (Saba CCC)") OR (MH "Unilateral Neglect (NANDA)")
- S14 .(MH "Perceptual Disorders+")
- S15 .(MH "Perception+")
- S16 .(MH "attention")
- S17 .TI (hemineglect or hemi-neglect) or AB (hemineglect or hemi-neglect)
- S18 .TI (unilateral or spatial or hemi#spatial or visual) or AB (unilateral or spatial or hemi#spatial or visual)

S19 .TI (neglect) or AB (neglect)

S20 .S18 AND S19

S21 .TI (inattention or hemi-inattention or extinction) or AB (inattention or hemi-inattention or extinction)

S22 .TI (perceptual or perception or visuo#spatial or visuo#perceptual or attention*) or AB (perceptual or perception or visuo#spatial or visuo#perceptual or attention*)

S23 .TI (disorder* or deficit* or impairment* or abilit*) or AB (disorder* or deficit* or impairment* or abilit*)

S24 .S22 AND S23

S25 .S13 OR S14 OR S15 OR S16 OR S17 OR S20 OR S21 OR S24

S26 .(MH "Drug Therapy+")

S27 .MW dt or MW de

S28 .(MH "Dopamine Agents") OR (MH "Dopamine Agonists+")

S29 .TI dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine

S30 .AB dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine

S31 .MW dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine

S32 .(MH "Adrenergic Agonists") OR (MH "Adrenergic Alpha-Agonists+") OR (MH "Adrenergic Beta-Agonists+")

S33 .TI ((adrenergic or noradrenergic) N5 agonist*) or AB ((adrenergic or noradrenergic) N5 agonist*)

S34 .TI norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methylidopa or xylazine

S35 .AB norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methylidopa or xylazine

S36 .MW norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methylidopa or xylazine

S37 .TI clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine

S38 .AB clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine

S39 .MW clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine

S40 .TI (((drug or pharmacol*) N5 (therap* or treat* or effect*))) OR AB (((drug or pharmacol*) N5 (therap* or treat* or effect*)))

S41 .TI pharmacotherap* or Ab pharmacotherap*

S42 .S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41

S43 .S12 AND S25 AND S42

Appendix 4. EMBASE (Ovid) search strategy

1. stroke/ or cerebrovascular disease/ or exp basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke patient/ or stroke unit/

2. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.

3. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.

4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.

5. hemiparesis/ or hemiplegia/ or paresis/

6. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. exp perception disorder/ or exp perception/ or exp attention/ or attention disturbance/ or visual deprivation/ or neglect/ or hemispatial neglect/ or "unilateral neglect syndrome"/

9. (hemineglect or hemi-neglect).tw.

10. ((unilateral or spatial or hemi?spatial or visual) adj5 neglect).tw.

11. (inattention or hemi-inattention or extinction).tw.

12. ((perceptual or perception or attention\$ or visuo?spatial or visuo?perceptual) adj5 (disorder\$ or deficit\$ or impairment\$ or abilit\$ or dysfunction\$)).tw.

13. 8 or 9 or 10 or 11 or 12

14. (dt or pd).fs. or exp drug therapy/

15. exp dopamine receptor stimulating agent/

16. (dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine).mp.

17. exp adrenergic receptor stimulating agent/

18. ((adrenergic or noradrenergic) adj5 agonist\$).tw.

19. (norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyl dopa or xylazine).mp.

20. (clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine).mp.

21. ((drug or pharmacol\$) adj5 (therap\$ or treat\$ or effect\$)).tw.

22. pharmacotherap\$.tw.

23. or/14-22

24. Randomized Controlled Trial/
25. Randomization/
26. Controlled Study/
27. control group/
28. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
29. Crossover Procedure/
30. Double Blind Procedure/
31. Single Blind Procedure/ or triple blind procedure/
32. placebo/
33. drug comparison/ or drug dose comparison/
34. "types of study"/
35. random\$.tw.
36. (controlled adj5 (trial\$ or stud\$)).tw.
37. (clinical\$ adj5 trial\$).tw.
38. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
39. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
40. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
41. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
42. (cross-over or cross over or crossover).tw.
43. placebo\$.tw.
44. sham.tw.
45. (assign\$ or allocat\$).tw.
46. controls.tw.
47. trial.ti. or (RCT or RCTs).tw.
48. or/24-47
49. 7 and 13 and 23 and 48
50. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
51. 49 not 50
52. (neonat\$ or newborn\$ or new born or pediatric or paediatric or birth or infant or infants or perinatal or peri-natal or baby or babies or child or children).ti.
53. 51 not 52

Appendix 5. PsycINFO search strategy

1. cerebrovascular disorders/ or cerebral hemorrhage/ or exp cerebral ischemia/ or cerebrovascular accidents/ or subarachnoid hemorrhage/
2. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.

3. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
5. hemiparesis/ or hemiplegia/
6. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. sensory neglect/
9. exp perceptual disturbances/
10. exp perception/
11. exp attention/
12. "extinction (learning)"/
13. (hemineglect or hemi-neglect).tw.
14. ((unilateral or spatial or hemispatial or visual) adj5 neglect).tw.
15. (inattention or hemi-inattention or extinction).tw.
16. ((perceptual or perception or visuo?spatial or visuo?perceptual or attention\$) adj5 (disorder\$ or deficit\$ or impairment\$ or abilit\$)).tw.
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp drugs/ or exp drug therapy/ or exp psychopharmacology/
19. exp dopamine agonists/
20. exp catecholamines/
21. exp adrenergic drugs/
22. exp sympathomimetic drugs/
23. (dopamine or dopaminergic or amantadine or amphetamine or benserazide or benzphetamine or carbidopa or dihydroxyphenylalanine or fusaric acid or levodopa or L-dopa or memantine or methamphetamine or apomorphine or bromocriptine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotaxine or fenoldopam or lisuride or metergoline or pergolide or piribedil or quinpirole or rotigotine).mp.
24. ((adrenergic or noradrenergic) adj5 agonist\$).tw.
25. (norepinephrine or noradrenaline or levarterenol or levonoradrenaline or levonorepinephrine or levophed or levonor or arterenol or epinephrine or etilefrine or naphazoline or octopamine or oxymetazoline or phenylpropanolamine or synephrine or ergotamine or mephentermine or metaraminol or methoxamine or midodrine or phenylephrine or clonidine or dexmedetomidine or guanabenz or guanfacine or medetomidine or methyl dopa or xylazine).mp.
26. (clenbuterol or isoproterenol or isoxsuprine or nylidrin or oxyfedrine or tretoquinol or dobutamine or etilefrine or prenalterol or xamoterol or albuterol or fenoterol or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or terbutaline or fluoxetine or rivastigmine).mp.
27. ((drug or pharmacol\$) adj5 (therap\$ or treat\$ or effect\$)).tw.
28. pharmacotherap\$.tw.
29. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 7 and 17 and 29

Appendix 6. LILACS search strategy

1. (Drug Therapy or Drug Therapies or Chemotherapy or Chemotherapies or Pharmacotherapy or Pharmacotherapies)

2. (Perceptual Disorder or Somatosensory Discrimination Disorder or Somatosensory Discrimination Disorders or Sensory Neglect or Sensory Neglects or Hemisensory Neglect or Hemisensory Neglects or Hemispatial Neglect or Hemispatial Neglects)

3. (Stroke or Strokes or Apoplexy or CVA (Cerebrovascular Accident) or CVAs (Cerebrovascular Accident) or Cerebrovascular Accident or Cerebrovascular Accidents or Cerebrovascular Apoplexy or Cerebrovascular Stroke or Cerebrovascular Strokes or Brain Vascular Accident or Brain Vascular Accidents or Cerebral Stroke or Cerebral Strokes or Acute Stroke or Acute Strokes or Acute Cerebrovascular Accident or Acute Cerebrovascular Accidents)

4. 1 and 2 and 3

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In addition, Professor Luiz Antônio de Lima Resende made a large contribution to the development of this review. He provided guidance regarding unilateral spatial neglect after stroke and assisted with the methods of the review.

DECLARATIONS OF INTEREST

Gustavo José Luvizutto: none known.

Rodrigo Bazan: none known.

Gabriel Pereira Braga: none known.

Silméia Garcia Zanati Bazan: none known.

Luiz Antônio de Lima Resende: none known.

Regina El Dib: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

None

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have included quasi-RCTs in the review because of the small number of RCTs identified. Disability was a prespecified primary outcome in the protocol; however, this was considered a secondary outcome in the full review because the review authors considered that the pharmacological intervention has a primary effect on modulation of the perception of the central nervous system (USN), and has a secondary effect on other functions (eg, disability).

INDEX TERMS**Medical Subject Headings (MeSH)**

Administration, Cutaneous; Neuroprotective Agents [*therapeutic use]; Nicotine [administration & dosage] [*therapeutic use]; Nicotinic Agonists [administration & dosage] [*therapeutic use]; Perceptual Disorders [*drug therapy] [rehabilitation]; Randomized Controlled Trials as Topic; Rivastigmine [*therapeutic use]; Stroke [*complications]; Stroke Rehabilitation

MeSH check words

Humans