Pharmacotherapy of Aphasia
A Critical Review

Steven L. Small, MD, PhD

Background Communication problems are a common sequela of cerebrovascular disease and other central nervous system disorders. Behavioral treatment of these disorders aims to harness uninjured parts of the brain to improve the communicative life of the individual. While pharmacotherapy has held promise for the treatment of aphasia for over 50 years, it has not fulfilled this promise. This article reviews both the promise and the disappointment of aphasia pharmacotherapy.

Summary of Review Diverse theories of the underlying neurological deficits in aphasia have led to different pharmacologic rationales for therapy. Animal studies have demonstrated decreased levels of brain catecholamines after cortical stroke and more rapid stroke recovery with therapy aimed at augmenting brain norepinephrine and dopamine. These studies have led to recent attempts to hasten or extend language and sensorimotor rehabilitation after human stroke by administration of catecholaminergic drugs. When used as an adjunct to behavioral therapy, such pharmacotherapy appears to have benefit.

Conclusions While drug therapy is unlikely to revolutionize the treatment of aphasia, it nonetheless holds promise as an adjunct to behavioral speech and language therapy to decrease performance variability and consequently to improve mean performance in patients with mild to moderate language dysfunction. Additional studies with carefully designed methods are necessary to assess the full potential of aphasia pharmacotherapy. (Stroke. 1994;25:1282-1289.)

Key Words • aphasia • language • pharmacology

While language processing difficulties are a common manifestation of cerebrovascular disease and other central nervous system (CNS) disease, treatment remains unsatisfactory for many. The frustrations of neurological rehabilitation are accentuated in the treatment of aphasia. A person often has lost brain tissue and associated functioning, and in most cases, this will never completely return to normal. In the case of aphasia, a person has lost the use of language, the principal feature that makes humans cognitive.

Behavioral techniques of various kinds are the mainstay of treatment, with attempts to remediate impaired linguistic processing or to improve functional communication. Unfortunately, the most common techniques are nonspecific "stimulation" strategies. While pharmacotherapy has held promise for the treatment of aphasia for over 50 years, it has not fulfilled this promise. A critical examination of the literature shows that drug therapy has less promise as solitary therapy than as an adjunct to behavioral therapy in certain individuals. The majority of experimental studies in this area have not been designed to assess accurately this outcome but instead have focused on unrealistic hopes for a therapeutic miracle.

Pharmacotherapy of Cognitive Disorders

The neuropharmacology of human brain systems has an increasing role in the study of therapeutic neurology and psychiatry. Many neurotransmitter systems are used by the brain in distinct functional tasks, and certain of these systems have been manipulated pharmacologically to produce therapeutic benefit to human patients. In some cases, specific or nonspecific manipulation of such systems has been helpful to patients even without a clear theoretical rationale.

In the realm of cognition, pharmacotherapy has had its greatest impact in psychiatry. Drug treatment has become a standard component of treatment in depression and schizophrenia, and patients now can expect far better treatment outcomes than they could during the previous eras of behavioral therapy. Much optimism now surrounds research into the treatment of the memory disorder of Alzheimer's disease, with some success achieved by directing therapy at improving cholinergic neurotransmitter systems. The greatest excitement in therapy for Alzheimer's disease currently involves prevention of glutamate excitotoxicity and the consequent neuronal damage from oxidation.

Memory disorders and aphasia share the characteristic of being symptoms rather than disease entities. Of course, this bears significantly on therapy. The memory loss of Alzheimer's disease is thought to be improved by cholinergic therapy because of a postulated defect in central cholinergic mechanisms that accompany the disorder. There is no reason to think this same therapy would be useful in another disease in which memory loss played a major role. As a major symptom of cerebral infarction, aphasia shares common physiological and neurochemical features with other stroke manifestations, such as supranuclear motor pareses and central sensory loss. Consequently, techniques aimed at stroke rehabilitation through direct CNS effects are equally applicable to language recovery and sensorimotor recovery.

Table 1 briefly reviews the drugs that have been used in therapeutic studies of rehabilitation of physical or...
TABLE 1. Brief Guide to Drugs Used in Motor and Language Rehabilitation After Stroke

<table>
<thead>
<tr>
<th>Drug</th>
<th>Neurotransmitter</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Norepinephrine</td>
<td>Increased release from storage</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Dopamine</td>
<td>Increased release from storage</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Dopamine</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Norepinephrine (α)</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Norepinephrine (β)</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Dopamine</td>
<td>Agonist</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Dopamine</td>
<td>Blocks metabolic breakdown</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>Norepinephrine</td>
<td>Blocks metabolic breakdown</td>
</tr>
<tr>
<td>Sodium amytal</td>
<td>γ-Aminobutyric acid (GABA)</td>
<td>Potentiation of inhibition</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Unknown (?opiate)</td>
<td>CNS depression</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Dopamine</td>
<td>Agonist</td>
</tr>
<tr>
<td>Methylenidate</td>
<td>Norepinephrine</td>
<td>Release from storage sites</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Dopamine</td>
<td>Release from storage sites</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>γ-Aminobutyric acid (GABA)</td>
<td>Potentiation of inhibition</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Unknown (?adenosine)</td>
<td>CNS stimulation</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system. For each drug, a neurotransmitter and the effect of the drug on that transmitter are listed. Possible effects include agonism, antagonism, release from storage sites, potentiation of function, and inhibition of metabolic breakdown. Drugs that affect serotonin concentration have been omitted, even though they have an important role in treatment of depression.

