

## Pharmacological Treatment of Visuospatial Neglect: A Systematic Review

Jet van der Kemp, BSc,<sup>\*,1,2</sup> Marit Dorresteyn, BSc,<sup>†,1</sup> Antonia F. Ten Brink, MSc,<sup>\*</sup>  
Tanja C.W. Nijboer, PhD,<sup>\*,†</sup> and Johanna M.A. Visser-Meily, MD<sup>\*</sup>

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**Objectives:** The aims of the current review were (1) to give an overview of human studies investigating pharmacotherapy to ameliorate visuospatial neglect and (2) to evaluate the quality of those studies. **Methods:** A systematic literature search using PubMed, Scopus, and ResearchGate was conducted in regard to studies that evaluated pharmacological interventions aiming to ameliorate poststroke visuospatial neglect. The search was limited in the following features: species (human), adults ( $\geq 18$  years of age), language (English), and type of neglect (visuospatial). Two independent authors extracted data on study content and effectiveness and evaluated the quality of studies and methods. **Results:** A total of 11 studies were identified. Three studies were considered to be of moderate quality, the others of low quality. Seven studies represented dopaminergic treatment; 3 studies represented cholinergic treatment; and 1 study represented noradrenergic treatment. Three dopaminergic studies showed primarily positive effects of dopaminergic stimulation on visuospatial neglect, whereas three others showed adverse effects. All 3 cholinergic studies found positive effects in some outcome measures concerning visuospatial neglect. Noradrenergic stimulation improved maintenance of attention when exploring space. **Conclusions:** Currently, cholinergic therapy might be the best option for future research. However, we must emphasize the explorative nature and the limited quality of the reviewed studies. **Key Words:** Stroke—visuospatial neglect—pharmacological treatment—rehabilitation.

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From the \*Center of Excellence in Rehabilitation Medicine, Brain Center Rudolf Magnus, University Medical Center Utrecht and De Hoogstraat Rehabilitation, Utrecht, The Netherlands; and †Department of Experimental Psychology, Helmholtz Institute, Utrecht University, Utrecht, The Netherlands.

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Address correspondence to Tanja C.W. Nijboer, PhD, Brain Centre Rudolf Magnus, Centre of Excellence for Rehabilitation Medicine, University Medical Centre Utrecht, Department of Rehabilitation Medicine, Heidelberglaan 1, 3584 CS Utrecht, Netherlands. E-mail: [t.c.w.nijboer@uu.nl](mailto:t.c.w.nijboer@uu.nl).

<sup>1</sup> These authors contributed equally to this work and are both regarded as first authors.

<sup>2</sup> Medical student, participating in the Honours program of the Faculty of Medicine, UMC Utrecht.

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## Introduction

Visuospatial neglect (VSN) is a common disorder post stroke.<sup>1</sup> Patients with VSN fail to report, orient toward, or respond to visual stimuli in the contralesional hemispace.<sup>1</sup> VSN can result from left or right hemispheric lesions, but is most profound and persistent following right hemispheric lesions.<sup>2</sup> Nearly half of all stroke patients are affected by VSN in the (sub)acute phase post stroke.<sup>3</sup> Estimations are that 40%<sup>3</sup> to 75%<sup>3,4</sup> of these patients develop chronic symptoms up to 1 year post stroke in at least a mild form. In addition to motor impairments,<sup>5</sup> stroke has many adverse behavioral consequences on the cognitive level, hampering participation in a wide range of everyday activities.<sup>6,7</sup>

Due to the high prevalence of poststroke VSN and its negative consequences, effective remediation techniques are needed. Promising remediation techniques have emerged over the past decades, including prism adaptation,<sup>8-10</sup> virtual reality training,<sup>6,11</sup> visuospatial and scanning training,<sup>12</sup> galvanic vestibular stimulation,<sup>13,14</sup> transcutaneous electrical nerve stimulation,<sup>15</sup> motivational manipulations,<sup>16</sup> optokinetic stimulation,<sup>17</sup> video game-based remediation,<sup>10,18</sup> and upcoming noninvasive brain stimulation techniques such as transcranial magnetic stimulation<sup>19,20</sup> and transcranial direct current stimulation.<sup>21-23</sup> However, the effectiveness of almost all techniques has not been investigated thoroughly enough to allow firm conclusions.<sup>6,24</sup> Pharmacological techniques represent another promising remediation approach. As pharmacotherapy affects the whole brain, it addresses the factors causing VSN instead of using compensational techniques to conceal deficits. Therefore, pharmacotherapy will be the topic of the current review.

### *Pharmacotherapy in VSN: a Brief History*

Several animal studies on the effectiveness of pharmacotherapy have been published over the last 3 decades,<sup>25-29</sup> and have generally focused on dopaminergic agonists and progesterone. VSN symptoms have been assessed by regular<sup>25,26</sup> and Morris water mazes,<sup>26,27</sup> adhesive removal tests,<sup>27,28</sup> and simple observations of orientation behavior<sup>29</sup> in a variety of induced-stroke models.<sup>25-29</sup> In general, results showed the positive effects of progesterone<sup>26-28</sup> and apomorphine<sup>29</sup> on VSN, and of amphetamine on cognitive functioning.<sup>25</sup> Similarly, human studies on the topic emerged about 3 decades ago.<sup>30</sup> Yet, in human studies, pharmacotherapy does not get as much attention as the other techniques in treating VSN.

### *How Pharmacotherapy Might Work*

Neuronal functioning depends on network structures, the balance between excitation and inhibition of neurons, and the resulting impulse transmission between connected neurons. About 50 neurotransmitters have been

identified, either excitatory or inhibitory.<sup>31</sup> If a neurological condition is caused by an imbalance in excitation and inhibition while neuronal connections are functionally preserved, manipulating these electrochemical processes may improve neuronal function. A neurological “hypofunction” like VSN may improve by decreasing inhibition or increasing excitation. In this manner, pharmacological agents can have positive therapeutic effects.

