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Poststroke Aphasia
Epidemiology, Pathophysiology and Treatment

Marcelo L. Berthier

Centro de Investigaciones Médico-Sanitarias (CIMES), University of Malaga, Malaga, Spain

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Abstract

Aphasia, the loss or impairment of language caused by brain damage, is one of the most devastating cognitive impairments of stroke. Aphasia is present in 21–38% of acute stroke patients and is associated with high short- and long-term morbidity, mortality and expenditure. Recovery from aphasia is possible even in severe cases. While speech-language therapy remains the mainstay treatment of aphasia, the effectiveness of conventional therapies has not been conclusively proved. This has motivated attempts to integrate knowledge from several domains in an effort to plan more rational therapies and to introduce other therapeutic strategies, including the use of intensive language therapy and pharmacological agents.

Several placebo-controlled trials suggest that piracetam is effective in recovery from aphasia when started soon after the stroke, but its efficacy vanishes in patients with chronic aphasia. Drugs acting on catecholamine systems (bromocriptine, dexamfetamine) have shown varying degrees of efficacy in case series, open-label studies and placebo-controlled trials. Bromocriptine is useful in acute and chronic aphasias, but its beneficial action appears restricted to nonfluent aphasias with reduced initiation of spontaneous verbal messages. Dexamfetamine improves language function in subacute aphasia and the beneficial effect is maintained in the long term, but its use is restricted to highly selected samples.

Pharmacological agents operating on the cholinergic system (e.g. donepezil) have shown promise. Data from single-case studies, case series and an open-label study suggest that donepezil may have beneficial effects on chronic poststroke

aphasia. Preliminary evidence suggests that donepezil is well tolerated and its efficacy is maintained in the long term. Randomised controlled trials of donepezil and other cholinergic agents in poststroke aphasia are warranted.

Stroke is the most frequent serious neurological disorder in the world and the third leading cause of death in industrialised countries.[1] It has a high incidence in Europe (the annual incidence in the age group 25–74 years varies between 318 and 372 in men and between 195 and 240 in women per 100 000 of the population) and is commonly highly disabling or lethal.[1-5] Among the diverse cognitive deficits caused by stroke lesions, aphasia is the most devastating, to the extent that some aphasic individuals consider themselves to have lost their personhood.[6] Aphasia is defined as a loss or impairment of the complex process of interpreting and formulating language symbols caused by acquired brain damage affecting a widely distributed network of cortical and subcortical structures of the language-dominant hemisphere.[7] Aphasia is a multimodal disorder affecting auditory comprehension, reading, oral-expressive language and writing, but it must not be viewed as a domain-specific disorder because other predominantly left-hemisphere cognitive processes (e.g. auditory-verbal short-term memory, attention) necessary for language processing are affected as well.[7]

1. Epidemiology

Aphasia is present in 21–38% of acute stroke individuals.[3,4,8,9] In light of this high prevalence, it is surprising that public awareness of the condition still remains lower than that for other neurological conditions with lower or similar incidence and prevalence rates, such as Parkinson's disease.[10,11]

In right-handed individuals, poststroke aphasia is nearly always the result of left hemisphere lesions; only rarely (2–10%) does it follow right hemisphere damage (crossed aphasia).[3,8,12] Vascular damage to the left hemisphere, causing aphasia, mostly involves the perisylvian cortex and structures beneath it such as the basal ganglia, internal capsule and periventricular white matter, which are perfused by the middle cerebral artery.[12] On the other hand, aphasia as a result of infarctions involving the arterial border zones between the middle cerebral artery and either the anterior cerebral artery or the posterior cerebral artery is considerably less frequent.[12] Ischaemic infarctions account for approximately 80% of cases, whereas haemorrhagic damage is less frequent and its location is not constrained by vascular arrangements.[4,12]

Global and nonclassified aphasias account for 50% of cases admitted to acute stroke units, especially among patients with previous strokes,[13] whereas well defined classic aphasic profiles (anomia, Broca's, conduction, Wernicke's and transcortical) are more frequent when patients with single lesions are considered.[4,5,14] Classic syndromes, such as Broca's aphasia or aphasias with atypical features (e.g. hypophonia, perseverations) can also follow pure striatocapsular or thalamic infarctions and haemorrhages.[15-17] In these instances, the aphasic symptoms are most likely a result of sustained cortical hypoperfusion[15-18] or selective cortical neuronal loss resulting from prolonged vascular occlusion and insufficient collateral circulation.[16,19] A difficult to ascertain proportion of aphasic individuals cannot easily be assigned to the classic syndrome categories, whereas others (approximately 15%) display atypical clinicoradiological correlations (e.g. Wernicke's aphasia associated with frontal lobe lesions), in part, a result of the idiosyncratic brain organisation of language networks.[20-23] However, other right-handed individuals show no aphasia despite having large lesions in the left hemisphere because in such cases language is innately lateralised to the right hemisphere.[12,22]

Large scale studies show that poststroke aphasia is associated with increased mortality in both the short term and long term.[3,4] Nearly one-third of patients with acute aphasia die during the hospital stay and the high long-term mortality, accounting for half of the deaths, is the consequence of cardioembolic strokes related to atrial fibrillation.[4]

Recovery is always possible even in patients with severe aphasia.[4,24] and the type of aphasia nearly always changes to a less severe form during the first

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year.[5] Studies of spontaneous recovery have shown that greatest improvement occurs in the first 2 or 3 months, with the amount of improvement being less discernible in the following months, and most patients reaching a plateau after 1 year.[3,9,25-27] Several factors can influence the recovery of aphasia, but the crucial role of aphasia severity in predicting outcome is undisputed,[3,5,24-26,28] whether this is assessed in the acute stage[3] or 6 months after onset in cases with severe global aphasia.[24] By contrast, the analysis of other factors, such as age, sex, education, handedness, time from onset, and lesion site and size on recovery has yielded conflicting results.[26,29] The interaction between lesion site and size, aphasia profile and demographic factors is extremely complex[29,30] and the relative weight of these individual factors in the recovery is undetermined. This requires further studies using multidimensional evaluations.[9,30] Future studies also need to include psychiatric comorbidity as a predictive factor of outcome in aphasia,[31,32] because depression, anxiety and social withdrawal can have a negative impact on rehabilitation and psychosocial functioning.[30]

