Running title: Pharmacological Treatment of Neglect

Pharmacological Treatment of Visuospatial Neglect: A Systematic Review

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Abstract

Objectives: The aims of the current review are (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 post-stroke visuospatial neglect. The search was limited in the following features: species (human), adults (≥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 represent dopaminergic, three cholinergic, and one noradrenergic treatment. Three dopaminergic studies showed primarily positive effects of dopaminergic stimulation on visuospatial neglect, whereas three others showed adverse effects. All three cholinergic studies found positive effects in some outcome measures concerning visuospatial neglect. The noradrenergic stimulation improved maintaining attention when exploring space.

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

Introduction

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

Due to the high prevalence of post-stroke VSN and its negative consequences, effective remediation techniques are needed. Promising remediation techniques have emerged over the last decades, including prism adaptation (8–10), virtual reality training (6,11), visuospatial and scanning training (12), galvanic vestibular stimulation (13,14), transcutaneous electrical nerve stimulation (15), motivational manipulations (16), optokinetic stimulation (17), video-game based remediation (10,18), and upcoming non-invasive brain stimulation techniques such as transcranial magnetic stimulation (19,20) and transcranial direct current stimulation (21–23). However, the effectiveness of almost all techniques has not been investigated thoroughly enough to allow firm conclusions (6,24). 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 three decades (25–29), and have generally focussed on dopaminergic agonists and progesterone. VSN symptoms have been assessed by regular (25,26) and Morris water mazes (26,27), adhesive removal tests (27,28), and simple observations of turn direction to stimuli (29) in a variety of induced-stroke models (25–29). In general, results showed positive effects of progesterone (26–28) and apomorphine (29) on VSN, and of amphetamine on cognitive functioning (25). Similarly, human studies on the topic emerged about three decades ago (30). 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 of inhibitory (31). 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. Neurological ‘hypofunction’ like VSN may improve by decreasing inhibition and/or increasing excitation. In this manner, pharmacological agents can have positive therapeutic effects.

As the core symptoms of VSN comprise attention deficits, it is evident 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 network. VSN has been associated with all of them (32–34). The alerting network is modulated by noradrenaline (33,35,36). 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 (32,33). Acetylcholine is the major neurotransmitter in the peripheral nervous system at the neuromuscular junction, but also in the autonomic nervous system. In the brain it has a modulating effect on information processing, including plasticity, arousal and sustained attention. It 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 (33,35), and believed to affect the spatial bias in VSN (37). 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 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 (38).

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 phase I, 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 are (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 (39) 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 two studies. 'Lower-quality' studies however should also be reported, as they may add important knowledge for future studies, especially given 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 art of the field. In sum, the current review provides a more comprehensive overview of available studies on pharmacological treatment of VSN and may therefore give a broader overview of the current state of 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 Hemi-Neglect, Spatial Neglect, Visual Inattention, Spatial Inattention, Visual Hemispatial Inattention, Hemispatial Inattention, Visual Hemineglect, Visual Hemi-Neglect, Sensory Neglect, Personal Neglect, Behavioral Neglect, Behavioural Neglect, Motor Neglect, Hemi-inattention, Peri-Personal Neglect, 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 (≥18 years of age), language (English), and type of neglect (visuospatial). Intervention studies aiming at enhancing attention and/or decreasing VSN symptoms post-stroke were selected when they met the following inclusion criteria: (1) study population described 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 (seven studies), we additionally released our time span criterion to include studies published in any year, and found four additional studies published prior to 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 was compared and discrepancies were discussed amongst 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 milligrams). 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 treatment officer, (5) blinding of researchers, (6) comparability of groups at the start of the study, (7) reporting of effect size, (8) reporting completeness of follow-up, (9) equal treatment of groups, aside from intervention (40). We added three relevant elements to evaluate methodological quality: (10) comparison of an experimental and control group that received either an alternative form of treatment or no intervention, (11) group size (≥10 per group), and (12) 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 three groups. Studies were subsequently divided into high (total score ≥9), moderate (5-8), and low (≤4) quality studies.

Results

Initially, 38 articles were identified, 11 of which met the inclusion criteria (see Figure 1 for a flowchart of the article selection process). Of these studies, seven studies investigated dopaminergic therapy, three studies considered cholinergic therapy, and one 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, three studies were considered to be of moderate quality (41–43) and the other eight were considered low quality studies (4,30,44–49). An overview of study and participant characteristics is listed in Table 2. Only one study (42) included a true patient control group, while the remaining ten studies (4,30,41,43–49) used an A-B(-A) design in which all individual patients served as their own control. We considered four studies in the chronic phase (4,42,45,49), one study in the sub-acute phase (47), and one study in the acute phase post-stroke (48). Time post-stoke was variable in the remaining five studies, in which both patients in the sub-acute phase and patients in the chronic phase were included (30,41,4344,46). Only five studies (43,45–47,49) focussed primarily on VSN by using exclusively VSN tests (e.g. bisection, cancellation, visual search and detection tests) as outcome measures, while six studies (4,30,41,42,44,48) focussed 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 calculate effect sizes ourselves (41–43,45–47), these are presented in Tables 3-5.