As the core symptoms of VSN comprise attention deficits, it makes sense to focus on those neurotransmitters that exert their effects on attention networks. Three networks of attention can be distinguished, namely, the alerting, orienting, and executive networks. VSN has been associated with all of these networks.<sup>32-34</sup> The alerting network is modulated by noradrenaline.<sup>33,35,36</sup> The inhibitory or excitatory effects are complex, but in general terms, noradrenaline activates the brain and body for action, which is reflected in functions like increased alertness, focus, and attention. The orienting network has been linked to acetylcholine.<sup>32,33</sup> Acetylcholine is the major neurotransmitter not only in the peripheral nervous system at the neuromuscular junction but also in the autonomic nervous system. In the brain, acetylcholine has a modulating effect on information processing, including plasticity, arousal, and sustained attention. Acetylcholine usually has an excitatory effect. Acetylcholine agonists can directly act on receptors and increase receptor activation. The executive network of attention is modulated by dopamine<sup>33,35</sup> and is believed to affect the spatial bias in VSN.<sup>37</sup> Dopamine is a neurotransmitter found in distinct dopamine pathways, with a modulating role in specific functional networks (i.e., involving reward-motivated behavior). The inhibitory and excitatory effects have an effect on ion channels via a second messenger system and depend on the postsynaptic type of dopamine receptor. So, patients with VSN could benefit from pharmacological intervention through modulation of surviving neuronal networks by targeting specific neurotransmitters.<sup>38</sup>

Despite the appealing advocacy of pharmacotherapy as a means to ameliorate VSN symptoms, it appears to be largely overlooked when it comes to human treatment phases I and II, or intervention studies (i.e., evaluation of [side] effects and comparison with placebo or standard treatment).

### *Objectives and Distinctiveness*

The aims of the current review were (1) to give an overview of human studies investigating pharmacotherapy to ameliorate VSN symptoms and (2) to evaluate the quality of those studies. These aims parallel those made in a Cochrane review<sup>39</sup> on the pharmacological treatment of VSN, published shortly before we completed the current review. However, several differences positively distinguish the current review from the Cochrane review. First, strict inclusion criteria for a Cochrane review limited

the number of reviewed studies: only (quasi-)RCTs were included, resulting in a total of 2 studies. “Lower-quality” studies, however, should also be reported, as they may add important knowledge for future studies, especially given the potential shortcomings in their designs. Additionally, we applied more criteria for assessment compared to the Cochrane review, such as the allocation of patients and blinding treatment officers, which gives a more extensive overview of the current state-of-the-art of the field. In sum, the current review provides a more comprehensive overview of available studies on the pharmacological treatment of VSN and may therefore give a broader overview of the current state-of-the-art of the field.

## Methods

### *Search Methods and Article Selection*

Initially, the systematic literature search was performed using Pubmed, Scopus, and ResearchGate for studies published between January 2000 and July 2016 using the terms neglect, visual neglect, spatial hemineglect, hemispatial neglect, unilateral neglect, unilateral spatial neglect, unilateral hemispatial neglect, visuospatial neglect, visuospatial hemineglect, spatial neglect, visual inattention, spatial inattention, visual hemispatial inattention, hemispatial inattention, visual hemineglect, sensory neglect, personal neglect, behavioral neglect, motor neglect, hemi-inattention, peripersonal neglect, pharmacotherapy, remediation, rehabilitation, medication, therapy, (nor)epinephrine, (nor)adrenaline, dopamine, and choline. Note that “unilateral neglect,” “hemispatial neglect,” or any other inconsistent labels are under the same overall VSN syndrome, which is why those terms were included in the current search. The search was limited in the following features: species (human), adults ( $\geq 18$  years of age), language (English), and type of neglect (visuospatial). Intervention studies aiming at enhancing attention or decreasing VSN symptoms post stroke were selected when they met the following inclusion criteria: (1) the study population included patients experiencing visuospatial attention deficits resulting from stroke, and (2) the study reported outcome measures aimed directly at the VSN syndrome, or aimed at general attention, which included subtests aimed at the VSN syndrome. Due to limited search results (7 studies), we additionally released our time-span criterion to include studies published in any year and found 4 additional studies published before 2000. These studies were subsequently included for review.

Two authors (J.v.d.K. and M.D.) independently conducted the search and screened the articles. Duplicates were excluded. Full-text articles were collected or requested. In case of doubt concerning inclusion, the other authors were consulted.

### *Data Extraction*

J.v.d.K. and M.D. independently performed the data extraction. Extracted data were compared and discrepancies were discussed among J.v.d.K. and M.D. The following study characteristics were extracted from the articles: study design, number of patients, outcome measures, *P* value, effect size (calculated when possible given the reported data in the original papers), and timing of measurements. The following intervention characteristics were extracted: aim of the intervention, type of intervention, duration (minutes to weeks), and intensity (micro- to milligram). The following patient characteristics were extracted: diagnostic criteria, age, sex, time post stroke, stroke type, and lesion site.

### *Quality Assessment*

J.v.d.K. and M.D. independently evaluated the characteristics and the quality of the selected studies. A third author (A.F.T.B.) was consulted in case of dual doubt on scoring. The methodological quality was based on the following criteria: (1) randomization of intervention or different conditions, (2) blinded allocation of the intervention, (3) blinding of patients, (4) blinding of the treatment officer, (5) blinding of researchers, (6) comparability of groups at the start of the study, (7) reporting of the effect size, (8) reporting of the completeness of the follow-up, and (9) equal treatment of groups, aside from intervention.<sup>40</sup> We added 3 relevant elements to evaluate methodological quality: (10) comparison of an experimental group and a control group that received either an alternative form of treatment or no intervention, (11) group size ( $\geq 10$  per group), and (12) reporting time post stroke. This 12-point checklist yielded a total score between 0 and 12 for each study, creating a natural 4-point demarcation for 3 groups. Studies were subsequently divided into high-quality (total score  $\geq 9$ ), moderate-quality (5-8) and low-quality ( $\leq 4$ ) studies.

## Results

Initially, 38 articles were identified, 11 of which met the inclusion criteria (see Fig 1 for a flowchart of the article selection process). Of these studies, 7 studies investigated dopaminergic therapy; 3 studies considered cholinergic therapy; and 1 study targeted (nor)adrenergic therapy. Findings of the methodological quality of the studies, based on the elements mentioned above, are presented in Table 1. There was an initial 95% agreement between J.v.d.K. and M.D. regarding quality assessment, which was 100% after consultation. None of the studies were qualified to be of high quality according to our criteria; 3 studies were considered to be of moderate quality<sup>45,47,48</sup>; and the other 8 were considered low-quality studies.<sup>4,30,41-44,46,49</sup> An overview of study and participant characteristics is listed in Table 2. Only 1 study<sup>47</sup>