2. Pathophysiology

Over the past several years, clinical observations, structural and functional neuroimaging studies and neurophysiological investigations have provided greater insight into the pathophysiology of poststroke aphasia. Studies using structural magnetic resonance imaging (MRI) have revised the clinicoradiological correlations of aphasia.[12-17,33-37] Although most findings already described by early localisationists using postmortem analysis have been consolidated,[12-17,33-37] several assumptions made about specific clinicoradiological correlations have had to be reconsidered (e.g. the role of the arcuate fasciculus in language repetition).[33,36,37] Experimental models and clinical studies of brain-behaviour relationships using MRI and modern statistical procedures (classification tree testing) are currently being used to establish more precise associations between certain aphasic features and specific lesion sites.[35,38] Moreover, studies combining structural MRI and fine-grain language analysis document not only heterogeneity in the clinical presentation and anatomic correlates of classic aphasic syndromes,[17,39,40] but also fractionate the linguistic components of different subtypes according to discrete differences in lesion sites (e.g. supra- and infrasylvian conduction aphasia).[34,36] This contributes to the better prediction of outcomes and identification of candidates for specific rehabilitation programmes.[41]

In addition, a far deeper understanding of the dynamic neurobiological mechanisms underlying poststroke aphasia and the processes implicated in recovery is provided by modern functional studies with positron emission tomography (PET),[42-46] functional MRI,[42-46] perfusion-weighted imaging and diffusion-weighted imaging,[47,48] proton magnetic resonance spectroscopy[49] and functional transcranial Doppler sonography,[50] as well as by neurophysiological investigations with evoked potentials,[51] magnetoencephalography[51] and transcranial magnetic stimulation.[52]

In acute aphasia, changes in brain activity can occur both ipsilateral to the stroke lesion and contralateral to it.[53,54] Since the brain is capable of employing different compensatory mechanisms to promote recovery, the patterns of cerebral activity may be different from patient to patient. Some strategies are automatically generated, allowing the restitution of function in the weeks or months immediately following the stroke,[42-46] whereas compensatory mechanisms in cases showing incomplete recovery are ignited in the long term either spontaneously or in response to speech-language therapy and drugs.[55-57] Based on functional imaging findings, some researchers have suggested that recovery from aphasia depends upon either the activity of language eloquent regions around the infarction or the partial resolution of the area of infarction.[44-48,58-62] In acute aphasia, the more possible mechanism of recovery is the restitution of cerebral blood flow and oxygen in the area of ischaemic penumbra, a still viable neural tissue surrounding the infarction which may recover or die.[48,63,64] Recovery relying on the restitution of function in the infarcted area is less frequent as it can only be expected when the lesion is relatively small and spares no fewer than 10–20% of cells and connections.[55,56,59,60] Some researchers claim that the repair of left hemisphere networks originally devoted to language functions is associated with more favourable outcomes than the recruitment of homologous regions in the right hemisphere.[46,58-62]

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By contrast, the results of other imaging studies have shown that recovery from aphasia can also be achieved through a compensatory shift of language function to homologous regions of the right hemisphere.[43,54,65-67] This mechanism is operative in cases with either extensive damage to language areas of the left hemisphere or to the pre-existence of right hemisphere neural pathways devoted to language.[39,40,46,60,62] Such a compensatory activation may occur in the early postacute stroke, presumably as a result of the release of the left hemisphere inhibitory control over right hemisphere structures[51] or it may result from the gradual learning over several years of new processing strategies to deal with language tasks.[39,40,54,68]

There are some divergent findings in the analysed literature mainly due to methodological differences across studies (e.g. fluent versus nonfluent patterns, single-case analysis versus group averaging, different paradigms of activation). However, combined evidence from studies using neuroimaging[44-46,58,69] and other ancillary methods, such as evoked potentials and lateralised lexical decision through hemifield visual presentation,[51,70,71] strongly suggest complex and variable patterns of bi-hemispheric reorganisation of language in recovered aphasic patients.

3. Language Assessment: Methodological Issues

The assessment of language deficits in aphasia is an extremely important area of research as it may be a prerequisite for establishing empirically based recommendations for the clinical practice of aphasia rehabilitation.[72-75] At present, there is unanimous consensus that evaluation of aphasic deficits should be comprehensive to allow the planning of rational therapies.[5,14,28,29,76-82] However, there is less agreement regarding the language assessment methodology, with debate centred on two principal themes: (i) the different levels of analysis that should be implemented to formally assess language impairments; and (ii) the number of patients ('n') that should be included in the sample (e.g. group studies versus single-case studies).

Some researchers recommend evaluation of groups of aphasic patients using standardised batteries.[5,12,14,76-78] These batteries examine oral language, reading and writing and provide subtest summary profiles. The results obtained are intended to provide syndrome-based diagnoses (e.g. Broca's aphasia) that reflect specific brain-behaviour relationships. It has been suggested that grouping patients with the same syndrome provides an important framework for clinicians as most of these syndromes are correlated with well defined lesion localisations.[5,12,14,76-78] The estimation of the initial aphasia severity and its clinical profile using standardised assessment batteries coupled with mapping of lesion size and site are likewise important for predicting evolution, managing language recovery and informing the patient and family.[3,25,77]

Some of the standardised batteries currently in use combine the information gathered from different language subtests that assess spontaneous speech, comprehension, repetition and naming to obtain a graphic profile of performance (e.g. Boston Diagnostic Aphasia Examination [BDAE][83]), overall scores of aphasia severity (e.g. Western Aphasia Battery [WAB][84]) or measures of communicative ability (e.g. Porch Index of Communicative Abilities [PICA][85]). Although standardised aphasia batteries were not originally devised to predict a prognosis or to guide therapy,[79] their overall scores are increasingly being used as primary outcome measures to estimate changes in the global level of performance after behavioural[86] and pharmacological treatments.[87,88]

The alternative position for evaluating aphasia is the cognitive neuropsychological approach, a methodology that examines the nature of both normal and abnormal language functioning in terms of current information-processing models.[72-74,89-92] Advocates of this approach assess single cases (n = 1), arguing that the 'group study' approach is not a legitimate strategy because the individual data are not analysed and the averaged data across several patients can attenuate interindividual differences.[72-74] Furthermore, it has been contended that damage to the functional architecture of language processing systems cannot be inferred on the basis of clinical aphasic syndromes (e.g. Broca's aphasia) as they do not have a unitary functional basis, but rather a cluster of impairments that results from damage to several discrete cognitive systems.[72,79] One popular

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assessment tool is the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA),[93] which is useful for identifying the different clusters of linguistic impairments as well as the residual areas of strength in the aphasic patient.

