

Review Article

Pharmacological Treatment of Visuospatial Neglect: a Systematic Review

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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 (≥ 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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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 1 year post stroke in at least a mild form. In addition to motor impairments,⁵ stroke has many adverse behavioral consequences on the cognitive level, hampering participation in a wide range of everyday activities.^{6,7}

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,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 noninvasive 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 3 decades,²⁵⁻²⁹ and have generally focused 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 orientation behavior²⁹ in a variety of induced-stroke models.²⁵⁻²⁹ In general, results showed the positive effects of progesterone²⁶⁻²⁸ and apomorphine²⁹ on VSN, and of amphetamine on cognitive functioning.²⁵ Similarly, human studies on the topic emerged about 3 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 or 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. 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.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 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^{33,35} and is 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 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.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 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 review³⁹ 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

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