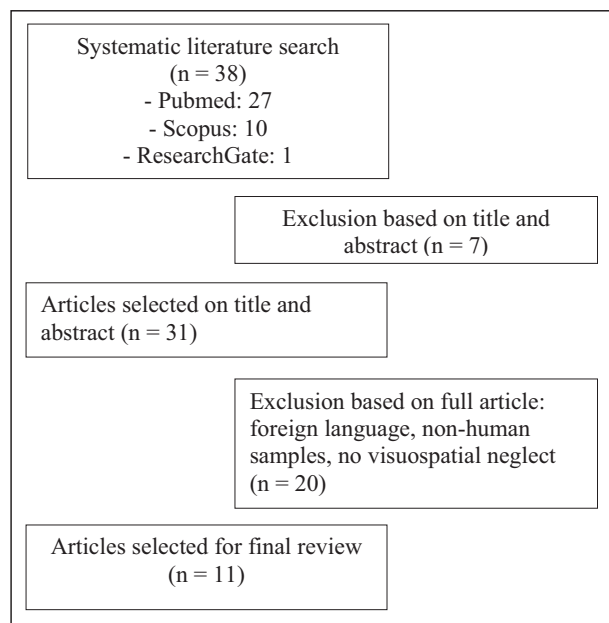


Figure 1. Flowchart of the article selection process.

included a true patient control group, whereas the remaining 10 studies<sup>4,30,41-46,48,49</sup> used an A-B(-A) design in which all individual patients served as their own control. We considered 4 studies in the chronic phase,<sup>4,46,47,49</sup> 1 study in the subacute phase,<sup>43</sup> and 1 study in the acute phase post stroke.<sup>44</sup> Time post stroke was variable in the remaining 5 studies, in which both patients in the subacute phase and patients in the chronic phase were

included.<sup>30,41,42,45,48</sup> Only 5 studies<sup>42,43,46,48,49</sup> focused primarily on VSN by using exclusively VSN tests (e.g., bisection, cancellation, visual search, and detection tests) as outcome measures, whereas 6 studies<sup>4,30,41,44,45,47</sup> focused more generally on recovery or enhancing attention, and additionally included VSN tests in their outcome measures. None of the 11 studies reported effect sizes. Six studies reported enough data to enable us to calculate effect sizes ourselves<sup>42,43,45,47-49</sup>; these data are presented in Tables 3-5.

Discrepancies were also observed regarding patient characteristics, such as diagnostic criteria, stroke type, and lesion site. Diagnostic criteria regarding VSN were highly variable among all studies, and many different assessments were used in each study. Eight<sup>4,41-43,45-48</sup> out of 11 studies reported assessing VSN before the study. Five of these studies<sup>42,43,46-48</sup> reported patients' scores on these assessments. Stroke type was unaccounted for in 3<sup>4,41,49</sup> out of 11 studies. Overall, ischemic stroke was reported more frequently compared to hemorrhagic stroke. Concerning lesion site, all dopaminergic studies reported on hemispheric lesion location, which were all right sided.<sup>4,30,41-45</sup> The cholinergic studies all included right-hemisphere patients too, with 1 patient in 2 studies showing additional left hemisphere lesions.<sup>47,48</sup> Additional information on affected arteries was provided in 2 studies.<sup>47,48</sup> Three studies analyzed patients' lesion sites more thoroughly by means of computed tomography or magnetic resonance imaging data,<sup>45,46,48</sup> and the effect of specific lesion location on therapy effectiveness was evaluated in 2 additional studies.<sup>41,43</sup> Moreover, discrepancies were observed

Table 1. Quality assessment scores

Study	1	2	3	4	5	6	7	8	9	10	11	12	Total score	Quality
<b>Dopamine</b>														
Fleet et al, 1987 <sup>30</sup>	0	0	0	0	0	0	0	0	0	0	0	1	1	Low
Grujic et al, 1998 <sup>41</sup>	0	0	0	0	0	1	0	0	0	0	0	1	2	Low
Geminiani et al, 1998 <sup>42</sup>	0	0	0	0	0	1	0	0	0	0	0	1	2	Low
Barrett et al, 1999 <sup>43</sup>	0	0	0	0	0	0	0	0	0	0	0	1	1	Low
Mukand et al, 2001 <sup>44</sup>	0	0	0	0	0	1	0	0	0	0	0	1	2	Low
Buxbaum et al, 2007 <sup>4</sup>	0	0	1	0	1	1	0	0	0	0	0	1	4	Low
Gorgoraptis et al, 2012 <sup>45</sup>	0	1	1	1	1	1	0	0	0	0	1	1	7	Moderate
<b>Acetylcholine</b>														
Vossel et al, 2010 <sup>46</sup>	0	0	1	0	0	0	0	0	1	0	0	1	3	Low
Paolucci et al, 2010 <sup>47</sup>	1	1	0	0	0	1	0	0	1	1	1	0	6	Moderate
Lucas et al, 2013 <sup>48</sup>	1	1	1	1	1	0	0	0	0	0	1	1	7	Moderate
<b>Norepinephrine</b>														
Malhotra et al, 2006 <sup>49</sup>	0	1	1	0	1	0	0	0	0	0	0	1	4	Low

0 indicates negative; 1 indicates positive. Studies were considered to be of high quality at a total score of 9 or higher; moderate quality, 5-8; and low quality, 4 or lower. Elements: (1) randomization of intervention or different conditions; (2) blinded allocation of the intervention; (3) blinding of patients; (4) blinding of the treatment officer; (5) blinding of researchers; (6) comparability of groups at the start of the study; (7) reporting of the effect size; (8) reporting of the completeness of follow-up at 3 months or more; (9) equal treatment of groups, aside from intervention; (10) comparison of an experimental group and a control group that received either an alternative form of treatment or no intervention; (11) group size ( $\geq 10$  per group); and (12) reporting of time post stroke.

