

Update on Pharmacology

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Pharmacotherapy of Aphasia

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MANY efforts have been undertaken at helping patients with aphasia recover from their deficits by using various rehabilitation techniques. A number of studies have also been carried out to investigate the role of pharmacological agents in the treatment of aphasia. Aphasia can result from a variety of injuries to the brain, including trauma and stroke. However, most of the research has focused on stroke due to the focal nature of the lesions and the vascular territories resulting in a more homogeneous patient population for study. Therefore, any possible benefits for people with traumatic brain injury must be extrapolated from the studies on subjects with stroke.

A number of drugs have been developed for the treatment of Alzheimer's disease. The *N*-methyl-D-aspartic acid receptor antagonists have also demonstrated benefits in patients with vascular dementia on batteries of cognitive tests that prominently feature language,¹ suggesting that benefits might also result for patients undergoing rehabilitation for aphasia. Studies with cholinesterase inhibitors have also demonstrated significant benefits in patients with vascular dementia, and specifically in the treatment of patients with aphasia.^{2,3}

A derivative of gamma aminobutyric acid, piracetam, with reported benefits for cognition and memory, has also been examined in the treatment of patients with aphasia. Significant benefits have been observed in these patients a few weeks to 3 years after onset of aphasia, at a dose of 2.4 mg twice a day.⁴ Use of piracetam in aphasia is also associated with an increase in language task-related activation on functional neuroimaging.⁵ How-

ever, the mechanism of action of these effects is not fully understood.

The types of aphasia are not specified in many of these studies, raising questions as to their utility for each of the varying degrees and subtypes of aphasic syndromes. However, Albert et al⁶ reported on a patient with transcortical motor aphasia due to a hemorrhagic stroke that had occurred 3½ years earlier. The hypothesis for the pharmacotherapeutic plan was that since speech initiation is impaired in such patients, as is observed in patients with Parkinson's disease, perhaps an improvement might result from treatment with a dopaminergic agonist. In the study, a decrease was observed in the proportion of pauses during speech in this patient while increasing the dose to 15 mg and then to 30 mg of bromocriptine per day, as well as improvements in naming and paraphasic errors. A number of follow-up studies, though, have not demonstrated this finding in larger groups of patients.⁷

Several studies, including randomized, double-blinded, placebo-controlled trials, have examined stimulant therapy with amphetamine, which evidence suggests enhances neural plasticity in the subacute time period postinjury. These studies have demonstrated significant benefits in patients with aphasia using 10 mg amphetamine paired with speech therapy (preceding therapy by 30 minutes) 16 to 45 days after ischemic stroke.⁸ There appeared to be no specificity of this response to stroke subtype. Furthermore, no problems were experienced with tolerability at this modest dose.⁹ The improvement did not correlate with blood pressure, suggesting that the benefit did not appear to simply be the result of a general hemodynamic effect.⁹ However, this beneficial effect did not occur in patients over a year after their stroke.¹⁰

The noradrenergic system is believed to have an effect on the signal-to-noise ratio within the cerebral cortex.¹¹ More recent studies have suggested a related modulatory role of the noradrenergic system on performance of problem-solving tasks dependent upon access to the lexical-semantic networks. Specifically, decreased

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noradrenergic tone benefited broad searches within the network such as with solving anagrams in normal individuals.^{12,13} This effect in normal subjects does not appear to be due to a general anxiolytic effect.¹⁴ Patients with expressive aphasia are aware of their deficits and have difficulty accessing the networks representing phonological output. Therefore, perhaps decreased noradrenergic activity would benefit those patients with intact error monitoring in their search of these networks, particularly those who are chronic and therefore not likely to benefit from stimulant therapy. In contrast, patients unaware of their deficits, with impaired error monitoring, might as a result have a greater access to a range of potential incorrect responses due to an expanded network search. A pilot study examining naming performance in 4 patients with expressive aphasia 7 months to 4 years after an ischemic stroke revealed superior performance after 40 mg of propranolol as compared to placebo.¹⁵ Subjects were tested after single doses of the drug, so further study will be necessary to examine response to sustained treatment. Follow-up studies would also be important to determine at what point in time after stroke the benefit from amphetamine ends and the benefit from propranolol begins. Patients with known blood pressure instability

causing variation in language performance should avoid propranolol, however, due to risk of cortical hypoperfusion with any antihypertensive drug. Also, aphasic patients of other types, and in particular, those with poor awareness of deficits, may not benefit from these proposed noradrenergic antagonism benefits on the flexibility of access to the phonological output or lexical-semantic networks. Therefore, studies in a variety of aphasia subtypes as well as examination of a range of noradrenergic blocking agents and other anxiolytic agents should also be performed in future in order to better understand this effect. To some extent, propranolol may also be treating anxiety in this population. Awareness of the deficit can be frustrating for patients with expressive aphasia, and as a result, anxiety may be a significant component of the problem in this population.

Much needs to be learned in order to optimize the pharmacological treatment of aphasia, including better understanding of drugs' mechanisms of action, timing of treatment, and ultimately the roles of combinations of drugs. Once these issues are better understood, combining pharmacotherapy with other modes of therapy will hopefully yield greater benefits for this disabling condition.

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