# Pharmacotherapy to Improve the Acquired Aphasia following Brain Damages: A Review Study

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## Abstract

**Background & Aim:** Using pharmaceutical agents in treatment of aphasia has caught the attention of many neurologists and neuroscientists. This short review study has sought the role of pharmacotherapy in treatment of aphasia, a linguistic impairment after acquired brain lesions. The pharmacological principles and mechanisms related to the effects of drugs used in aphasia rehabilitation are pointed. Then, some evidence of clinical trials on different drugs in this field is presented.

**Methods & Materials/Patients:** A comprehensive search in databases including MEDLINE, Cochrane, PubMed, Scopus, EMBASE, Science Direct on experimental studies and clinical trials associated with pharmacotherapy of aphasia after neurological damages was performed.

**Results:** Pharmacological interventions through manipulating neurochemical levels in synapses, the pre- and post-synaptic spaces and even inside neurons start to modulate the disturbed balance of neurotransmitters due to brain lesions. Pharmacotherapy is based on the principle that drugs via balancing the molecular signaling cascades triggered due to neuronal damage can restore the function of neurons, facilitate the brain plasticity process and improve the linguistic deficits in aphasic patients. Among the drugs that have been studied in treatment of aphasia, those acting on central cholinergic and glutamergic systems were more effective and led to better clinical outcomes.

**Conclusion:** Although existing evidence has proved the pivotal role of pharmacotherapy in treatment of aphasia after acquired brain lesions in adults, further research is required to assure the clinicians in using pharmacotherapy as a standard approach in treatment of aphasia.

**keywords:** Pharmacotherapy; Aphasia; Traumatic Brain Injury

## Introduction

Acquired aphasia due to traumatic brain injury with any degree of severity results in serious problems for patients in their social relations and communications (1-4). Disability in verbal communications leads to defective behavior and psychological symptoms such as depression, irritability and aggression, affecting their family's quality of life as well as theirs(5, 6). One of the proposed solutions is "conventional aphasia therapy" but its sufficiency is still under debate. Recently, to obtain faster and more effective results, a combination of speech and language therapy with other complementary therapies namely pharmacotherapy and transcranial magnetic stimulation (TMS) has been very emphasized (7). Today, in rehabilitative interventions, a neuroscience-based intervention called Constraint-induced aphasia therapy (CIAT), the use of language in communicative interactions and daily life demands, has become very common since its effectiveness as well as its advantages in efficient verbal communication remains constant

(8-15). Yet, these improvements are attributed to regeneration of the language areas around the left hemisphere lesions and increased use of intact homologous regions of right hemisphere to compensate diminished function of left hemisphere injured areas (16-18). TMS has been suggested as an effective treatment for aphasia (19). Combined TMS and pharmacotherapy was first proposed by Naeser (2005) for treatment of aphasia (20). One of the discussed approaches in treatment of aphasia is pharmacological intervention. Much effort have been put on aphasia pharmacotherapy in past half century particularly revealing conflicting results on dopaminergic agonists. Dopaminergic drugs if taken along with aphasia therapy would be effective in patients with mild to moderate fluent aphasia, though not expected in other conditions (7,21-24). The recent two decades has seen accelerated developments in neuroscience research in favor of pharmacotherapy to improve the language deficits (8). Drugs in treatment of aphasia are mediators involved in activities of different neurotransmitter

systems including noradrenergic (amphetamines), dopaminergic (levodopa), serotonergic (fluvoxamine), cholinergic (doenepezil) and glutamatergic (memantine) (25), which can potentially impact on the cognitive processes and is of high importance in refining attention and memory disorders (26-34). In general, this type of treatment strategy influences the neurotransmitters and facilitates recovery process of neural networks infrastructure of language processing (35). Positron Emission Tomography ( PET) studies indicate that aphasia recovery after taking these medicine facilitates and accelerates the reactivation of left hemisphere (36,37). Nevertheless, researchers have not attained specific biomarkers which can prove the pharmacotherapy efficiency on improvement of the neural circuitry associated with language (7).