**Table 2.** Overview of study and participant characteristics

Authors	Patients (N, follow-up)	Sex (N, male/female)	Mean age in years (SD)	Time post stroke	Type of stroke	Lesion site	Diagnostic criteria*
Fleet et al, 1987 <sup>30</sup>	2 (2)	1/1	46 (4)	2-6 mo	Ischemic	Right: f, t, p	Large right frontotempoparietal infarcts, neglect
Grujic et al, 1998 <sup>41</sup>	7 (7)	7/0	55 (8.6)	18.7 mo	Not specified	Right: in, st, f, t, p	Right-handed subjects, lesions involving the right hemisphere
Geminiani et al, 1998 <sup>42</sup>	4 (4)	2/2	64 (10.8)	18 d-15 mo	Ischemic	Right	Right-hemispheric ischemic lesions, unilateral neglect, normal vigilance, absence of mental deterioration (MMSE >22)
Barrett et al, 1999 <sup>43</sup>	1 (1)	1/0	58 (0)	4 wk (T1) 6 wk (T2)	Ischemic	Right: MCA	Unilateral neglect from right-cerebral infarction involving both cortical and striatal structures, failure of the action–intention system (akinesia and abulia, motor neglect)
Mukand et al, 2001 <sup>44</sup>	4 (3)	0/4	71 (4)	6 d (av)	3 ischemic, 1 hemorrhagic	Right: f, t, p, o, bg	Functional deficits, BIT score lower than 120
Buxbaum et al, 2007 <sup>4</sup>	4 (3)	Not specified	75 (1.9)	6-35 mo	Not specified	Right: f, t, p, o, th, in, bg	Chronic right-hemisphere stroke patients, having at least moderate neglect, 6-36 mo post stroke
Gorgoraptis et al, 2012 <sup>45</sup>	16 (16)	14/2	57 (13.6)	30-1990 d	11 ischemic, 5 hemorrhagic	Right: prefrontal	Hemispatial neglect, unilateral weakness following right-hemisphere stroke
Vossel et al, 2010 <sup>46</sup>	9 (9)	8/1	67 (10.6)	22.1 mo (av)	“of vascular etiology”	Right (all + 1 patient small lesions left)	Right hemispheric lesions of vascular etiology, signs of neglect (chronic spatial neglect, symptoms persisting for >6 mo post stroke), signs of neglect in at least two of the NET, TAP, or visual search tasks in a placebo session
Paolucci et al, 2010 <sup>47</sup>	20 (20)	10/10	66 (11.2)	>1 mo (acute)	Ischemic	Right: ACI	First right hemispheric ischemic stroke, MMSE score higher than 22
Lucas et al, 2013 <sup>48</sup>	10 (10)	2/8	69 (10)	1-15 mo	5 ischemic, 4 hemorrhagic, 1 combination	9 right, 1 left: MCA, ACA, PCA	Spatial neglect after first-ever unilateral right-hemisphere stroke (except 1 patient with left-hemisphere stroke)
Malhotra et al, 2006 <sup>49</sup>	3 (3)	Not specified	Not specified	>23 mo	Not specified	Right: f, t, p, in	Right-hemisphere patients, chronic neglect; DLPFC damage in 1 subject (to test proposal that guanfacine exerts its effects through DLPFC)

Abbreviations: ACA, anterior cerebral artery; ACI, anterior circulation infarcts; av, average; bg, basal ganglia; BIT, Behavioral Inattention Test; DLPFC, dorsolateral prefrontal cortex; f, frontal; in, insula; MCA, middle cerebral artery; MMSE, Mini-Mental State Examination; NET, neglect test; o, occipital; p, parietal; PCA, posterior cerebral artery; SD, standard deviation; st, striatum; t, temporal; TAP, Test Batterie zur Aufmerksamkeitsprüfung; th, thalamus.

\*Note that “unilateral neglect,” “hemispatial neglect,” or any other inconsistent labels are under the same overall visuospatial neglect syndrome, which is why those studies were included in the current systematic review.

concerning the nature, duration, frequency, and dosage of the medicaments used.

Overall, we must emphasize the explorative nature of the reviewed studies. Comprehensive characteristics of the studies are presented per class of medicaments in [Tables 3-5](#).

### *Dopaminergic Therapy*

Seven studies investigated dopaminergic therapy.<sup>4,30,41-45</sup> One study was considered to be of moderate quality.<sup>45</sup> The remaining 6 studies were considered to be of low quality.<sup>4,30,41-44</sup>

First, Gorgoraptis et al<sup>45</sup> used a double-blind, placebo-controlled A-B-A design to study the effects of rotigotine on VSN, spatial working memory, selective and sustained attention, and motor control. Outcome measures included an extensive battery of pen-and-paper and computerized tests (see [Table 3](#) for a more detailed description). Sixteen patients received a 9.0 mg rotigotine skin patch on a daily basis in the B-phase for 7-11 days. When compared to baseline and placebo conditions, VSN performance improved on the Mesulam Shape Cancellation test. All other tests (assessing VSN, spatial working memory, selective and sustained attention, and motor control) failed to show improvements of function.<sup>45</sup>

Second, Fleet et al<sup>30</sup> conducted a small-sample, open-label study. Two patients were given 15 mg of bromocriptine orally for 3-4 weeks on a daily basis and were tested before, during, and after treatment. Outcome measures included basic reaction tests (e.g., shoulder tapping and arm raising on command) and pen-and-paper neglect tests (letter, line, and shape cancellation, and line bisection). One patient showed a positive result on all measures compared to both baseline performance and performance after discontinuing treatment; the other patient (this patient had a frozen shoulder and could not reliably perform 2 of the 8 tests) showed positive results on 6 tests compared to baseline performance, but only on 4 tests compared to performance after treatment discontinuation.<sup>30</sup>

Third, Grujic et al<sup>41</sup> investigated the effect of bromocriptine on VSN. Seven patients received a single 2.5 mg dose of bromocriptine. The main outcome measure was a computerized target search paradigm. Patients were tested before and after receiving their dose. Results indicated an increase of the rightward bias: bromocriptine caused 6 out of 7 subjects to spend more time exploring the ipsilesional space, and therefore the relative VSN of the contralesional left hemispace increased. Target detection accuracy and reaction time did not change in either hemispace after administration of bromocriptine compared to baseline.<sup>41</sup>

Fourth, a single case report by Barrett et al<sup>43</sup> presented an absolute adverse effect of dopaminergic stimulation. The patient received an oral dose of

bromocriptine during 9 days, which was gradually increased until a peak dose of 20 mg was reached after 3 days. Subsequently, dose was gradually decreased. Performance on a line bisection task worsened while taking bromocriptine, and improved when bromocriptine was terminated.<sup>43</sup>

Fifth, Geminiani et al<sup>42</sup> conducted a placebo-controlled, open-label trial in which 4 patients received a single subcutaneous dose of 2 mg of apomorphine on the first day of the study, followed by a placebo injection 24 hours later. Outcome measures included pen-and-paper circle cancellation, counting, and pointing tests, which were administered before and after apomorphine and placebo administration. Performance at a circle cancellation test was positively modified by apomorphine: all patients crossed more targets after taking apomorphine compared to baseline and placebo control. Postapomorphine results of the counting and pointing tests did not differ significantly when compared to performance at baseline and after placebo control.<sup>42</sup>