However, the cognitive neuropsychological approach has some disadvantages. For instance, the single-subject research design may be flawed by the possibility of idiosyncratic performance, the difficulty of replication, and the lack of generalisation of outcomes.[28,29,82] Moreover, administration of the PALPA or similar batteries is not always feasible, because they are time-consuming and not applicable to patients with severe aphasia (e.g. global aphasia),[94,95] which regrettably represents more than one-third of the acute aphasias.[4,77]

In recent years, there has been a growing convergence between these two assessment approaches.[82] Accumulating evidence suggests that the surface symptoms of aphasia and its global severity are better recognised using standardised aphasia batteries such as the WAB or PICA,[86-88] whereas evaluations using the cognitive neuropsychological approach and tools such as the PALPA more appropriately assess the nature of language deficits. Moreover, given that quality of life is negatively affected by aphasia,[96] there has been increasing interest in developing reliable and valid instruments of assessment (e.g. Stroke and Aphasia Quality of Life Scale-39).[97]

4. Treatment

4.1 General Considerations

The treatment of poststroke aphasia needs to be logically construed taking into consideration the multiple negative factors that may influence recovery. When planning therapy, it is important to consider that aphasia embraces a broad scope of interdependent factors, including the severity and characteristics of aphasia, physical illness, emotional and psychological comorbidities and the impact of aphasia on the patient's quality of life.[28,30]

Before implementing the available options for the treatment of aphasia, several factors have to be taken into consideration. First, clinicians should avoid, whenever possible, using drugs (e.g. haloperidol, phenobarbital) that can exert a potentially detrimental effect on recovery by reducing plastic reorganisation of the brain.[55,98,99] Second, depression and other emotional disorders associated with poststroke aphasia reduce attention capacity to suboptimal levels, thereby interfering with evaluation and therapy. In consequence, comorbid psychiatric disorders need to be recognised during the early stages of language recovery and treated before undertaking prolonged evaluations of aphasia or implementing speech-language therapy.

4.2 Speech-Language Therapy

Speech-language therapy is almost unanimously considered the mainstay of treatment of aphasia.[5,28,75,100-109] However, over the past few decades there has been much debate about whether or not speech-language therapy of aphasia is really effective, mainly because of the fact that analyses of clinical outcomes have yielded mixed results.[5,28,75,100-109]

Divergent results have presumably emerged from insurmountable methodological problems. For example, investigators have examined the efficacy of therapy using a wide array of methods in heterogeneous groups of aphasic patients, making it difficult to compare study results.[28] Robey[103] conducted a meta-analysis of 21 studies dealing with the effectiveness of aphasia treatment. He evaluated three classes of effect size: untreated recovery, treated recovery, and treated versus untreated recoveries. Single-case studies and reports containing insufficient information were excluded from this analysis. The main result of this study was that when treatment was begun in the acute period, the recovery of treated patients was nearly twice as extensive as the recovery of untreated individuals.

Robey[104] confirmed and expanded these results further in a subsequent meta-analysis that included the clinical outcomes of 55 reports. Four important dimensions were examined, namely, the amount of treatment, the type of treatment, the severity of aphasia and the type of aphasia. The studies included in this meta-analysis used quasi-experimental designs; this means that a patient was neither randomly selected, nor randomly assigned to a group, but that the patient's attribute (e.g. aphasia) determined group membership. The overall results were

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as follows: outcomes for treated patients were superior to those for untreated patients in all stages of recovery; the average effect size for treated patients was >1.83 times that for untreated individuals when treatment was begun in the acute stage; treatment provided in a >2-hour per week schedule induced greater changes than when it was provided in shorter durations; and treatment of moderately severe and severe aphasias had positive therapeutic outcomes when given by speech-language therapists in the chronic stage of evolution, but not in the postacute stage. Thus, it appears that intensive speech-language therapy over a short period of time can provide better outcomes than less intensive regimens over a longer period of time.[103,104]

Recent meta-analyses[108,109] have replicated Robey's original findings.[104] In one meta-analysis,[109] a MEDLINE search of clinical trials examining the impact of speech-language therapy on aphasia recovery in stroke victims showed a significant treatment effect for intensive treatment during a short period of time (8.8 hours per week over 11.2 weeks) but not for less intensive treatment administered over more weeks (2 hours per week over 22.9 weeks). The number of hours of therapy per week was positively correlated to greater improvement on the PICA ($p = 0.001$) and the Token Test ($p = 0.027$), whereas the total length of therapy showed an inverse correlation with the mean change of PICA scores ($p = 0.0001$).[109]

While these optimistic results are in agreement with those reported in extensive and thoughtful reviews of the aphasia-treatment literature,[75,110] the benefits of speech-language therapy are less impressive when only randomised controlled trials are examined. Greener et al.[107] reported the results of a systematic analysis of the efficacy of speech-language therapy for aphasia associated with stroke. After reviewing the Cochrane Stroke Group Trials Register (last literature search March 1999) and other relevant sources to December 1998 the investigators could not establish whether or not formal speech-language therapy was superior to informal support. The investigators examined 60 randomised controlled trials. However, only 12 of them satisfied the selection criteria for analysis and only two of these 12 trials were included in Robey's meta-analysis.[104] Thus, divergent conclusions about the efficacy of aphasia therapy in these two studies may have resulted, at least in part, from examining different populations. Furthermore, not enough of the 12 trials reviewed by Greener et al.[107] were sufficiently recent, nor did they contain sound methodology to permit them to draw firm conclusions. Based on these somewhat disappointing results, Greener et al.[107] recommended that decisions about the management of aphasic patients should be adopted on the basis of other lines of evidence and that future randomised controlled trials should be comprehensively designed and performed with larger samples in order to reach an adequate statistical power.

Although randomised controlled trials are the gold standard for evaluating treatment effectiveness, it has been argued that they cannot provide useful information about the efficacy of aphasia therapy.[111,112] In recent years, specific rehabilitation techniques motivated by model-based descriptions of aphasic deficits in single patients (e.g. case-series research design or controlled multiple-baseline designs across subjects or interventions) have become popular.[75,111,112] At present, these treatments are mainly offered to chronic aphasic patients after they have reached a plateau with more conventional therapies. Some theory-assisted therapies, including the constraint-induced therapy (30–35 hours of treatment over 10 days restricting the patient to a verbal modality and discouraging the use of nonverbal communication),[86] the modality-focused therapy (using either repetition, naming, phonemic cueing or orthographic cueing),[113-117] and multimodal strategies [118,119] have shown positive outcomes for treated target items with variable generalisation of improvement to other language domains.

Other rehabilitation techniques also show promise. Computer-assisted aphasia therapy has been found to be effective as an adjunct to clinician-guided therapy in chronic aphasia. [120,121] Community-based aphasia treatment significantly ameliorated language impairment and functional communication (mean overall improvement range 6.6–19.8%) in patients with acute and chronic aphasias.[122] Finally, it should be noted that rehabilitation in patients with severe aphasia cannot be guided entirely by cognitive theory, and more broad-based strategies (e.g. word-to-picture matching tasks,

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'modular therapies') may turn out to be more effective and easier to implement.[81,95,106,123]

5. Pharmacotherapy: the Neuroreplacement Approach

Conventional speech-language therapy may be of little help in the remediation of language deficits in chronic aphasia, except when prolonged and/or intensive therapies are applied.[106,108,109] Regrettably, these therapies are time consuming, difficult to implement and very expensive. Moreover, in some instances the beneficial effect is short-lived or not generalised to everyday activities. Therefore, it can be speculated that the addition of new treatment options (e.g. drugs) to speech-language therapy would provide better outcomes.