## Methods and Materials

A comprehensive advanced search was performed in following databases: MEDLINE, Cochrane, PubMed, Scopus, EMBASE, Science Direct. All English-written experimental articles and clinical trials performed so far in following areas: 1. The role of different neurotransmitter systems on cognitive and language function 2. Aphasia neuropathology 3. The drugs acting on different neurotransmitter systems for treatment of aphasia, were studied by three researchers from 2012 to 2014.

## Disscussion

Pharmacotherapy has evolved as a promising treatment approach for acquired aphasia due to brain lesion. In this review, we discuss the major neurotransmitter systems that involve in aphasia and appoint to more famous drugs which successfully act on the neural recovery. We focus on specific applicable medicines in this area and summarize the results from clinical studies that will be explained in continue.

### 1. Effective drugs on central cholinergic and glutamatergic systems

Among the numerous clinical trials focused on the effect of drug on improvement of aphasia and cognitive deficits in patients with primary progressive aphasia (PPA), Alzheimer, vascular dementia, acute and chronic brain stroke and head trauma, the role of memantine as voltage-dependent uncompetitive antagonist at glutamatergic NMDA receptor (9,38), and anti-cholinesterase drugs such as donepezil (39-46), galantamine (47,48) and physostigmine (49) are remarkable.

### 2. Central anti-cholinesterase action

Donepezil is a central cholinesterase inhibitor. Preliminary evidence suggests that donepezil has the potential for improving aphasic patients by better control of local cerebral blood flow regulation (50,51) and restoration of neural networks of cerebral cortex in stroke patients (22,39). Donepezil increases post-synaptic neural activity in pyramidal neurons of several cortical layers through selective inhibition of cholinesterase enzyme (52). Moreover, by activating nitric oxide enzymes responsible for dilation of the parenchymal arterioles it regulates cerebral blood flow (53). Neuroscience research shows that acetylcholine plays a major role as a cortical moderator in practice-related plasticity and long-term potentiation that is physiologic base of memory consolidation (54). Since anticholinergic mediators such as scopolamine selectively distorts the function of 25-60% of healthy subjects in tasks including naming objects, verbal fluency, reading and writing, possibly cholinergic systems play an important role in phonological and verbal processes (55). Based on previous studies in healthy people, it has been revealed that

enriched cholinergic system with donepezil improves cognitive functions related to language such as verbal memory encoding (56), perceptual processes during visual task performance (57) and speed of information processing. Studies on living and dead brain tissues have indicated that cortical and subcortical vascular lesions reduce cholinergic neurotransmitters by rupturing the cholinergic pathways which connects the both basal forebrain to perisylvian language areas (59,60) and brainstem to thalamic nuclei (43). One of the most common causes of acquired aphasia is traumatic brain injury (TBI) particularly in youngsters (61-63). Post-traumatic aphasia may arise from the direct damage to neural networks of the cerebral cortex, the sub-cortical and brain stem structures or a secondary insult from neural damage and death due to glutamate-induced excitotoxicity triggered by the prolonged influx of $Ca2+$ ions (64). Post-traumatic aphasia has cognitive-communicative nature. In other words, impairment in cognitive dimensions and executive functions related to frontal and fronto-limbic lobe is the most important comorbidities after trauma considered as the infrastructure in patients' communicative and verbal disorders (65-69). Experimental studies on TBI animal models have shown that following traumatic damage to brain, acetylcholine vesicular transporter declines up to 50% in the basal ganglia of basal forebrain, motor cortex, striatum, nucleus of the thalamus, the hypothalamus, and gigantocellular nucleus of reticular formation. About 20% decrease is also seen in acetylcholine nicotinic receptor density in all mentioned regions except the basal forebrain. Similarly, acetylcholine muscarinic receptors diminish in the areas mentioned as well as in the corpus callosum and olfactory nuclei (70).

The application of central anticholinesterase drugs such as donepezil in treatment of aphasia is based on the assumption that this drug can potentially improve the deficits of semantic-lexical processing, verbal memory, aphasia and motor aspects of speech by regulating cholinergic neural pathways (7,22,39). Furthermore, increased top-down processing of sensory input and facilitating the encoding of verbal stimuli and filtering the irrelevant stimuli, improves language deficiencies (8,54). Donepezil plays a neuroprotective role by increasing the activity of alpha-7 nicotinic receptors of acetylcholine, inhibition of apoptosis, increasing the concentration of extracellular acetylcholine, neuron protection against glutamate-induced toxicity and finally by inducing the activity of involved genes in neural protection (71).