Sixth, Mukand et al<sup>44</sup> used a case series design and included 4 patients to evaluate the efficacy of carbidopa L-dopa (Sinemet) on reducing left-sided VSN symptomatology. Patients received half a tablet of 25/100 mg of Sinemet 3 times daily for 2 days, followed by 1 tablet 3 times daily for the rest of the week. Patients were tested with a shortened version of the Behavioral Inattention Test (BIT) and the Functional Independent Measure (FIM) test before and after this week. Three patients showed enhanced BIT scores, and all 4 patients showed enhanced FIM scores after Sinemet intake. Results were presented as being significant, but *P* values were not mentioned.<sup>44</sup>

Last, a double-blind, placebo-controlled, within-subject study was performed by Buxbaum et al<sup>4</sup> using an A-B-A design. The effect of a 100 mg amantadine injection, given twice a day, on VSN was studied in 4 patients. In total, 13 tests were administered, including pen-and-paper tests (e.g., letter cancellation and line bisection; see [Table 3](#) for a more detailed description) and computerized tests (i.e., a Dual-Task and a lateralized target test and lateralized response test), as well as functional independency tests (Naturalistic Action Test) and questionnaires (e.g., Family Burden and Anosognosia). Reaction times on the Sustained Attention to Response Test (SART) improved significantly in 2 patients (patients 2 and 3), as well as the percentage of correct responses (patient 2) and mean response times in the lateralized tests (patient 4). However, negative effects were seen on lateralized mean response times (patient 4), on the Dual-Task (patient 2), and on the number of correct responses on the SART (patient 2). All other measures showed no significant effect.<sup>4</sup>

To summarize, only 1 study was found to be of moderate quality. This study found a positive effect of dopaminergic therapy on VSN.<sup>45</sup> Of the remaining

**Table 3.** Dopamine, study and intervention characteristics\*

Authors	Design	Patients (N)	Study characteristics				Intervention characteristics			
			Outcome measures	P value	Effect size	Measurements (follow-up†)	Aim	Intervention	Duration/intensity	Most important findings
Fleet et al, 1987 <sup>30</sup>	Open-label study	2	ST ES RA EC TP LB LC LEC GC	.004 (N1; all 8 tests) .16 (N2, all tests except limb akinesia)	Not available	Pre Post	Evaluate effects of dopaminergic stimulation (bromocriptine) on chronic hemispatial neglect	Bromocriptine (D2 dopamine agonist)	N1 reached 15 mg in 1 wk N2 reached 15 mg within 10 d Continuing for 4 wk	Bromocriptine induced an improvement in all tests evaluating hemispatial neglect. After stopping bromocriptine, the test results declined significantly as well.
Grujic et al, 1998 <sup>41</sup>	Open-label study	7	CTSP TTS  NP  RT ADT	Less than .05‡ (less time spent in left hemispace) Less than .05‡ (less number of pixels covered in left hemispace) NS NS	Not available	Pre Post	Study the effects of bromocriptine on visual search	Bromocriptine	Single dose, 2.5 mg	Bromocriptine caused the subjects to spend more time exploring the ipsilesional hemispace and therefore increased the relative neglect of the contralesional left hemispace. However, neither RT nor target detection accuracy did change. Bromocriptine thus had a differential impact on the exploratory–motor versus sensory–perceptual components of directed attention.
Geminiani et al, 1998 <sup>42</sup>	Placebo-controlled study	4	CCT  CPT	.012 (baseline versus on drugs) .093 (placebo versus on drugs) NS	1.78 1.30	Pre Post	Determine whether acute dopaminergic stimulation had differing effects on the premotor and perceptual aspects of the neglect syndrome	Apomorphine (D1 and D2 dopamine agonist)	Single dose, 2 mg, subcutaneously	The results suggest that dopaminergic neuronal networks may mediate, in different ways, both premotor and perceptual components of the neglect syndrome. The pointing (motor exploration) of CPT was more improved after apomorphine than the counting task (oculomotor exploration).
Barrett et al, 1999 <sup>43</sup>	Case report	1	LB	Less than .01‡	.08	Pre Post	Examine the effect of bromocriptine on line bisection	Bromocriptine	36 d poststroke, 5 mg twice daily; 39 d, 10 mg twice daily; 43 d, 10 mg daily; 44 d, 5 mg daily	Motor–intentional neglect worsened on bromocriptine. The patient's lesion on MRI showed right putaminal hyperintensity, thereby probably suppressing dopaminergic effects on right subcortical (basal ganglia) motor systems.
Mukand et al, 2001 <sup>44</sup>	Open-label study	4	sBIT FIM	NG NG	Not available	Pre Post	Evaluate the efficacy of carbidopa L-dopa in reducing left spatial neglect after stroke	Carbidopa L-dopa (precursor of dopamine)	25/100 mg half a tablet 3 times daily for 2 d and then 1 tablet 3 times daily	Three out of 4 subjects showed significant ( <i>P</i> values were not given) improvements in their modified BIT scores and their functional status on the FIM.

(continued on next page)

Table 3 (continued)

Authors	Design	Patients (N)	Study characteristics				Intervention characteristics			
			Outcome measures	P value	Effect size	Measurements (follow-up <sup>†</sup> )	Aim	Intervention	Duration/intensity	Most important findings
Buxbaum et al, 2007 <sup>4</sup>	Double-blind, placebo-controlled, within-subject design	4	LEC	NS	Not available	Pre Post	Evaluate whether amantadine has a positive effect on hemispatial neglect as had been seen in parkinsonian syndromes	Amantadine (glutamate antagonist)	Patients were titrated to 100 mg twice daily	Amantadine induced no change in the vast majority of measures. Only 4 measures revealed significant improvement, whereas 3 measures revealed a negative effect.
			LB	NS						
			LLC	NS						
			BT	NS						
			FT	NS						
			SART RT	.04 (case 2)						
				.01 (case 3)						
			CR	.01 (case 2) <sup>‡</sup>						
			DTT RT	.001 (case 2) <sup>‡</sup>						
			LTT	NS						
			LRT pC	.04 (case 2)						
			RT	.04 (case 3) <sup>‡</sup>						
				.002 (case 4)						
			AQ	NS						
			NAT	NS						
			FIM	NS						
			FBQ	NS						
Gorgoraptis et al, 2012 <sup>45</sup>	Double-blind, placebo-controlled, within-subject design	16	LB	NS	.13	Pre Post	Investigate whether rotigotine would have a beneficial effect on hemispatial neglect and its cognitive components in stroke patients and whether this effect would depend on the extent of preservation of the right prefrontal cortex	Rotigotine (D1 dopamine agonist)	Daily 9.0 mg, skin patch	Rotigotine induced an improvement in visual search, which was associated with an enhancement in selective attention but not with the measures of working memory or sustained attention. This improvement was not associated with the degree of preservation of the prefrontal cortex.
			MSC	.012 (on drug versus pre and post)						
				.039 (on drug versus post)						
			BC	NS						
			VSTS	NS						
			CSST	NS						
			RCT	NS						
			VSVT RT	NS						
			CR	NS						
			MI	NS						
			GPD	NS						
			NPT	NS						
			BBT	NS						
			10MW	NS						

