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1 **Running title: Pharmacological Treatment of Neglect**

2 **Pharmacological Treatment of Visuospatial Neglect: A Systematic Review**

3

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23

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30

## 31 Abstract

32 **Objectives:** The aims of the current review are (1) to give an overview of human studies  
33 investigating pharmacotherapy to ameliorate visuospatial neglect, and (2) to evaluate the  
34 quality of those studies.

35 **Methods:** A systematic literature search using PubMed, Scopus, and ResearchGate was  
36 conducted in regard to studies that evaluated pharmacological interventions aiming to  
37 ameliorate post-stroke visuospatial neglect. The search was limited in the following features:  
38 species (human), adults ( $\geq 18$  years of age), language (English), and type of neglect  
39 (visuospatial). Two independent authors extracted data on study content and effectiveness and  
40 evaluated the quality of studies and methods.

41 **Results:** A total of 11 studies were identified. Three studies were considered to be of moderate  
42 quality, the others of low quality. Seven studies represent dopaminergic, three cholinergic, and  
43 one noradrenergic treatment. Three dopaminergic studies showed primarily positive effects of  
44 dopaminergic stimulation on visuospatial neglect, whereas three others showed adverse effects.  
45 All three cholinergic studies found positive effects in some outcome measures concerning  
46 visuospatial neglect. The noradrenergic stimulation improved maintaining attention when  
47 exploring space.

48 **Conclusions:** Currently, cholinergic therapy might be the best option for future research.  
49 However, we must emphasize the explorative nature and limited quality of the reviewed  
50 studies.

51

## 52 **Introduction**

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

61

62 Due to the high prevalence of post-stroke VSN and its negative consequences, effective  
63 remediation techniques are needed. Promising remediation techniques have emerged over the  
64 last decades, including prism adaptation (8–10), virtual reality training (6,11), visuospatial and  
65 scanning training (12), galvanic vestibular stimulation (13,14), transcutaneous electrical nerve  
66 stimulation (15), motivational manipulations (16), optokinetic stimulation (17), video-game  
67 based remediation (10,18), and upcoming non-invasive brain stimulation techniques such as  
68 transcranial magnetic stimulation (19,20) and transcranial direct current stimulation (21–23).  
69 However, the effectiveness of almost all techniques has not been investigated thoroughly  
70 enough to allow firm conclusions (6,24). Pharmacological techniques represent another  
71 promising remediation approach. As pharmacotherapy affects the whole brain, it addresses the

72 factors causing VSN, instead of using compensational techniques to conceal deficits.  
73 Therefore, pharmacotherapy will be the topic of the current review.

74

#### 75 **Pharmacotherapy in VSN: a brief history**

76 Several animal studies on the effectiveness of pharmacotherapy have been published over the  
77 last three decades (25–29), and have generally focussed on dopaminergic agonists and  
78 progesterone. VSN symptoms have been assessed by regular (25,26) and Morris water mazes  
79 (26,27), adhesive removal tests (27,28), and simple observations of turn direction to stimuli  
80 (29) in a variety of induced-stroke models (25–29). In general, results showed positive effects  
81 of progesterone (26–28) and apomorphine (29) on VSN, and of amphetamine on cognitive  
82 functioning (25). Similarly, human studies on the topic emerged about three decades ago (30).  
83 Yet, in human studies pharmacotherapy does not get as much attention as the other techniques  
84 in treating VSN.

85

#### 86 **How pharmacotherapy might work**

87 Neuronal functioning depends on network structures, the balance between excitation and  
88 inhibition of neurons, and the resulting impulse transmission between connected neurons.  
89 About 50 neurotransmitters have been identified, either excitatory or inhibitory (31). If a  
90 neurological condition is caused by an imbalance in excitation and inhibition while neuronal  
91 connections are functionally preserved, manipulating these electrochemical processes may  
92 improve neuronal function. Neurological ‘hypofunction’ like VSN may improve by decreasing  
93 inhibition and/or increasing excitation. In this manner, pharmacological agents can have  
94 positive therapeutic effects.