The idea of using drugs to improve language deficits is relatively new and still controversial.[124-128] The potential effect of pharmacotherapy on language performance in aphasia has been addressed in a number of studies of pharmacotherapy as an adjuvant to speech-language therapy. Agents that augment the activity of neurotransmitter systems depleted by stroke lesions have shown that deficits in spontaneous speech, naming and comprehension are amenable to pharmacological interventions.[126]

Although a variety of agents have been employed to treat poststroke aphasia, the rationale for early studies using drugs such as amobarbital, meprobamate, chlordiazepoxide, propranolol, haloperidol and thiazide diuretics was unjustified, with some agents showing no positive effect and others even provoking a detrimental effect on language performance.[126,127]

The current motivation for using drugs in aphasia is based on theoretically-driven cognitive neuroscience and in the past few years several approaches for pharmacological intervention have been outlined.[126,127] The following sections discuss pharmacological interventions based on replacement or augmentation of depleted neurotransmitters.

5.1 Drugs Acting on the GABA-Minergic System

5.1.1 Piracetam

Piracetam is a cyclic derivative of GABA with neuroprotective and antithrombotic effects that have a potential role in cognitive, language and memory functions.[129] Piracetam tends to normalise metabolic functions in compromised but still viable tissue in the vicinity of the infarct (ischaemic penumbra). It reduces capillary vasospasm and decreases platelet aggregation.[129] Piracetam also improves learning and memory by enhancing neurotransmission of acetylcholine and excitatory aminoacids in animals and humans, mainly through postsynaptic modulation of receptor density and activity.[129] These restorative mechanisms acting in concert could promote the positive effects of piracetam on the recovery of aphasia and associated cognitive impairments. Piracetam has been evaluated as a treatment of poststroke aphasia in several randomised controlled trials in which patients started treatment at different times after stroke onset.[57,130-135] At present, some researchers consider piracetam as the only promising drug for the treatment of poststroke aphasia.[136] However, an important shortcoming of piracetam is that the reported benefits were demonstrated only in the acute stage.[129]

Two small, double-blind, placebo-controlled pilot trials of piracetam in acute stroke reported a statistically significant effect for piracetam compared with placebo in aphasia and motor function.[130,131] In one study, 20 of 27 (74%) patients receiving piracetam showed improvement from aphasia after 28 days, whereas only 6 of 29 (21%) receiving placebo improved ($p < 0.05$).[130] In the other study, 7 of 11 (64%) patients receiving piracetam had complete remission of aphasia, as compared with one of six (17%) patients on placebo ($p < 0.05$).[131]

Enderby et al.[132] performed a 12-week, double-blind, parallel group, placebo-controlled, multicentre pilot trial of piracetam among patients with acute aphasia (6–9 weeks poststroke onset) secondary to infarction in the carotid artery territory or haemorrhage. Patients ($n = 137$) were assigned randomly to piracetam (4.8 g/day) or placebo. Thirty patients on piracetam and 37 on placebo were aphasic on entry.

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Aphasia was assessed with the Aachen Aphasia Battery (AAT) and standardised measures of activities of daily living (e.g. Barthel Index) and perception (Rivermead Perception Assessment Battery). At baseline, patients were matched for demographic data, stroke-related deficits and type and severity of aphasia. Tests were administered at baseline, at weeks 5 and 12, and 12 weeks after withdrawal of piracetam or placebo.

Multivariate analysis of improvements in AAT revealed that piracetam was more effective than placebo (n = 66) and a statistically significant improvement in overall language measures was observed in the piracetam group at week 12 relative to baseline assessment (p = 0.02). However, in the patients (n = 41) who were available for evaluation 12 weeks after drug withdrawal, the obtained benefits were not maintained. No improvement in activities of daily living or perception measures was found.[132] Methodological criticisms of this trial have recently been raised:[128] the patients in the placebo group were older and waited longer before starting the treatment than the patients in the piracetam group and the type, duration and intensity of speech-language therapy for each group were not mentioned. Other potential confounding factors (e.g. different methods of language therapy, expertise of the speech therapist) were inherent to the multicentre design of the trial.[128]

In another double-blind, parallel group study, the effects of piracetam were examined using the AAT in 50 patients with either acute or chronic aphasia (4 weeks to 36 months [mean 10.5 months] poston-set).[133] Patients received piracetam (4.8 g/day) or placebo and concomitant intensive speech therapy (10 hours/week) for 6 weeks. The group receiving piracetam showed higher mean scores for all AAT subtests, yet on univariate analysis between groups the differences reached significance only for 'written language' (piracetam 58.3, placebo 45.5, p = 0.03) and approached significance for the Token Test (piracetam group 51.0, placebo group 42.2, p = 0.07) after 6 weeks. Piracetam was also superior to placebo according to the 'profile height' (a clinically relevant weighted average of subtest scores) analysis at 6 weeks (piracetam group 51.2, placebo group 48.5, p = 0.04). There were no significant between-group differences for any of the 6 scales of spontaneous speech of the AAT, although there was a strong trend for improvement in syntactical structure in the piracetam-treated group (p = 0.07).[133] The result of this study should be interpreted with caution as not all participants were aphasic due to stroke.

In a subanalysis of the PASS (Piracetam in Acute Stroke Study), 373 patients who had aphasia at baseline received intravenous bolus piracetam 12mg or placebo within 12 hours of stroke.[134] It was found that more patients treated with piracetam recovered from aphasia than those receiving placebo (piracetam group 59/180 [33%], placebo group 45/193 [23%], p = 0.04). Regrettably, aphasia in the PASS was assessed only with the Frenchay Aphasia Screening Test (FAST), an inadequate instrument evaluating improvement of aphasic deficits.[128] A subsequent publication based on the data from this study reported the effects of piracetam on recovery from aphasia.[135] Language assessment at 12 weeks showed that more patients on piracetam (59/180 [33%]) had recovered from aphasia than those receiving placebo (45/193 [23%] (p = 0.04).[135]

A more recent prospective, randomised, double-blind, placebo-controlled trial investigated whether or not piracetam paired with language therapy promoted recovery from aphasia.[57] Interestingly, the potential brain changes after combined piracetam and language therapy were examined with PET. Twenty-four right-handed patients with acute left hemisphere strokes who had various aphasia types ranging from mild to moderate severity received either piracetam (2.4g twice daily) or placebo and intensive speech therapy (5 hours/week) for 6 weeks. Language was assessed with the AAT and regional cerebral blood flow (rCBF) changes were measured with two PET scans (baseline at 2 weeks and follow-up at 8 weeks) carried out at rest and during activation with a word-repetition task in all patients. Both groups showed improvement in written naming, comprehension and Token Test, but only the group receiving piracetam (12 patients) showed a significant improvement in spontaneous speech (communicative verbal behaviour and syntactic/semantic structure of speech). Significant piracetam-induced rCBF changes were documented in response to task-specific activation only in the left temporal and frontal cortices as compared with

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baseline measures, whereas the placebo group showed an increase of activation only in the left precentral gyrus (vocalisation area). These results suggest that in acute poststroke aphasia, piracetam paired with speech-language therapy promotes the reactivation of functionally hypoactive tissue in the left temporal and frontal lobe structures around the infarct.