Abbreviations: ADT, percentage of accurately detected targets; AQ, Anosognosia Questionnaire; BBT, Box and Block Test; BC, Bells Cancellation; BIT, Behavioral Inattention Test; BT, Bell Test; CCT, Circle Crossing Test; CPT, Counting and Pointing Test; CR, correct response; CSST, Corsi Spatial Span Test; CTSP, Computerized Target Search Paradigm; DTT, Dual-Task Test; EC, eye closure; ES, extinction to stimuli; FBQ, Family Burden Questionnaire; FIM, Functional Independent Measure; FT, Fluff Test; GC, geometric cancellation; GPD, grip and pinch dynamometry; LB, line bisection; LC, line cancellation; LEC, letter cancellation; LLC, large-letter cancellation; LTT, Lateralized Target Task; LRT, Lateralized Response Task; MI, motricity index; MRI, magnetic resonance imaging; MSC, Mesulam Shape Cancellation; NAT, Naturalistic Action Test; NG, not given; NP, number of pixels covered; NPT, Nine-Hole Peg Test; NS, not significant; pC, percent correct; RA, raising arms; RCT, revisiting previously cancelled targets; RT, reaction time; SART, Sustained Attention to Response Test; sBIT, shortened Behavioral Inattention Test; ST, shoulder tapping; TP, tongue protrusion; TTS, total time spent; VSTS, Visual Search Task on Touch Screen; VSVT, Visual Saliency and Vigilance Task; 10MW, 10-Meter Walk.

\*Note that "unilateral neglect," "hemispatial neglect," or any other inconsistent labels are under the same overall visuospatial neglect syndrome, which is why those studies were included in the current systematic review.

<sup>†</sup>Follow-up is mentioned if conducted at least 1 month after treatment.

<sup>‡</sup>Negative effect.

(low-quality) studies, 2 studies found a positive effect,<sup>30,42</sup> yet 3 studies found negative effects.<sup>4,41,43</sup> The positive effects were exclusively found on 1 out of 4,<sup>45</sup> on 6 out of 8,<sup>30</sup> and on 1 out of 3 tests,<sup>42</sup> which were used to measure VSN. One study found a positive effect of dopaminergic therapy on measures of behavioral inattention and functional independence.<sup>44</sup>

### *Cholinergic Therapy*

Three studies investigated cholinergic therapy (see Table 4). Two studies were considered to be of moderate quality,<sup>47,48</sup> and 1 study was considered to be of low quality.<sup>46</sup>

Lucas et al<sup>48</sup> described the effects of nicotine on spatial attention in a small-sample ( $n = 10$ ), double-blind, placebo-controlled within-subject study. Outcome measures included pen-and-paper Bells, letter, and shape cancellation tests, a line bisection test, and a compound-word reading test, as well as computerized cued (Posner paradigm) and lateralized detection tests. A single 10 mg dose of nicotine was administered through a transdermal patch. The average search performance of patients with VSN improved on all cancellation tests and in lateralized visual detection, as the number of target omissions reduced significantly and search time increased relative to placebo and baseline conditions. No significant improvement of the attentional bias was found on line bisection, compound-word reading, and cued detection tests.<sup>48</sup>

Furthermore, an open-label, randomized, and slightly larger sample ( $n = 20$ ) study was conducted by Paolucci et al<sup>47</sup> to evaluate the efficacy of rivastigmine. All subjects received cognitive rehabilitation and half of the group received add-on pharmacotherapy. This last group received 1.5 mg of rivastigmine twice a day for the first week. Thereafter, the dose was increased to 3 mg twice a day for 7 more weeks. Outcome measures included a letter cancellation test, the Barrage test, a sentence-reading test, and the Wundt–Jastrow Area Illusion Test, as well functional data scores at discharge (Barthel Index and Rivermead Mobility Index). Patients who received rivastigmine showed significantly improved letter cancellation and Wundt–Jastrow scores at discharge compared to the control group. No significant differences were found at follow-up, as the nonrivastigmine group further improved and achieved the same results as the rivastigmine group. In fact, the former group reached their maximum performance before the latter group.<sup>47</sup>

The study by Vossel et al<sup>46</sup> applied a small-sample ( $n = 9$ ), double-blind, placebo-controlled within-subject design to investigate whether cholinergic stimulation by nicotine facilitated attentional reorienting. The main measure of outcome was reaction time on a Posner cuing task. A Nicorette gum consisting of 2 mg of nicotine (Pharmacia/Pfizer, Helsingborg, Sweden) was chewed on for half an hour. The patients' reaction times were lower for both

valid and invalid trials after nicotine, without any differences in the magnitude of the left validity effect in the whole patient group. Responses were comparable in neutral and uncued trials.<sup>46</sup>

To summarize, all 3 studies found cholinergic therapy to significantly improve function on attentional reorienting,<sup>46</sup> spatial attention,<sup>47,48</sup> and functional measures,<sup>47</sup> but only in 3 out of 6<sup>48</sup> and in 2 out of 6 outcome measures used in these studies.<sup>47</sup> Most importantly, the observed positive effect in the Paolucci et al<sup>47</sup> study disappeared at follow-up; therefore, rivastigmine was merely found to accelerate early-phase cognitive recovery in Paolucci et al's study.

### *(Nor)Adrenergic Therapy*

The only identified study on noradrenergic therapy by Malhotra et al was considered to be of low quality.<sup>49</sup> Three right-hemisphere patients with chronic VSN received a placebo and a single dose of oral guanfacine (29 µg/kg) 1 week apart in a counterbalanced and double-blind manner (see Table 5). Outcome measures included pen-and-paper tests (line bisection and Bells cancellation), computerized tests for measures of space exploration, single-target visual search, and naming objects, as well as a sustained attention test and a spatial working memory test. One patient performed significantly better after guanfacine administration compared to placebo on the space exploration test as total search time increased. None of the patients performed significantly better on pencil-and-paper VSN tests after guanfacine administration compared to placebo.<sup>49</sup>

To summarize, even though 2 out of 3 patients cancelled more stars post guanfacine administration, line bisection deviations increased in one of these subjects and overall performance on pen-and-paper VSN tests did not improve significantly after (nor)adrenergic therapy.