### 2.1.Clinical Trials

Studies on anti-cholinesterase in aphasia treatment began by works on galantamine in nearly half a century ago which was effective in patients with primary progressive aphasia and aphasia due to vascular dementia (47,48). However, in the last decade, research on the effective anti-cholinesterase on aphasia mostly concentrated on donepezil. In a double-blind clinical trial, patients with chronic aphasia underwent conventional aphasia therapy in which received donepezil for 16 weeks. They, compared with patients receiving placebo, showed significant refined naming skill at the end of treatment. Aphasia quotient and verbal communication ability improved in treatment rather than control group, but treatment-induced improvement was not persistent in the four weeks washout period (41). In a similar study, not considering control group, 5 mg/daily donepezil in 4 first weeks of the treatment phase and 10 mg/daily in 12 weeks later in aphasic patients were assessed. After chronic stroke, phonemic discrimination of non-words, word and non-word repetition, objects naming and matching the image with auditory verbal data were all improved at 16th weeks. Comparing the

results of the evaluation between the end of treatment phases with 5 mg/daily and 10 mg/daily were not significantly different. In assessments of the end of twentieth week, it was revealed that medicine withdrawal in 4-week washout period leads to poor skill of matching the image with auditory verbal data. Moreover, aphasia quotient increased 12% and 20% in the first 4 weeks and at the end of treatment, respectively (39). In a case study on donepezil use in patients with aphasia after acute stroke, it was indicated that both of groups 5 mg/daily donepezil and placebo for 12 weeks, had significant improvement in comprehension and repetition skills, verbal naming, spontaneous speech and aphasia quotient. However, these improvements in treatment group (60%) was significantly higher in control group (26%) (42). In a case study, one patient with brain trauma-induced bilateral subarachnoid hemorrhage and small contusion in supra-orbital regions of right frontal and temporal lobe, also suffering short-term memory deficit, constructional apraxia and fluent aphasia, donepezil 5 mg/daily within 20 days was remarkably effective in amelioration of different distorted dimensions of cognition due to moderate TBI (72).

### 3.Glutamatergic Antagonists Action

Increased release and reduced reuptake of glutamate transmitter from synapses, increased activity of NMDA receptors and increased calcium influx in postsynaptic neurons are important neurobiological events after brain lesions which are the starting point of calcium-related processes involved in neuronal death (73,74,75).

Decreased neuronal death in hippocampal areas including CA2 to 50% and CA3 to 59% following TBI and (76), preventing the apoptosis of CA3 hippocampus area and anterior cingulate cortex in both hemispheres after bilateral brain trauma even in mild TBI (77), by memantine a voltage-dependent uncompetitive antagonist of NMDA receptor at least a week after injury have been revealed in experimental animal models. In animal model (78,79) and human studies (80), evidence suggest that severe TBI especially in patients with diffuse axonal injury (DAI), results in diffuse brain atrophy which may augment in first months or even in first years after injury. It is believed that this progressive neurodegeneration includes Valerian degenerescence process of white matter pathways that occurs following DAI. But most likely, other mechanisms such as inflammation, apoptosis and excitotoxicity may also have a role (78,79). This occurs more in patients with early loss of consciousness (81). The longer the duration of coma after brain injury, the more the changes of brain volume in the following months after injury would be (82). The evidence support the effective role of glutamate stimulus neurotransmitter as a biological mechanism responsible for secondary neuronal process after brain lesion (83,84). Apoptotic process in neurons and neuroglial usually associated with cerebral edema have been shown in both focal and diffuse neurodegenerative damage (85,86). These pathological consequences are strongly related to cognitive, behavioral and emotional deficits after brain damage at all severity levels of injuries (87). Although recently the potential use of memantine in TBI management has increased (76,88), clinical report of its effect on TBI outcomes is still scarce. According to PET findings, memantine therapy improves the cognitive function after TBI by increasing glucose metabolism in left middle and inferior frontal gyrus and parietal lobule (89). Perhaps, memantine due to its restorative potential and the revival of activity in prefrontal cortex, precuneus, supramarginal angular gyrus particularly possesses positive effect on attention, working