95

96 As the core symptoms of VSN comprise attention deficits, it is evident to focus on those  
97 neurotransmitters that exert their effects on attention networks. Three networks of attention can  
98 be distinguished, namely the alerting, orienting, and executive network. VSN has been  
99 associated with all of them (32–34). The alerting network is modulated by noradrenaline  
100 (33,35,36). The inhibitory or excitatory effects are complex, but in general terms noradrenaline  
101 activates the brain and body for action, which is reflected in functions like increased alertness,  
102 focus and attention. The orienting network has been linked to acetylcholine (32,33).  
103 Acetylcholine is the major neurotransmitter in the peripheral nervous system at the  
104 neuromuscular junction, but also in the autonomic nervous system. In the brain it has a  
105 modulating effect on information processing, including plasticity, arousal and sustained  
106 attention. It usually has an excitatory effect. Acetylcholine agonists can directly act on  
107 receptors and increase receptor activation. The executive network of attention is modulated by  
108 dopamine (33,35), and believed to affect the spatial bias in VSN (37). Dopamine is a  
109 neurotransmitter found in distinct dopamine pathways, with a modulating role in specific  
110 functional networks (i.e. involving reward-motivated behavior). The inhibitory and excitatory  
111 effects have effect on ion channels via a second messenger system and depend on the  
112 postsynaptic type of dopamine receptor. So, patients with VSN could benefit from  
113 pharmacological intervention through modulation of surviving neuronal networks by targeting  
114 specific neurotransmitters (38).

115

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

119

120 **Objectives and distinctiveness**

121 The aims of the current review are (1) to give an overview of human studies investigating  
122 pharmacotherapy to ameliorate VSN symptoms, and (2) to evaluate the quality of those studies.  
123 These aims parallel those made in a Cochrane review (39) on the pharmacological treatment of  
124 VSN, published shortly before we completed the current review. However, several differences  
125 positively distinguish the current review from the Cochrane review. First, strict inclusion  
126 criteria for a Cochrane review limited the number of reviewed studies: only (quasi-)RCTs were  
127 included, resulting in a total of two studies. 'Lower-quality' studies however should also be  
128 reported, as they may add important knowledge for future studies, especially given potential  
129 shortcomings in their designs. Additionally, we applied more criteria for assessment compared  
130 to the Cochrane review, such as the allocation of patients and blinding treatment officers, which  
131 gives a more extensive overview of the current state of art of the field. In sum, the current  
132 review provides a more comprehensive overview of available studies on pharmacological  
133 treatment of VSN and may therefore give a broader overview of the current state of art of the  
134 field.

135

## 136 **Methods**

### 137 **Search methods and article selection**

138 Initially, the systematic literature search was performed using Pubmed, Scopus, and  
139 ResearchGate for studies published between January 2000 and July 2016 using the terms:  
140 Neglect, Visual Neglect, Spatial Hemineglect, Hemispatial Neglect, Unilateral neglect,  
141 Unilateral Spatial Neglect, Unilateral Hemispatial Neglect, Visuospatial Neglect, Visuospatial  
142 Hemi-Neglect, Spatial Neglect, Visual Inattention, Spatial Inattention, Visual Hemispatial  
143 Inattention, Hemispatial Inattention, Visual Hemineglect, Visual Hemi-Neglect, Sensory  
144 Neglect, Personal Neglect, Behavioral Neglect, Behavioural Neglect, Motor Neglect, Hemi-  
145 inattention, Peri-Personal Neglect, Peripersonal Neglect, Pharmacotherapy, Remediation,

146 Rehabilitation, Medication, Therapy, (Nor)Epinephrine, (Nor)Adrenaline, Dopamine, and  
147 Choline. Note that ‘unilateral neglect’, ‘hemispatial neglect’, or any other inconsistent labels  
148 are under the same overall VSN syndrome, which is why those terms were included in the  
149 current search. The search was limited in the following features: species (human), adults ( $\geq 18$   
150 years of age), language (English), and type of neglect (visuospatial). Intervention studies  
151 aiming at enhancing attention and/or decreasing VSN symptoms post-stroke were selected  
152 when they met the following inclusion criteria: (1) study population described patients  
153 experiencing visuospatial attention deficits resulting from stroke, and (2) the study reported  
154 outcome measures aimed directly at the VSN syndrome, or aimed at general attention, which  
155 included subtests aimed at the VSN syndrome. Due to limited search results (seven studies),  
156 we additionally released our time span criterion to include studies published in any year, and  
157 found four additional studies published prior to 2000. These studies were subsequently  
158 included for review.