## **Discussion**

The aims of this review were (1) to give an overview of human studies investigating pharmacotherapy to ameliorate VSN and (2) to evaluate the quality of those studies. We found 11 studies, evaluating 3 pharmacological approaches: 7 studies on dopaminergic therapy, 3 studies on cholinergic therapy, and 1 study on (nor)adrenergic therapy. Quality assessment showed that none of the reviewed studies were of high quality; only 3 recent studies were of moderate quality; and the 8 remaining studies were of low quality, according to our criteria. None of the studies completed all full requirements of a randomized controlled trial.

The results of the dopaminergic studies (one of moderate quality, six of low quality) were not consistent to draw firm conclusions: both promising effects (i.e., decrease of VSN) and increase of VSN were observed. Cholinergic treatment (2 studies of moderate quality, 1

**Table 4.** *Acetylcholine, study and intervention characteristics\**

Authors	Design	Patients (N)	Study characteristics				Intervention characteristics			
			Outcome measures	P value	Effect size	Measurements (follow-up <sup>†</sup> )	Aim	Intervention	Duration/intensity	Most important findings
Vossel et al, 2010 <sup>46</sup>	Double-blind, placebo-controlled within-subject crossover design	9	LCP (RT)	Less than .05 (drug main) Less than .01 (cue main) Less than .01 (hemimain)	Not available	Pre Post	Investigate whether cholinergic stimulation with nicotine facilitates attentional reorienting in spatial neglect patients	Nicotine (Nicorette polacrilex gum, Pharmacia/Pfizer)	2 mg, chewed for 35 min at a rate of approximately 1 chew every 3 s	Nicotine speeded up RTs in valid and invalid trials nonspecifically, without modulating the validity effect in the location-cuing task in the whole group of patients.  In patients with chronic spatial neglect, the performance in the location-cuing paradigm can be modulated by a cholinergic stimulant provided that the lesion spares right parietal and temporal cortices
Paolucci et al, 2010 <sup>47</sup>	Open-label, randomized, experimental design	20	LC WJ BI RMI B SR	.026 .039 NS NS NS NS	1.09 .99	Pre Post  1 mo	Evaluate efficacy and safety of rivastigmine as add-on treatment to specific cognitive rehabilitation for unilateral spatial neglect	Rivastigmine (AchEI)	1.5 mg twice a day (first week) 3 mg twice a day for next 7 wk	RIV + patients showed significantly better discharge scores compared to controls. However, no significant difference at follow-up (due to further improvement of controls) was observed. Rivastigmine may accelerate recovery.
Lucas et al, 2013 <sup>48</sup>	Double-blind, placebo-controlled within-subject design	10	BC O ST LC O ST SC O ST CWR LB CD LVD	Less than .0001 Less than .01 Less than .0001 Less than .01 Less than .0001 Less than .01 NS NS NS Less than .05	.69 .48	Pre Post	Evaluate effects of procholinergic therapy (nicotine) on spatial attention	Nicotine (Nicorette patch)	Single dose, 10 mg, transdermal	Nicotine induced systematic improvement on cancellation tasks and facilitated orienting to single visual targets but had no significant effect on other tests. Results suggest a global effect of nicotine on arousal and attention, but no effect on other spatial mechanisms

Abbreviations: AchEI, acetylcholinesterase inhibitor; B, barrage; BC, Bells Cancellation; BI, Barthel Index; CD, cued detection; CWR, compound-word reading; LB, line bisection; LC, letter cancellation; LCP, location-cuing paradigm; LVD, lateralized visual detection; NS, not significant; O, omission; RMI, Rivermead Mobility Index; RT, reaction time; SC, shape cancellation; SR, sentence reading; ST, search time; WJ, Wundt–Jastrow.

\*Note that “unilateral neglect,” “hemispatial neglect,” or any other inconsistent labels are under the same overall visuospatial neglect syndrome, which is why those studies were included in the current systematic review.

<sup>†</sup>Follow-up is mentioned if conducted at least 1 month after treatment.

**Table 5.** Norepinephrine, study and intervention characteristics\*

Authors	Design	Patients (N)	Study characteristics				Intervention characteristics			
			Outcome measures	P value	Effect size	Measurements (follow-up <sup>†</sup> )	Aim	Intervention	Duration/intensity	Most important findings
Malhotra et al, 2006 <sup>49</sup>	Double-blind, placebo-controlled within-subject design	3	SA O	.05 (case 1)	5.09	Pre Post	Investigate whether guanfacine improves leftward neglect by enhancing maintained attention when exploring space	Guanfacine (noradrenergic agonist that modulates DLPFC)	Single dose (29 µg/kg body weight), oral	Guanfacine improves leftward space exploration in selected right-hemisphere patients with neglect. Positive effects associated with extended ability to maintain attention on task
			RT	NS (cases 2 and 3)	14.4					
				Less than .0001 (case 1)						
				NS (cases 2 and 3)						
			LB	Not specified						
			BC	Not specified						
			STVS	Not specified						
			PON	Not specified						
			SWM	Not specified						
			SET	Less than .0001 (case 1)	13.0					
				.017 (case 2)						No improvement in patient 3 (DLPFC)
					6.78					Consistent with proposal that guanfacine exerts its effects via actions on DLPFC

Abbreviations: BC, Bells Cancellation; DLPFC, dorsolateral prefrontal cortex; LB, line bisection; NS, not significant; O, omission; PON, projected objects named; RT, reaction time; SA, sustained attention; SET, Space Exploration Task; STVS, single-target visual search; SWM, spatial working memory.

\*Note that “unilateral neglect,” “hemispatial neglect,” or any other inconsistent labels are under the same overall visuospatial neglect syndrome, which is why those studies were included in the current systematic review.

<sup>†</sup>Follow-up is mentioned if conducted at least 1 month after treatment.

study of low quality) was found to be effective in ameliorating VSN symptoms in all 3 studies. However, positive effects were measured on some, yet not all tests. Only 1 (nor)adrenergic study showed some positive effects, but the quality of this study was considered low, so no firm conclusions can be drawn. Moreover, none of the studies reported effect sizes, which hampered the interpretation of the study outcomes. Effect sizes are needed to evaluate clinical significance, whereas *P* values only represent the randomness of the obtained effects.<sup>50</sup> Overall, the methodological limitations of the included studies limit us in drawing clear conclusions on the effectiveness of the pharmacological treatment of VSN.