5.2 Drugs Acting on Catecholamine Systems

5.2.1 Bromocriptine

The ascending dopamine pathways are long-length systems arising from the cell groups of the substantia nigra and ventral tegmental area.[137] The majority of cells projecting to the cortex (supplementary motor area and prefrontal agranular regions) arise from the ventral tegmental area and the medial half of the substantia nigra pars compacta.[137] These dopamine pathways are part of a distributed network involving the anterior cingulate, dorsolateral prefrontal and inferior parietal cortices that play a key role in arousal, attention and motivation.[137] Vascular lesions in the left supplementary area, anterior cingulate cortex or in subcortical structures (basal ganglia, thalamus and internal capsule) often produce nonfluent aphasia, deficits in focusing attention on language (e.g. performance monitoring, response selection) and decreased motivation due to a reduction in the availability of dopamine in axons ending in these cortical and subcortical regions.[6,39,124,125,138-150]

The potential beneficial effects of dopamine agonists in acquired brain injury, including stroke lesions, are broad.[137] The dopamine systems have been implicated in a wide variety of functions (motor control, cognition, language, arousal and recovery of function) and dopamine agonists, most notably bromocriptine, have shown a positive influence in the recovery from nonfluent aphasia,[6,39,124-128,138-147] hemispatial neglect[148,149] and motivational deficits.[150] The rationale for using bromocriptine in poststroke aphasia is that certain distinctive features of the nonfluent aphasias (verbal adynamia, hesitation and reduced spontaneous word production) may result from selective disruption of the dopamine mesocortical and mesolimbic projection system at the level of basal ganglia, dorsolateral frontal cortex or supplementary motor area region.[6,39] Thus, some investigators have advocated the use of bromocriptine (dosage range 10–60 mg/day) alone or as an adjunct to conventional speech-language therapy among patients with different types of nonfluent aphasias, most notably transcortical motor aphasia (TCMA).[6,124,125] Bromocriptine has been extensively studied for the treatment of nonfluent aphasia mostly in single-case studies, small case series and open-label trials (table I).

In single-case studies and case series, bromocriptine was effective in most patients, with one study reporting similar benefits in Broca's aphasia or TCMA[145] and another study showing improvement limited to patients with TCMA.[125] Two studies showed little improvement or no benefit with bromocriptine in nonfluent aphasia.[142,146] In some studies, positive effects have been noticed in speech initiation, pauses and hesitation in connected speech, verbal fluency, and visual naming accuracy and response latency.[6,39,124,125,138,139,145] By contrast, other studies showed positive effects restricted to measures of speech fluency at variable dosages (10–20 mg/day)[143,147] or no response at higher dosages (25 mg/day).[142] Benefits in language deficits obtained during the bromocriptine treatment returned to baseline during withdrawal in nearly all single-case studies and small case series of patients with chronic aphasia,[6,138,139,145] but gains were long lasting in a patient with an acute crossed TCMA.[147]

Sabe et al.[139] reported an open-label trial in a group of seven patients with chronic (mean duration 2 years [range 1–3 years]) nonfluent poststroke aphasia who received various bromocriptine dosages (15–60 mg/day). Spontaneous speech was evaluated with a picture description of the WAB. Based on the composite spontaneous speech (SS) score (range 0–20) of this battery, the patients were classified as having moderate (SS score >10) or severe (SS score ≤10) nonfluent aphasia. Efficacy measures were the number of content words, content units, grammatical morphemes within the content unit, number of pauses during picture description and verbal fluency. The main finding of this study was that patients with nonfluent aphasia of moderate severity (TCMA n = 3, mean Aphasia Quotient [AQ] score 78) had significant improvements in verbal fluency, number of meaningful words and

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Table I. Summary of single-case studies, small case series and open-label trials of bromocriptine in poststroke nonfluent aphasia

Aphasia type (no. of patients)	Study design/dosage	Main findings	Reference
Chronic TCMA (1)	Open-label 6 weeks/30 mg/day	Reduced latency of response, decreased paraphasias and pauses; increased naming ability	124
		Language returned to baseline after drug withdrawal	
		Facial tics	
Chronic TCMA (1)	Open-label/15–40 mg/day	During therapy language performance improved substantially; language returned to baseline after drug withdrawal[a]	125
Chronic mixed (1)		No improvement on formal evaluation	
Chronic Broca's (1)		No improvement on formal evaluation	
Chronic Broca's (1)	Open-label/10 mg/day (low dose), 30 mg/day (high dose)	Improved repetition and naming, increased number of words/minute	140
Chronic TCMA (1)		Marked improvement in number of words/minute; improved speech fluency at low dose; positive change in mood	
Chronic TCMA (1)	Single-blind, multiple baseline 4 weeks; placebo 7 weeks/15 mg/day; withdrawal	Increased number of words and correct information units; no change in naming and fluency	138
		Improvement in mood and communication questionnaire during treatment (patient's report only)	
		Language, mood and communication returned to baseline after drug withdrawal	
Chronic TCMA (4) Chronic Broca's (4) Global (1)	Open-label 14 weeks/15–60 mg/day; withdrawal	Increased number of words/minute and fluency if moderate, but not severe, aphasia Language returned to baseline after drug withdrawal Painful dystonia (n = 4); nausea (n = 6)	139
Chronic Broca's (2) Chronic global (1) Chronic TCMA (1)	Open-label/10–25 mg/day	No change on any language test scores	142
Chronic TCMA (1)	Open-label 12 weeks/20 mg/day	Reduced latency of response, hesitation and pauses Increased number of words and narrative capacity Increased naming ability Improvement in mood and communication questionnaire during treatment	39
TCMA (1)	Open-label	No changes in language performance Improvement with donepezil (effect maintained after treatment was stopped)	146
Chronic Broca's (2) Chronic TCMA (2)	Open-label, ABBA design 10 weeks/ 15 mg/day	Improved word retrieval (picture naming) in 4/4 and faster reaction times in 3/4 Word retrieval returned to baseline after drug withdrawal in 3/4	145
Acute crossed TCMA (1)	Open-label, ABAB withdrawal design/ escalating dosages up to 20 mg/day	Improved letter and discourse fluency Lack of effect on gesture or emotional prosody Effect maintained after treatment was stopped	147

a Reported in Albert et al.[124]

TCMA = transcortical motor aphasia.

pauses produced during picture description, whereas these improvements were not observed in patients with severe nonfluent aphasia (Broca's [n = 2]; global [n = 1]; TCMA [n = 1]; mean AQ score 31.5).[139] Adverse reactions were common; six patients reported gastrointestinal distress (nausea) during the first week of treatment and four developed painful dystonia on the paretic side while receiving high dosages of bromocriptine (30–60 mg/day).[151]