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

provided in two studies (42,43). Three studies analysed patients' lesion sites more thoroughly by means of CT and/or MRI data (41,43,49), and the effect of specific lesion location on therapy effectiveness was evaluated in two additional studies (44,47). Moreover, discrepancies were observed 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 (4,30,41,44,46–48). One study was considered to be of moderate quality (41). The remaining six studies were considered to be of low quality (4,30,44,46–48) .

First, Gorgoraptis et al. (2012) 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). 16 patients received a 9.0 mg rotigotine patch on a daily basis in the B-phase for 7 to 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 (41).

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

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 two of the eight tests) showed positive results on six tests compared to baseline performance, but only on four tests compared to performance after treatment discontinuation (30).

Third, Grujic et al. (1998) 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 prior to, and after receiving their dose. Results indicated an increase of the rightward bias: bromocriptine caused six out of seven 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 (44).

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

Fifth, Geminiani et al. (1998) conducted a placebo-controlled, open-label trial in which four 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 a pen-and-paper circle cancellation, counting, and pointing test, which were administered prior to 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. Post-apomorphine results of the counting and pointing tests did not differ significantly when compared to performance at baseline and after placebo control (46).

Sixth, Mukand et al. (2001) used a case series design and included four 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 one tablet 3 times daily for the rest of the week. Patients were tested with a shortened version of the Behavioural Inattention Test (BIT) and Functional Independent Measure (FIM) test prior to, and after this week. Three patients showed enhanced BIT scores, and all four patients showed enhanced FIM scores after Sinemet intake. Results were presented as being significant, but p-values were not mentioned (48).

Last, a double-blind, placebo-controlled, within-subject study was performed by Buxbaum et al. (2007), using an A-B-A design. The effect of a 100 mg amantadine injection, given twice a day, on VSN was studied in four 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. Dual-Task test and the lateralized target 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 two patients (patient 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), the Dual-Task test (patient 2), and on the number of correct responses on the SART (patient 2). All other measures showed no significant effect (4).

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

Cholinergic therapy

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

Lucas et al. (2013) 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's 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 (43).

Furthermore, an open-label, randomized, and slightly larger sampled (n=20) study was conducted by Paolucci et al. (2010) to evaluate 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 seven 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 non-rivastigmine 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 (42).

The study by Vossel et al. (2010) 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 cueing task. A Nicorette gum consisting of 2 mg of nicotine was chewed on for half an hour. 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 neutrally and uncued trials (49).

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

(Nor)adrenergic therapy

The only identified study on noradrenergic therapy by Malhotra et al. (2006) was considered to be of low quality (45). Three right-hemispheric patients with chronic VSN received a single placebo injection and a 29 μg/kg guanfacine injection one 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 and a spatial working memory test. One patient performed significantly better after guanfacine 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 compared to placebo (45).

To summarize, even though two out of three 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 three pharmacological approaches: seven studies on dopaminergic therapy, three studies on cholinergic therapy, and one study on (nor)adrenergic therapy. Quality assessment showed that none of the reviewed studies were of high quality, only three recent studies were of moderate quality, and the eight 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 (two studies of moderate quality, one of low quality) was found to be effective in ameliorating VSN symptoms in all three studies. However, positive effects were measured on some, yet not all tests. Although the only (nor)adrenergic study showed some positive effects, the quality of this study was considered low, so no firm conclusions can be drawn. Moreover, none of the studies reported effect sizes, which hampers interpreting the study outcomes. Effect sizes are needed to evaluate clinical significance, while p-values only represent the randomness of the obtained effects (52). Overall, methodological limitations render us in drawing clear conclusions on the effectiveness of 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 two identical cholinergic studies have been 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

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

Additionally, the more standard pen-and-paper tests (including the abovementioned cancellation tests, line bisection tests, copying and drawing) are generally regarded not sensitive enough to capture mild VSN, especially in the late sub-acute 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 (54,55), search strategies during cancellation tests can be evaluated (56), and stimuli can be presented in a dynamic way (e.g. during cueing tests) (57). As a result, these tests are able to identify more subtle deficits that standard pen-and-paper tests might miss (54,58–60), which enables to detect VSN at the immediate moment of occurrence. Furthermore, common clinical tests might lose accuracy in the chronic phase of VSN (54). Computerized tests, on the other hand, are found to maintain accuracy, even in the chronic phase of VSN (54). 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 (58,61). 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 visualising changes induced by the medicament. Although costly, these techniques could help tackle the problems of inter-assessor 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 analysed 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 sub-acute and chronic phase 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 (3,62). In case patients in the sub-acute phase post-stroke are included, a control group is necessary for future research to monitor the effects of spontaneous recovery. Only one of our 11 reviewed studies included a control group (42), 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 one 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 timeframes 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 (63).

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/results from animal studies targeting disorders of attention and/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 (64–70). For example, both Jorge et al. (2010) and Adams et al. (2012) found that anti-depressives may enhance motor and cognitive recovery after stroke (68,69). Perhaps, anti-depressives 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 three substances, we cautiously consider cholinergic therapy to be the most promising in treating VSN. Therefore, we believe future research should focus on cholinergic therapy.

Declaration of Interest

The authors report no declarations of interest.

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Figures legends

Figure 1. Flowchart of the article selection process