159

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

163

#### 164 **Data extraction**

165 J.v.d.K. and M.D. independently performed the data extraction. Extracted data was compared  
166 and discrepancies were discussed amongst J.v.d.K. and M.D. The following study  
167 characteristics were extracted from the articles: study design, number of patients, outcome  
168 measures, p-value, effect size (calculated when possible given the reported data in the original  
169 papers), and timing of measurements. The following intervention characteristics were  
170 extracted: aim of the intervention, type of intervention, duration (minutes to weeks), and



171 intensity (micro- to milligrams). The following patient characteristics were extracted:  
172 diagnostic criteria, age, sex, time post-stroke, stroke type, and lesion site.

173

#### 174 **Quality assessment**

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

187

188

#### 189 **Results**

190 Initially, 38 articles were identified, 11 of which met the inclusion criteria (see Figure 1 for a  
191 flowchart of the article selection process). Of these studies, seven studies investigated  
192 dopaminergic therapy, three studies considered cholinergic therapy, and one study targeted  
193 (nor)adrenergic therapy. Findings of the methodological quality of the studies, based on the  
194 elements mentioned above, are presented in Table 1. There was an initial 95% agreement  
195 between J.v.d.K and M.D. regarding quality assessment, which was 100% after consultation.

196 None of the studies were qualified to be of high quality according to our criteria, three studies  
197 were considered to be of moderate quality (41–43) and the other eight were considered low  
198 quality studies (4,30,44–49). An overview of study and participant characteristics is listed in  
199 Table 2. Only one study (42) included a true patient control group, while the remaining ten  
200 studies (4,30,41,43–49) used an A-B(-A) design in which all individual patients served as their  
201 own control. We considered four studies in the chronic phase (4,42,45,49), one study in the  
202 sub-acute phase (47), and one study in the acute phase post-stroke (48). Time post-stroke was  
203 variable in the remaining five studies, in which both patients in the sub-acute phase and patients  
204 in the chronic phase were included (30,41,43,44,46). Only five studies (43,45–47,49) focussed  
205 primarily on VSN by using exclusively VSN tests (e.g. bisection, cancellation, visual search  
206 and detection tests) as outcome measures, while six studies (4,30,41,42,44,48) focussed more  
207 generally on recovery or enhancing attention, and additionally included VSN tests in their  
208 outcome measures. None of the 11 studies reported effect sizes. Six studies reported enough  
209 data to calculate effect sizes ourselves (41–43,45–47), these are presented in Tables 3-5.

210

211 Discrepancies were also observed regarding patients characteristics, such as diagnostic criteria,  
212 stroke type, and lesion site. Diagnostic criteria regarding VSN were highly variable amongst  
213 all studies and many different assessments were used in each study. Eight (4,41–44,46,47,49)  
214 out of 11 studies reported assessing VSN prior to the study. Five of these studies  
215 (42,43,46,47,49) reported patients' scores on these assessments. Stroke type was unaccounted  
216 for in three (4,44,45) out of 11 studies. Overall, ischemic stroke was reported more frequently  
217 compared to haemorrhagic stroke. Concerning lesion site, all dopaminergic studies reported on  
218 hemispheric lesion location, which were all right-sided (4,30,41,44,46–48). The cholinergic  
219 studies all included right hemispheric patients too, with one patient in two studies showing  
220 additional left-hemispheric lesions (42,43). Additional information on affected arteries was

221 provided in two studies (42,43). Three studies analysed patients' lesion sites more thoroughly  
222 by means of CT and/or MRI data (41,43,49), and the effect of specific lesion location on  
223 therapy effectiveness was evaluated in two additional studies (44,47). Moreover, discrepancies  
224 were observed concerning the nature, duration, frequency, and dosage of the medicaments  
225 used.

226

227 Overall, we must emphasize the explorative nature of the reviewed studies. Comprehensive  
228 characteristics of the studies are presented per class of medicaments in Tables 3-5.