Three randomised controlled trials of bromocriptine in nonfluent poststroke aphasia have been published.[141,143,144] In a crossover study, seven chronic

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aphasic patients (mean duration 2.5 years [range 1–7 years]) received high dosages of bromocriptine (up to 60 mg/day) for 6 weeks.[141] This was followed by a 6 week placebo phase after a washout period of 3 weeks. Language was evaluated using the picture description of the WAB or the BDAE. Efficacy measures were the number of content words, content units, number of pauses during picture description, oral naming and verbal fluency. There were no statistical significant differences between the groups in any variable, though a slight improvement in all language variables was found in the placebo arm. Important limitations of this study are that all seven patients were randomised to receive bromocriptine in the first treatment arm, then placebo later in the second arm, and that language evaluations were repeated every week. Thus, any improvement in language performance found in the placebo period may have been a result of practice effect or the residual influence of the bromocriptine treatment (carryover effect). In addition, this study included a small sample with mixed aetiology (five infarction, two head trauma). In a similar study, 20 chronic nonfluent aphasic patients (mean duration 66 months [range 13–207 months]) secondary to stroke lesions were randomised to receive either low doses of bromocriptine (up to 15 mg/day) or placebo for 8 weeks.[143] This was followed by a period of drug reduction (2 weeks) and washout (4 weeks), after which the patients were crossed over to the alternative arm of the trial for 8 weeks. Five evaluation sessions were performed. Language was assessed using the WAB and the Boston Naming Test and a battery of memory and nonverbal cognition tests was also used. The AQ of the WAB decreased on average by only 0.06 points while the patients were taking bromocriptine. In addition, bromocriptine was not superior to placebo in measures of speech fluency and nonverbal cognition.[143]

In a two-phase study, the efficacy of bromocriptine and speech therapy was evaluated in 11 patients with chronic nonfluent aphasia (mean duration 2.1 years [range 0.5–8 years]) associated with stroke.[144] Of these patients, nine had Broca's aphasia and another two had global aphasia. After multiple baseline language evaluations, the patients were treated with placebo and speech therapy (two individual sessions weekly) followed by bromocriptine 30mg three times daily and speech therapy; a washout phase then followed. Compared with baseline, the investigators reported a significant improvement during the bromocriptine/speech therapy phase in dictation (47% improvement, $p < 0.004$), reading comprehension (32% improvement, $p < 0.0003$), repetition (23% improvement, $p < 0.01$) and verbal latency (baseline 7.14 ± 1.7 seconds, bromocriptine-speech therapy 4.8 ± 1.6 seconds, $p < 0.01$).[144] Since bromocriptine was introduced after the placebo phase, it is possible that practice effects accounted for the observed benefits. Moreover, only five of the 11 patients completed the drug trial, thus limiting the value of the positive responses reported under the drug. There also was an elevated occurrence of adverse effects during bromocriptine treatment. Cardiac arrhythmias, seizures and visual hallucinations were the main reasons for withdrawals from therapy. Furthermore, 14 (56%) of the 25 initially selected patients could not be included because of contraindications to use of bromocriptine. This indicates that bromocriptine may be used with confidence only in a small proportion of aphasic patients.

Taken together, the results of these studies are conflicting, since the positive effects reported in most single-case studies, small case series and open-label trials have not been confirmed in subsequent randomised controlled trials. These discrepant findings regarding the potential effect of bromocriptine on improving nonfluency and other expressive deficits in poststroke aphasia may depend, at least in part, on the distinct neural and cognitive bases for these functions among individuals with aphasia.[39,152] Patients with nonfluent Broca's and global aphasias have large lesions in the anterior perisylvian cortex, a critical region for mediating verbal fluency, speech articulation, phrase length, grammar, picture naming and linguistic prosody. Thus, the augmentation of brain dopamine with bromocriptine or similar drugs (levodopa, amantadine) in these cases with large lesions may not be sufficient to promote a modulating effect in verbal fluency and related expressive functions in the few brain language regions that escaped injury.[152] On the other hand, available information, though mainly anecdotal, strongly suggests that the effects of bromocriptine are more powerful in apha-

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sic patients with discrete damage to the mesocortical dopamine system and frontal cortex.[39,152] In this regard, two extensive reviews suggest that, at present, TCMA resulting from subcortical and frontal lobe (mesial and dorsolateral) lesions that spare large portions of the perisylvian language cortex seems to be the only class of syndrome amenable to pharmacological treatment with dopamine agonists.[40,152]

Additional randomised controlled trials of bromocriptine in larger numbers of patients with better sampling selection are warranted. Efforts should be concentrated on designing trials in patients with those nonfluent aphasias (e.g. TCMA) in which bromocriptine has already showed the most impressive results. The issue of whether more modern dopamine agonists (e.g. pergolide, pramipexole) are more potent, better tolerated, and associated with fewer adverse effects (e.g. painful dystonia) than bromocriptine in this aphasic population also needs to be investigated.

5.2.2 Dexamfetamine

The action of dexamfetamine facilitates the presynaptic release of the monoamines noradrenaline, dopamine and serotonin and inhibits their uptake from the synaptic cleft, an effect that alleviates neuronal synaptic dysfunction in other brain areas distant from the cerebral infarction (diaschisis).[87,126] Moreover, it also facilitates memory storage through its effects on memory consolidation by stimulating long-term potentiation and plasticity of language networks[87,126,153] The beneficial effect of dexamfetamine on recovery of motor and language function in stroke patients depends on concomitant experience.[87,154,155] In fact, there is some evidence that dexamfetamine paired with motor training favours plasticity at cortical and subcortical levels contributing to functional recovery after brain injury.[156] In poststroke aphasia, unblinded pilot studies[157] and a randomised controlled trial[87] found an increased rate of recovery from language deficits when a low dose of dexamfetamine was paired with speech-language therapy in acute aphasia, but not in a single patient with chronic aphasia.[158] In a recent double-blind study,[87] 21 patients with subacute aphasia (between days 16 and 45 postonset) secondary to single ischaemic infarctions in the territory of the middle cerebral artery were randomly assigned to receive dexamfetamine 10mg (12 patients) or placebo (nine patients) on a 3-day/4-day cycle for ten sessions over 5 weeks. All patients also received conventional speech-language therapy on an individual basis lasting 1 hour and commencing 30 minutes after the drug (or placebo) treatment. The primary outcome measure was the PICA for which overall scores were obtained at baseline, 1 week after cessation of treatment and again at 6 months. Although patients on dexamfetamine tended to be younger than those on placebo (51.8 years vs 61.3 years, $p = 0.0637$), the two groups were similar in terms of other demographic characteristics, lesion volumes and baseline PICA overall score as well as in the number of hours of treatment received (dexamfetamine group 33.0, placebo group 27.2, $p = 0.331$). There was a statistically significant between-group difference on PICA gain scores (dexamfetamine group 16.7, placebo group 11.3, $p = 0.0153$) at 1 week after completion of the treatment cycles. Although the between-group differences on PICA gain scores were maintained and even increased at 6 month follow-up, the differences did not reach statistical significance after Bonferroni correction for multiple comparisons. Strengths of this study are the inclusion of many patients with severe aphasia (PICA scores ≤30) and the lack of adverse events. It should be noted, however, that the projected sample size of 32 patients could not be achieved even though the patient recruitment period lasted 4 years. This is probably because of the number of dexamfetamine contraindications and means that its use in poststroke aphasia should be restricted to highly-selected populations.