memory and executive functions that are the most vulnerable in TBI (89). In patients with non-dementia brain damage, increased vesicular glutamate storage in the frontal central, will promote stable cognitive impairment (90). Therefore, not only memantine reduce excessive activity NMDA receptors while maintaining activity of physiological receptor in areas with normal level of glutamate and hence imposes neuroprotective effect (91-94), but also strengthens action dependent learning in language related areas via increased repair of synapses and long-term potentiation in intact neural networks (9,94,95).

### 3.1.Clinical trials

The effect of memantine on chronic aphasia was examined in a study with 5 phases including the end of week 16, 18, 20, 24 and 48 for the assessment of aphasia quotient. Patients in the first 16 weeks of treatment were randomly assigned to two groups treated with memantine and placebo. The aphasia therapy was then added to both of groups for 2 weeks until week 18 of treatment. From week 18 to 20, they only received medication. From week 20 to 24, they had no treatment. From week 24 to 48 both groups were treated with memantine. In all phases of the assessment, the aphasia quotient of medication compared to the control group had significant improvement. The effects of drug in patients who initially received memantine, maintained during long-term follow-up assessment. Replacement of placebo with drug inpatients who had initially received placebo had a beneficial effect (9). A study in 2010 in Japan was carried out that aims to examine the correlation between brain metabolism changes and MMSE scores recovery after memantine therapy in patients with post-traumatic cognitive deficit. Findings of the study showed that the association areas of prefrontal and parietal of structures related to pharmacological response to memantine in TBI population and increased metabolism in these areas correlated with promoted cognitive level of patient (89). In a research on patients with moderate to severe Alzheimer, the effect of memantine for 24 weeks on patients who underwent a routine dose of donepezil (10 mg/daily) at least three months before the start of treatment, helpful outcomes appeared in cognitive and linguistic function. These results in patients with a treatment of donepezil and placebo combination led to loss of those function. No significant difference was observed between the two groups in terms of drug tolerance (96). Another study was conducted on patients with moderate to severe Alzheimer aimed at improving aphasia by memantine. Patients were randomly treated daily with 20 mg memantine or placebo. Assessments at weeks 12, 24 and 28 were performed and the results showed a significant effect of memantine in improvement of aphasia. We have designed a study which has been running since 2013 so far (IRCT2013041613027N1). This clinical trial explores the impact of donepezil and memantine combination therapy compared to single therapy of each drug on aphasia quotient and Disability Rating Scale (DRS) in aphasic patients after traumatic brain injury. The results of this study have not been reported yet but will be issued in the near future.

### 4.Drugs acting on Catecholaminergic System

Pharmaceutical compounds such as bromocriptine, levodopa, amantadine and amphetamines appear to act on the dopaminergic and monoaminergic systems, and their effectiveness has been investigated in aphasic patients in the past 40 years. Among all, bromocriptine agonist of postsynaptic dopamine D2 receptor has been investigated more than others (7,21,23). Findings show

that the type of aphasia (22,23), the cause of aphasia (98), the treatment plan (99) and dose of medication (100) play a vital role in outcome. Bromocriptine functions on mesocortical dopaminergic neurons which project from mesencephalon to dorsal caudate nucleus of basal gangalia, supplementary motor area (SMA) and anterior cingulum (101). Hence, it is logical that aphasia due to widespread lesions around Sylvain fissure such as global aphasia and severe Broca do not response well to medication. In recent decade, researchers have considered the effect of levodopa on improvement of patients suffering aphasia. Daily intake of 100 mg levodopa compared to placebo boosted skills of naming, fluent speech and repetition skill in patients with frontal lobe lesion (102). Another pharmaceutical mediator which manipulates dopamine in the brain and was remarkably effective on improving aphasia, is amantadine strong agonists of dopamine and norepinephrine receptors as well as a weak antagonist of glutamatergic NMDA receptor. This drug improves cognitive and motivation deficits by increasing the release of dopamine and norepinephrine in neural terminals of mesolimbic and mesocortical pathway (103). Studies report on the recovery of sensory and motor transcortical aphasia by this drug (104). Amphetamine inhibits the reuptake of dopamine and norepinephrine. Though, there are studies which used amphetamine to investigate the drug effectiveness on aphasia which have proved to be helpful when accompanied with intensive speech and language therapy (105,106), still they are not recommended for the treatment of aphasia in clinics (107).