229

### 230 **Dopaminergic therapy**

231 Seven studies investigated dopaminergic therapy (4,30,41,44,46–48). One study was  
232 considered to be of moderate quality (41). The remaining six studies were considered to be of  
233 low quality (4,30,44,46–48) .

234

235 First, Gorgoraptis et al. (2012) used a double-blind, placebo-controlled A-B-A design to study  
236 the effects of rotigotine on VSN, spatial working memory, selective and sustained attention  
237 and motor control. Outcome measures included an extensive battery of pen-and-paper and  
238 computerized tests (see Table 3 for a more detailed description). 16 patients received a 9.0 mg  
239 rotigotine patch on a daily basis in the B-phase for 7 to 11 days. When compared to baseline  
240 and placebo conditions, VSN performance improved on the Mesulam shape cancellation test.  
241 All other tests (assessing VSN, spatial working memory, selective and sustained attention, and  
242 motor control) failed to show improvements of function (41).

243

244 Second, Fleet et al. (1987) conducted a small-sample, open-label study. Two patients were  
245 given 15 mg of bromocriptine orally for 3 to 4 weeks on a daily basis and were tested prior to,

246 during, and after treatment. Outcome measures included basic reaction tests (e.g. shoulder  
247 tapping and arm raising on command) and pen-and-paper neglect tests (letter, line and shape  
248 cancellation, and line bisection). One patient showed a positive result on all measures compared  
249 to both baseline performance and performance after discontinuing treatment, the other patient  
250 (this patient had a frozen shoulder and could not reliably perform two of the eight tests) showed  
251 positive results on six tests compared to baseline performance, but only on four tests compared  
252 to performance after treatment discontinuation (30).

253

254 Third, Grujic et al. (1998) investigated the effect of bromocriptine on VSN. Seven patients  
255 received a single 2.5 mg dose of bromocriptine. The main outcome measure was a  
256 computerized target search paradigm. Patients were tested prior to, and after receiving their  
257 dose. Results indicated an increase of the rightward bias: bromocriptine caused six out of seven  
258 subjects to spend more time exploring the ipsilesional space and therefore the relative VSN of  
259 the contralesional left hemispace increased. Target detection accuracy and reaction time did  
260 not change in either hemispace after administration of bromocriptine compared to baseline  
261 (44).

262

263 Fourth, a single case report by Barrett et al. (1999) presented an absolute adverse effect of  
264 dopaminergic stimulation. The patient received an oral dose of bromocriptine during 4 weeks,  
265 which was gradually increased until a peak dose of 20 mg was reached after 2 weeks. Forth,  
266 the dose was gradually decreased. Performance on a line bisection task worsened while taking  
267 bromocriptine, and improved when bromocriptine was terminated (47).

268

269 Fifth, Geminiani et al. (1998) conducted a placebo-controlled, open-label trial in which four  
270 patients received a single subcutaneous dose of 2 mg of apomorphine on the first day of the

271 study, followed by a placebo injection 24 hours later. Outcome measures included a pen-and-  
272 paper circle cancellation, counting, and pointing test, which were administered prior to and  
273 after apomorphine and placebo administration. Performance at a circle cancellation test was  
274 positively modified by apomorphine: all patients crossed more targets after taking apomorphine  
275 compared to baseline and placebo control. Post-apomorphine results of the counting and  
276 pointing tests did not differ significantly when compared to performance at baseline and after  
277 placebo control (46).

278

279 Sixth, Mukand et al. (2001) used a case series design and included four patients to evaluate the  
280 efficacy of carbidopa L-dopa (Sinemet) on reducing left-sided VSN symptomatology. Patients  
281 received half a tablet of 25/100 mg of Sinemet 3 times daily for 2 days, followed by one tablet  
282 3 times daily for the rest of the week. Patients were tested with a shortened version of the  
283 Behavioural Inattention Test (BIT) and Functional Independent Measure (FIM) test prior to,  
284 and after this week. Three patients showed enhanced BIT scores, and all four patients showed  
285 enhanced FIM scores after Sinemet intake. Results were presented as being significant, but p-  
286 values were not mentioned (48).