The long-term efficacy of dexamfetamine for poststroke aphasia also needs further assessment. A recent study using a single-subject, double-blind, placebo-controlled multiple-baseline design of dexamfetamine paired with intensive lexical-semantic activation inhibition therapy (four times per week over a 6-week period) did not document a positive treatment effect in a patient with poststroke anomic aphasia of 3-year duration.[158]

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5.3 Drugs Acting on Acetylcholine Systems

Acetylcholine acts as a cortical modulator and plays a crucial role in cognitive processes, such as learning and memory.[137] It has also been implicated in the regulation of cortical arousal,[146] attentional processing[159] and spatial learning,[160] and plays an important role in long-term potentiation and experience-dependent plasticity in the cerebral cortex.[161-163] While the correlation between the decrease in cholinergic activity and cognitive impairment in Alzheimer's disease has led to attempts to develop cholinergic replacement therapy, the rationale for using cholinergic agents to treat poststroke cognitive disorders was, until recently, poorly understood.[164-168] Different sectors of the human cerebral cortex receive dense cholinergic input from the basal forebrain complex, whereas ascending pathways from the brainstem complex project to the thalamus and hypothalamus.[137,161] Recent neuroanatomical and histochemical studies have shown that the medial and lateral cholinergic pathways emanating from the neurons of the nucleus basalis of Meynert (nbM) [Ch4 cell group] course through structures (e.g. centrum semiovale, external capsule, claustrum) which are commonly involved in stroke lesions.[161] In fact, language and other cognitive impairments secondary to cortical[168] and subcortical[169] vascular lesions have been attributed to cholinergic depletion that resulting from interruption of cholinergic fibre pathways linking the nbM with the cerebral cortex. Mesulam et al.[169] have recently described neocortical cholinergic denervation subsequent to multiple pure subcortical infarcts (involving the white matter but sparing the nbM) in a young patient with vascular dementia and severe impairments in language, memory and visuospatial orientation. Interestingly, histochemical study revealed the interruption of the ascending cholinergic pathways in the external capsule and centrum semiovale, although some acetylcholine-rich fibres and cholinergic cortical neurons survived even in the areas of greatest cholinergic denervation, a finding that invited the authors to propose that cholinergic therapies may work in these patients.[169]

5.3.1 Donepezil

Donepezil, a reversible acetylcholinesterase inhibitor with a selective central action, is an effective and well tolerated palliative treatment for Alzheimer's disease.[170,171] It has a limited potential for causing clinically significant interactions when prescribed with other medications.[172] In the past few years, the beneficial effect of donepezil on cognition has been demonstrated in conditions other than Alzheimer's disease.[164-167,171,173] For example, randomised controlled trials in vascular dementia (studies 307 and 308) reported that donepezil significantly improved cognition, global function, and activities of daily living. [165,166] The observed benefits were greater in patients with cortical lesions as compared with those with subcortical lesions.[165,166] Moreover, recent *in vitro* studies have shown that donepezil has a protective effect against ischaemia-induced neuronal cell injury which appears unrelated to acetylcholinesterase inhibition.[174]

Preliminary clinical experience in single-case studies and small case series suggests that in non-demented patients with vascular lesions, donepezil can also improve aphasic deficits,[146] focal cognitive deficits (agnosia, apraxia and amnesia),[175,176] and unilateral sensory-motor deficits.[177] Although the available clinical data regarding the efficacy of donepezil in the treatment of poststroke aphasia are limited, a preliminary study suggests that donepezil may promote the amelioration of language deficits in chronic poststroke aphasia.[88] In this 20-week open-label study, donepezil was administered to 11 patients (ten men and one woman, mean age 56 years) with different types of chronic aphasia (mean duration 4.4 years). All patients were recruited from a language therapy centre where they received two weekly sessions of conventional speech-language therapy. Eligible patients were required to have a unilateral vascular lesion involving the perisylvian language cortex and an AQ score ≤93.8 on the WAB.

All patients received donepezil 5 mg/day for 4 weeks followed by 10 mg/day for another 12 weeks and then a withdrawal period of 4 weeks. The predefined primary efficacy variable was the AQ of the WAB, a measure of global severity, which results from the sum of information content, fluency, comprehension, repetition and naming subtest scores. Measures of spontaneous speech, including correct information units (CIU) [nonredundant content words that convey correct information about the

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Table II. Individual baseline and change scores[a] for aphasia quotient (AQ) of the Western Aphasia Battery in a preliminary open-label study of donepezil in patients with different types of chronic aphasia[88]

Patient number/sex	Age (years)	Aphasia type	AQ baseline	AQ week 4 donepezil 5mg	AQ week 16 donepezil 10mg	AQ week 20 washout	AQ 6-month follow-up donepezil 10mg
1/M	66	Broca's	54.6	+12.8	+11.6	+13.6	+14.4
2/M	41	Broca's	21.6	+1.4	+10	+8.4	+9
3/M	44	Broca's	42.8	+2	+7.2	+7.4	+7.4
4/M	27	Broca's	48.8	+1	+6.6	+6	+7.2
5/M[b]	67	Conduction	72.0	+4.8	NT	NT	NT
6/M	61	Conduction	45.8	+12	+7.8	+2.8	+3.4
7/M[c]	52	Conduction	76.0	+7.8	+12.4	+9	+12.4
8/M[c]	51	Conduction	61.6	+8.5	+17	+15.6	+20
9/M[c]	72	Conduction	79.8	+7.4	+7.2	+3.6	+9
10/F	64	Conduction	65.0	+6.6	+12.4	+9.6	+14.2
11/M	65	Wernicke's	39.2	+6	+3.6	+3	+0.4
Mean ± SD	**56 ± 13.2**		**55.1 ± 17.6**	**6.3 ± 3.9**	**9.5 ± 3.8**	**7.9 ± 4.3**	**8 ± 5.1**

a Change scores (weeks 4, 16 and 20 and 6 month follow-up) are always compared with baseline evaluation; positive numbers indicate increments in performance.

b This patient discontinued treatment after 1 month of donepezil because of subjectively perceived nonresponse.

c Although these three patients participated in the 6-month extension phase, their AQ scores were not included in statistical analyses because during this phase they received intensive modality-specific language therapy.