Our statements are comparable to those made in a recently published Cochrane review on the pharmacological treatment of VSN, in which 2 identical cholinergic studies have been reviewed.<sup>39</sup> However, the Cochrane review included a smaller number of studies and applied limited quality assessment criteria. The current review therefore provides a more complete overview of available studies on the pharmacological treatment of VSN.

Several cognitive processes appeared to be of importance regarding the potential mechanisms underlying the pharmacological treatment of VSN. Cholinergic treatment seemed to be the most effective in ameliorating VSN symptoms, which suggests that the orienting, perhaps most moldable, network of attention plays a role in VSN.<sup>32-34</sup> Dopaminergic and (nor)adrenergic stimulations decreased VSN symptoms in some cases. Hence, the alerting (noradrenaline) and executive (dopamine) networks might influence VSN as well.<sup>32-34</sup>

In the current review, it is clear that none of the studies, no matter what class of medicaments, showed a clear-cut improvement of VSN post stroke. Additionally, the methods of the 11 reviewed studies differed too much to compare them properly on inclusion criteria, outcome measures, medicaments used, their administration, and timing. The lack of large improvements on VSN and the different methods that were used, combined with the overall moderate-to-low quality of the studies, limits us in recommending a specific pharmacological approach to treat VSN. Therefore, we feel that a good starting point for future pharmacological studies targeting cognitive functional improvement in general, or the amelioration of VSN in particular, should be comparability. Below, we will discuss how to target this comparability.

First of all, varying diagnostic criteria and many different tests were used to assess VSN in the 11 reviewed studies. This variability turns out problematic when trying to compare studies. As described in this review, positive effects of pharmacotherapy on VSN symptoms were observed on some but not all tests. In this light, a consensus on, and implementation of, a more or less standard battery of tests could help future researchers to overcome these problems of comparison. At the level of function, the most widely used tests are cancellation tests,

line bisection tests, copying, and drawing. With respect to rehabilitation, tests at the level of activities of daily living should also be included. The Catherine Bergego Scale may be the solution, as this observation scale measures VSN in basic activities of daily living.<sup>51</sup>

Additionally, the more standard pen-and-paper tests (including the abovementioned cancellation, line bisection, copying, and drawing tests) are generally regarded as not sensitive enough to capture mild VSN, especially in the late subacute or chronic phase. The use of (tablet) computers and computerized tests would greatly improve the level of test specificity. For example, more accurate and precise reaction times can be recorded<sup>52,53</sup>; search strategies during cancellation tests can be evaluated<sup>54</sup>; and stimuli can be presented in a dynamic way (e.g., during cuing tests).<sup>55</sup> As a result, these tests are able to identify more subtle deficits that standard pen-and-paper tests might miss,<sup>52,56-58</sup> which enables detection of VSN at the immediate moment of occurrence. Furthermore, common clinical tests might lose accuracy in the chronic phase of VSN.<sup>52</sup> Computerized tests, on the other hand, are found to maintain accuracy, even in the chronic phase of VSN.<sup>52</sup> Furthermore, tests in a virtual reality environment may be an effective tool to assess VSN. Virtual reality allows patients to interact with an environment similar to real-life experience, but in a safe and controlled manner.<sup>56,59</sup> Hence, a more dynamic test is created, which provides better insight into the impairments of daily life.

One more issue of future interest could lie in the promising field of neuroimaging. New techniques could help to map neural networks, thereby visualizing changes induced by the medicament. Although costly, these techniques could help tackle the problems of interassessor variability in the assessment of clinical observations and problems related to the standardized testing of cognitive skills.

With respect to the pharmacological treatments, many different substances and subsequent doses were used in the reviewed studies. However, none of the reviewed studies analyzed the variability in dose-responses. In our opinion, future research should aim to make inferences on the effects of medicaments based on a spectrum of doses within the analysis of a medicament. In this way, information could be gathered on the strength and duration of the pharmaceutical effect. This should allow future researchers to make clearer recommendations in the remediation of VSN.

Importantly, time post stroke was highly variable in the reviewed studies. Studies were conducted with patients in both subacute and chronic phases post stroke. However, only results of studies with patients in the chronic phase post stroke can be reliably taken into account, as up to 3 months spontaneous recovery could have been achieved.<sup>3,60</sup> In case patients in the subacute phase post stroke are included, a control group is necessary for future research to monitor the effects of spontaneous recovery.

Only 1 of our 11 reviewed studies included a control group<sup>47</sup>; all the others lacked this important feature.

The addition of a follow-up phase would also positively add to the level of information gathering. Only one of the reviewed studies included a follow-up phase in which participants were assessed 1 month post treatment. Thus, in the other 10 studies, no information was given regarding the duration of the beneficial influence of pharmaceutical treatment. Future research should be able to tackle this problem and include one or more follow-up measurements, ideally up to 3 months post treatment. However, shorter time frames are the primary concern, as they will possibly reduce outcome variation due to events unrelated to the study, and therefore allow for the accurate assessment of functional outcomes and drug safety.<sup>61</sup>

### *Study Limitations*

The aim of the current review was to give an overview of human studies investigating pharmacotherapy to ameliorate VSN, thereby leaving out a substantial amount of data or results from animal studies targeting disorders of attention or VSN with pharmacological treatment. Although human studies are most relevant for rehabilitation purposes, results on timing of treatment, timing of drug administration, dose-response interactions, and lesion site differences from animal studies might have given better insight into how to set up better human studies.

Another limitation could lie in our selection process. We excluded studies in which attention deficits were treated, based on the lack of outcome measures aimed at the VSN syndrome. In fact, several human studies used pharmacotherapy as a treatment of attention and cognitive impairments after stroke.<sup>62-68</sup> For example, both Jorge et al and Adams and Robinson found that anti-depressives may enhance motor and cognitive recovery after stroke.<sup>66,67</sup> Perhaps, antidepressives could also beneficially influence recovery from VSN post stroke. Therefore, these animal and human studies should be kept in mind regarding future investigation.

### **Conclusions**

In conclusion, due to the methodologically weak quality of nearly all reviewed studies, we cannot make any clear-cut inferences on the effectiveness of pharmacotherapy on VSN post stroke. Nevertheless, regarding the 3 substances, we cautiously consider cholinergic therapy to be the most promising in treating VSN. Therefore, we believe future research should focus on cholinergic therapy.

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