287

288 Last, a double-blind, placebo-controlled, within-subject study was performed by Buxbaum et  
289 al. (2007), using an A-B-A design. The effect of a 100 mg amantadine injection, given twice a  
290 day, on VSN was studied in four patients. In total, 13 tests were administered, including pen-  
291 and-paper tests (e.g. letter cancellation and line bisection; see Table 3 for a more detailed  
292 description) and computerized tests (i.e. Dual-Task test and the lateralized target and lateralized  
293 response test), as well as functional independency tests (Naturalistic Action Test) and  
294 questionnaires (e.g. Family Burden and Anosognosia). Reaction times on the Sustained  
295 Attention to Response Test (SART) improved significantly in two patients (patient 2 and 3), as

296 well as the percentage of correct responses (patient 2), and mean response times in the  
297 lateralized tests (patient 4). However, negative effects were seen on lateralized mean response  
298 times (patient 4), the Dual-Task test (patient 2), and on the number of correct responses on the  
299 SART (patient 2). All other measures showed no significant effect (4).

300

301 To summarize, only one study was found to be of moderate quality. This study found a positive  
302 effect of dopaminergic therapy on VSN (41). Of the remaining (low-quality) studies, two  
303 studies found a positive effect (30,46), yet three studies found negative effects (4,44,47). The  
304 positive effects were exclusively found on one out of four (41), on six out of eight (30), and on  
305 one out of three tests (46), which were used to measure VSN. One study found a positive effect  
306 of dopaminergic therapy on measures of behavioural inattention and functional independence  
307 (48).

308

### 309 **Cholinergic therapy**

310 Three studies investigated cholinergic therapy (see Table 4). Two studies were considered to  
311 be of moderate quality (42,43), and one study was considered to be of low quality (49).

312

313 Lucas et al. (2013) described the effects of nicotine on spatial attention in a small sample  
314 (n=10), double-blind, placebo-controlled within-subject study. Outcome measures included  
315 pen-and-paper Bells, letter, and shape cancellation tests, a line bisection test, and a compound-  
316 word reading test, as well as computerized cued (Posner's paradigm) and lateralized detection  
317 tests. A single, 10 mg dose of nicotine was administered through a transdermal patch. The  
318 average search performance of patients with VSN improved on all cancellation tests and in  
319 lateralized visual detection, as the number of target omissions reduced significantly and search  
320 time increased relative to placebo and baseline conditions. No significant improvement of the

321 attentional bias was found on line bisection, compound-word reading, and cued detection tests  
322 (43).

323

324 Furthermore, an open-label, randomized, and slightly larger sampled (n=20) study was  
325 conducted by Paolucci et al. (2010) to evaluate efficacy of rivastigmine. All subjects received  
326 cognitive rehabilitation and half of the group received add-on-pharmacotherapy. This last  
327 group received 1.5 mg of rivastigmine twice a day for the first week. Thereafter, the dose was  
328 increased to 3 mg twice a day for seven more weeks. Outcome measures included a letter  
329 cancellation test, the Barrage test, a sentence-reading test, and the Wundt-Jastrow Area Illusion  
330 Test, as well functional data scores at discharge (Barthel Index and Rivermead Mobility Index).  
331 Patients who received rivastigmine showed significantly improved letter cancellation and  
332 Wundt-Jastrow scores at discharge compared to the control group. No significant differences  
333 were found at follow-up, as the non-rivastigmine group further improved, and achieved the  
334 same results as the rivastigmine group. In fact, the former group reached their maximum  
335 performance before the latter group (42).

336

337 The study by Vossel et al. (2010) applied a small sample (n=9), double-blind, placebo-  
338 controlled within-subject design to investigate whether cholinergic stimulation by nicotine  
339 facilitated attentional reorienting. The main measure of outcome was reaction time on a Posner  
340 cueing task. A Nicorette gum consisting of 2 mg of nicotine was chewed on for half an hour.  
341 Patients' reaction times were lower for both valid and invalid trials after nicotine, without any  
342 differences in the magnitude of the left validity effect in the whole patient group. Responses  
343 were comparable in neutrally and uncued trials (49).