### 5. Selective serotonergic reuptake inhibitors (SSRIs)

Previous studies have shown that serotonergic therapy improves naming skill in patients with mild to moderate fluent aphasia. A probable relationship is assumed between improved naming skill due to these medications and improved mood and reduced preseveration (108). The relationship between aphasia and depression has been previously reported (109). This led the researchers to the fact that SSRI may be able to improve aphasia by resolving depression, since depression is associated with frontal lobe lesions and non-fluent aphasia, also frontal lobe is the most common vulnerable lobe after trauma and stroke. Thus, it would be promising that the pharmacological intervention of depression can improve aphasia caused by frontal lobe lesions. Fluoxetine, sertraline, fluvoxamine and paroxetine are selective serotonin reuptake inhibitors which maintain high serotonin level in the brain by serotonergic system modulation. Serotonin is essential for learning and reorganization. So SSRIs elevates brain function by increasing the central serotonin level. Therefore, theoretically it is sensible that as these drugs aid reorganization of brain so integrating these medications with rehabilitation would be rather effective. They boost participation, motivation and activation and help to enhance the effectiveness of rehabilitation therapies. A double-blind study in 2001 by the Tanaka and Albert on 10 patients with Wernicke and jargon aphasia was implemented in which the researchers gave fluvoxamine and nilvadipine (calcium channel blocker) to two groups of patients for treatment of aphasia for 4 weeks.

After a 4-week washout period, patients received routine drugs. The results showed improved naming skills by an average of 20-25% and 30% decrease in preseveration in comparison to the baseline for the group receiving fluvoxamine. Nilvadipine group showed no change (108). At a last effort, a randomized clinical trial has been devised since 2012 (NCT01674868) where the effect of fluoxetine (20 mg/daily for 90 days), compared with placebo, on motor impairment, aphasia and neglect after ischemic stroke is investigated. The results of this study have not been reported yet.

## Conclusion

Aphasia after brain damages occurs following the disruption of main neurotransmitter pathways which connect brain stem and basal forebrain to cortical and subcortical areas of speech and language. Drugs which re-regulate the particular neurotransmitter activity, reinforce and stabilize the neural activity of mediator networks of lexical and semantic memory. It seems that dysfunction of central cholinergic and glutamatergic pathways induce aphasia more than other neurotransmitter pathways because the influences of drugs acting on these systems have been more significant than others. Fortunately, donepezil and memantine have few side effects and are very safe and well-tolerated. Clinical trial evidence has demonstrated the effectiveness of these two drugs on resolving aphasia. Finally, aphasia shows a poor response to late pharmacological interventions, sometimes absolutely fruitless. Thus, in use of this attractive therapeutic approach the necessity of early intervention is punctuated.

## Conflicts of Interest

The authors declare that they have no competing interests.

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## Comments

Ramezani and colleagues wrote a review paper on drugs which improve aphasia after traumatic brain injury (TBI) (1). They emphasize on the role of memantine an antagonist of glutamergic NMDA receptor and Donepezil a central cholinesterase inhibitor drugs. However, the design of the study and the type of review is not clear. It is not a narrative review because they mentioned that they performed a comprehensive review of different search engines in English language. However, narrative reviews are written by experts in the related field. The field is very broad and the method is unsystematic and informal. Authors may have bias and prepare not high quality evidence (2). In systematic review, we have a well prepared specific question based on PICO or similar items. Search strategy is written and everyone can perform the search in defined date with similar results. Titles, abstracts, full papers are read by two independent researchers. The results of each step is saved and demonstrated based on the PRISMA. Risk of biases and quality of evidences are well defined (3).

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