F = female; **M** = male; **NT** = no treatment.

stimulus], percentage of CIU (number of CIUs/number of words × 100), and pauses (number of pauses >3 seconds) during the description of the WAB picture (picnic scene) and the individual language subtest scores of the WAB (fluency, information content, comprehension, repetition and naming), were also used to rate changes in aphasia severity. Other efficacy measures included nine selected subtests of the Spanish version of the PALPA.[178] These tasks examine phoneme discrimination, lexical decision, semantic comprehension of word and sentences, repetition of word and nonwords, and naming. The effect of donepezil on aphasia severity was analysed using the Wilcoxon signed rank test. In this exploratory study statistical corrections for multiple comparisons were not performed.

Data were available from ten patients and one patient discontinued treatment after 1 month of donepezil because of subjectively perceived nonresponse (table II). Donepezil was well tolerated. Treatment-emergent adverse events (mild irritability and increased sexual drive) were observed in two patients on starting the 10mg dose.[88]

Donepezil significantly improved global aphasia severity as measured by changes from the baseline in AQ scores at week 4 (mean difference +6.3, $p < 0.01$) and at week 16 (mean difference +9.5, $p < 0.01$). Similarly, there was a significant improvement in measures of spontaneous speech at week 4 (CIU mean difference +24, $p < 0.003$) and at week 16 (CIU mean difference +19.5, $p = 0.007$, information content of the WAB mean difference +0.7, $p < 0.03$). Donepezil also increased PALPA scores in six of the nine domains. Significant improvements were seen at week 4 in phonemic discrimination of nonwords (mean difference +4.3, $p < 0.01$), word repetition (mean difference +2.7, $p < 0.01$), naming by frequency (mean difference +4.9, $p < 0.05$) and oral sentence-picture match (mean difference + 7.1, $p < 0.01$), and at week 16 in nonword repetition (mean difference +2.3, $p < 0.01$), oral word-picture match (mean difference +1.4, $p < 0.05$) and oral sentence-picture match (mean difference +4.4, $p < 0.01$). Language assessment 4 weeks after withdrawal of donepezil showed a statistically significant reduction in AQ score of the WAB (mean difference −1.6, $p < 0.05$) and oral word-picture match (mean difference −1.1, $p < 0.05$).[88]

The result of this pilot study should be interpreted with caution because of its open-label and uncontrolled design, the small number of patients, the

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possibility of practice effects and the patients' expectations of improvement with a new drug.[88] In spite of these important limitations, the results of this study suggest that donepezil may be effective in different linguistic domains, particularly in tests that assess input and output phonology and lexical-semantic processing.

In clinical settings, one important requisite to be met by a pharmacological agent is the maintenance of the therapeutic effect in the long term. The long-term efficacy of drugs in aphasia has not been systematically examined in most clinical trials and when it was considered (e.g. piracetam) the reported benefits were short-lived.[136] Therefore, after completing the withdrawal phase of the open-label trial of donepezil, seven patients with aphasia of moderate severity (mean baseline AQ score 45.3 ± 13.4) were invited to participate in a 6-month extension phase to examine if obtained benefits were still present in the long term (Berthier, unpublished data). Once again, they received donepezil 5 mg/day for 4 weeks and then 10 mg/day for the remaining 22 weeks. They also received two weekly sessions of conventional speech-language therapy. The remaining three patients who completed the open-label trial had aphasia of mild severity (mean baseline AQ score 72.4 ± 9.6) and were excluded from analysis because after completing the open-label trial they received donepezil paired with intensive modality-specific therapy.[115]

Language assessment in these seven patients after completion of the extension phase showed that the gains obtained before the washout period persisted (table II). Patients' performance on the AQ of the WAB remained significantly higher than at baseline evaluation (mean difference +8, $p < 0.01$), but similar to assessment at week 16 (donepezil 10 mg/day) (mean change 0.4, $p = 0.81$). Similar findings were found in 2 PALPA subtests, namely, word repetition (mean change relative to baseline +3.1, $p < 0.01$) and oral sentence-picture match (mean change relative to baseline +3.8, $p < 0.001$). These preliminary findings suggest that donepezil efficacy in aphasia is maintained at long-term follow-up.

6. Conclusion

Poststroke aphasia has a range of negative consequences on communicative skills, mood and behaviour, quality of life and occupational activities. In the past several years, experimental preclinical studies, clinical observations, structural and functional neuroimaging studies, and neurophysiological investigations have provided greater insight into the basic mechanisms underlying recovery from aphasia. This has led to the design of more rational and better focused speech-language therapies, and more attention is being directed to combing rehabilitation techniques with drugs. Much work needs to be done and a multidisciplinary approach is mandatory to embrace the broad range of domains affected in the aphasic individual.

Regarding the pharmacotherapy of poststroke aphasia, future research may examine which specific components of abnormal language may be amenable to pharmacological manipulation. The potential effects of drugs on functional communication, activities of daily living and psychiatric comorbidities need to be explored. It appears equally important to identify in which patients and at what stage of the aphasia evolution process a specific pharmacological therapy may work. In order to minimise biased outcome results, future studies should not be directed exclusively at patients with mild or moderately severe aphasia; patients with severe aphasia should be included as well. Randomised controlled trials using large sample sizes comparing drug versus placebo, another drug, or intensive speech-language therapy are recommended. Combined pharmacological therapies warrant evaluation in future studies. It is possible that agents such as donepezil tend to improve performance in language activities dependent upon the cholinergic circuitry in the temporal lobe but have less effect on others relying on frontal lobe function, where dopamine agonists (e.g. bromocriptine) may be the more potent pharmacological agents. Moreover, although it is imperative to prove the efficacy of donepezil and other acetylcholinesterase inhibitors in elderly poststroke aphasic patients, it appears desirable that pilot randomised controlled trials should be performed in relatively young patients to rule out the inclusion of patients with age-related changes or Alzheimer's disease-related lesions.

Patient recruitment for large randomised controlled trials is a difficult enterprise and explains the scarcity of studies in this area. Given the many

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difficulties and little success associated with the published randomised controlled trials, other designs such as single-case studies or, preferably, case series including patients with *a priori* defined language deficits and evaluated with standardised batteries and cognitive neuropsychological tests may be a viable alternative to randomised controlled trials. Observed improvements in these single-case or small group studies would hold more weight in the scientific community if they were correlated with resultant changes in the pattern of cerebral activity, as measured by functional imaging and other modern ancillary techniques.

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Correspondence and offprints: Dr *Marcelo L. Berthier*, Centro de Investigaciones Médico-Sanitarias (CIMES), Departamento de Medicina, Facultad de Medicina, Universidad de Málaga, Campus Universitario Teatinos, Málaga, 29071, España.

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