344

345 To summarize, all three studies found cholinergic therapy to significantly improve function on  
346 attentional reorienting (49), spatial attention (42,43), and functional measures (42), but only on  
347 three out of six (43), and two out of six outcome measures used in these studies (42). Most  
348 importantly, the observed positive effect in the Paolucci et al. (2010) study disappeared at  
349 follow-up, therefore rivastigmine was merely found to accelerate early-phase cognitive  
350 recovery in this study.

351

### 352 **(Nor)adrenergic therapy**

353 The only identified study on noradrenergic therapy by Malhotra et al. (2006) was considered  
354 to be of low quality (45). Three right-hemispheric patients with chronic VSN received a single  
355 placebo injection and a 29 µg/kg guanfacine injection one week apart in a counterbalanced and  
356 double-blind manner (see Table 5). Outcome measures included pen-and-paper tests (line  
357 bisection and Bells cancellation), computerized tests for measures of space exploration, single  
358 target visual search, and naming objects, as well as a sustained attention and a spatial working  
359 memory test. One patient performed significantly better after guanfacine compared to placebo  
360 on the space exploration test, as total search time increased. None of the patients performed  
361 significantly better on pencil-and-paper VSN tests after guanfacine compared to placebo (45).

362

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

367

## 368 **Discussion**



369 The aims of this review were (1) to give an overview of human studies investigating  
370 pharmacotherapy to ameliorate VSN, and (2) to evaluate the quality of those studies. We found  
371 11 studies, evaluating three pharmacological approaches: seven studies on dopaminergic  
372 therapy, three studies on cholinergic therapy, and one study on (nor)adrenergic therapy. Quality  
373 assessment showed that none of the reviewed studies were of high quality, only three recent  
374 studies were of moderate quality, and the eight remaining studies were of low quality,  
375 according to our criteria. None of the studies completed all full requirements of a randomized  
376 controlled trial.

377

378 The results of the dopaminergic studies (one of moderate quality, six of low quality) were not  
379 consistent to draw firm conclusions: both promising effects (i.e. decrease of VSN) and increase  
380 of VSN were observed. Cholinergic treatment (two studies of moderate quality, one of low  
381 quality) was found to be effective in ameliorating VSN symptoms in all three studies. However,  
382 positive effects were measured on some, yet not all tests. Although the only (nor)adrenergic  
383 study showed some positive effects, the quality of this study was considered low, so no firm  
384 conclusions can be drawn. Moreover, none of the studies reported effect sizes, which hampers  
385 interpreting the study outcomes. Effect sizes are needed to evaluate clinical significance, while  
386 p-values only represent the randomness of the obtained effects (52). Overall, methodological  
387 limitations render us in drawing clear conclusions on the effectiveness of pharmacological  
388 treatment of VSN.

389

390 Our statements are comparable to those made in a recently published Cochrane review on the  
391 pharmacological treatment of VSN, in which two identical cholinergic studies have been  
392 reviewed (39). However, the Cochrane review included a smaller number of studies and

393 applied limited quality assessment criteria. The current review therefore provides a more  
394 complete overview of available studies on pharmacological treatment of VSN.

395

396 Several cognitive processes appeared to be of importance regarding the potential mechanisms  
397 underlying pharmacological treatment of VSN. Cholinergic treatment seemed to be the most  
398 effective in ameliorating VSN symptoms, which suggests the orienting, perhaps most  
399 mouldable, network of attention to play a role in VSN (32–34). Dopaminergic and  
400 (nor)adrenergic stimulation decreased VSN symptoms in some cases. Hence, the alerting  
401 (noradrenaline) and executive (dopamine) networks might influence VSN as well (32–34).

402

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

411

412 First of all, varying diagnostic criteria and many different tests were used to assess VSN in the  
413 11 reviewed studies. This variability turns out problematic when trying to compare studies. As  
414 described in this review, positive effects of pharmacotherapy on VSN symptoms were observed  
415 on some but not all tests. In this light, a consensus on, and implementation of, a more or less  
416 standard battery of tests could help future researchers to overcome these problems of  
417 comparison. At the level of function, the most widely used tests are cancellation tests, line

418 bisection tests, copying and drawing. With respect to rehabilitation, tests at the level of  
419 activities of daily living should also be included. The Catharine Bergego Scale may be the  
420 solution, as this observation scale measures VSN in basic activities of daily living (53).

421

422 Additionally, the more standard pen-and-paper tests (including the abovementioned  
423 cancellation tests, line bisection tests, copying and drawing) are generally regarded not  
424 sensitive enough to capture mild VSN, especially in the late sub-acute or chronic phase. The  
425 use of (tablet) computers and computerized tests would greatly improve the level of test  
426 specificity. For example, more accurate and precise reaction times can be recorded (54,55),  
427 search strategies during cancellation tests can be evaluated (56), and stimuli can be presented  
428 in a dynamic way (e.g. during cueing tests) (57). As a result, these tests are able to identify  
429 more subtle deficits that standard pen-and-paper tests might miss (54,58–60), which enables to  
430 detect VSN at the immediate moment of occurrence. Furthermore, common clinical tests might  
431 lose accuracy in the chronic phase of VSN (54). Computerized tests, on the other hand, are  
432 found to maintain accuracy, even in the chronic phase of VSN (54). Furthermore, tests in a  
433 virtual reality environment may be an effective tool to assess VSN. Virtual reality allows  
434 patients to interact with an environment similar to real-life experience, but in a safe and  
435 controlled manner (58,61). Hence, a more dynamic test is created, which provides better insight  
436 into the impairments of daily life.

437

438 One more issue of future interest could lie in the promising field of neuroimaging. New  
439 techniques could help to map neural networks, thereby visualising changes induced by the  
440 medicament. Although costly, these techniques could help tackle the problems of inter-assessor  
441 variability in the assessment of clinical observations and problems related to the standardized  
442 testing of cognitive skills.

443

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

451

452 Importantly, time post-stroke was highly variable in the reviewed studies. Studies were  
453 conducted with patients in both sub-acute and chronic phase post-stroke. However, only results  
454 of studies with patients in the chronic phase post-stroke can be reliably taken into account, as  
455 up to 3 months spontaneous recovery could have been achieved (3,62). In case patients in the  
456 sub-acute phase post-stroke are included, a control group is necessary for future research to  
457 monitor the effects of spontaneous recovery. Only one of our 11 reviewed studies included a  
458 control group (42), all the others lacked this important feature.

459

460 The addition of a follow-up phase would also positively add to the level of information  
461 gathering. Only one of the reviewed studies included a follow-up phase in which participants  
462 were assessed one month post-treatment. Thus, in the other 10 studies, no information was  
463 given regarding the duration of the beneficial influence of pharmaceutical treatment. Future  
464 research should be able to tackle this problem and include one or more follow-up  
465 measurements, ideally up to 3 months post-treatment. However, shorter timeframes are the  
466 primary concern, as they will possibly reduce outcome variation due to events unrelated to the

467 study and therefore allow for the accurate assessment of functional outcomes and drug safety  
468 (63).

469

### 470 **Study limitations**

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

478

479 Another limitation could lie in our selection process. We excluded studies in which attention  
480 deficits were treated, based on the lack of outcome measures aimed at the VSN syndrome. In  
481 fact, several human studies used pharmacotherapy as a treatment of attention and cognitive  
482 impairments after stroke (64–70). For example, both Jorge et al. (2010) and Adams et al. (2012)  
483 found that anti-depressives may enhance motor and cognitive recovery after stroke (68,69).  
484 Perhaps, anti-depressives could also beneficially influence recovery from VSN post-stroke.  
485 Therefore, these animal and human studies should be kept in mind regarding future  
486 investigation.

487

488

### 489 **Conclusions**

490 In conclusion, due to the methodologically weak quality of nearly all reviewed studies, we  
491 cannot make any clear-cut inferences on the effectiveness of pharmacotherapy on VSN post-

492 stroke. Nevertheless, regarding the three substances, we cautiously consider cholinergic  
493 therapy to be the most promising in treating VSN. Therefore, we believe future research should  
494 focus on cholinergic therapy.

495

#### 496 **Declaration of Interest**

497 The authors report no declarations of interest.

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499

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695 **Figures legends**

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697 Figure 1. Flowchart of the article selection process

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