Pharmacotherapy of Sensorimotor Loss in Stroke

Before examining research directed at aphasia rehabilitation per se, it is important to review the data on brain chemistry and pharmacotherapy after experimental stroke in animal models, as well as studies of motor rehabilitation in human stroke patients. The results of these studies constitute some of the promise for drug therapy of aphasia.

Brain Catecholamines After Experimental Stroke

The concentrations of catecholamines in the rat and cat brain stem and the subcortex of the rat are decreased following cerebral cortical infarction. After the acute phase following rat unilateral cortical infarction (40 days), there remain decreases in ipsilateral norepinephrine concentrations in the cortex and brain stem and decreases in ipsilateral brain stem but not cortical dopamine concentrations. This catecholamine deficit may result from right cortical but not left cortical infarction. Such experimental stroke also causes widespread depression of glucose utilization in the cortex on both sides, the ipsilateral red nucleus, and the locus ceruleus bilaterally.

The postulated role of monoamines in stroke recovery led to a number of therapeutic studies in animal models, as summarized in Table 2. (In studies of recovery of function in animal models, it is useful to know that the duration of spontaneous recovery from a motor cortex lesion in a rat is about 2 weeks, and for a cat, spontaneous recovery takes several months.) A single dose of dextro-amphetamine (d-amphetamine), which augments postsynaptic catecholamines including norepinephrine and dopamine, led to accelerated recovery in a beam-walking task in rats with unilateral motor cortex ablation. A single dose of haloperidol, a dopamine antagonist, blocked the amphetamine effect. When given alone, haloperidol delayed spontaneous recovery, and phenoxybenzamine, an α-adrenergic antagonist, reproduced the deficits in recovered animals. Paradoxically, treatment with intraventricular norepinephrine, but not dopamine, reproduced the beneficial effect of d-amphetamine. Analogous results have been obtained with d-amphetamine therapy of motor system injury in the cat.

These motor system results generalize to the visual system. Bilateral ablation of the primary visual cortex of the cat causes impairment of visual depth perception. When given both visual experience and d-amphetamine, such cats demonstrate marked improvement in function. The effect was not seen when the d-amphetamine was unaccompanied by visual experience or when the visual experience was accompanied by saline instead of active drug.

As the locus ceruleus is the origin of diffuse noradrenergic arborizations throughout the cortex, the role of the locus ceruleus in stroke recovery was studied.
TABLE 2. Animal Studies of Pharmacotherapy in Recovery From Cortical Infarction

<table>
<thead>
<tr>
<th>Drug</th>
<th>System</th>
<th>Dose/Route</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-Amphetamine</td>
<td>Motor</td>
<td>2-4 mg/kg IP</td>
<td>Improves performance only with practice</td>
<td>21</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Motor</td>
<td>0.4 mg/kg IP</td>
<td>Blocks effects of d-amphetamine and inhibits recovery</td>
<td>21</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Motor</td>
<td>Intraventricular</td>
<td>Improves performance</td>
<td>23</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Motor</td>
<td>Intraventricular</td>
<td>No effect</td>
<td>23</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Motor and cerebellar</td>
<td>10 mg/kg IP</td>
<td>Reinstates deficit after recovery</td>
<td>23</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Cerebellar</td>
<td>20 mg/kg IP</td>
<td>No effect</td>
<td>23</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Cerebellar</td>
<td>IP injection</td>
<td>No effect</td>
<td>23</td>
</tr>
<tr>
<td>d,l-Amphetamine</td>
<td>Motor</td>
<td>5-8 mg/kg IP</td>
<td>Reverses deficit before expected recovery</td>
<td>24</td>
</tr>
<tr>
<td>d-Amphetamine</td>
<td>Motor</td>
<td>5-8 mg/kg IP</td>
<td>Better but more toxic than racemic</td>
<td>24</td>
</tr>
<tr>
<td>l-Amphetamine</td>
<td>Motor</td>
<td>5-8 mg/kg IP</td>
<td>Less benefit than racemic</td>
<td>24</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Motor</td>
<td>0.25-0.5 mg/kg IP</td>
<td>Weak restoration</td>
<td>24</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Motor</td>
<td>0.4 mg/kg IP</td>
<td>Blocks effects of amphetamines and inhibits recovery</td>
<td>24</td>
</tr>
<tr>
<td>d-Amphetamine</td>
<td>Vision</td>
<td>5 mg/kg IP</td>
<td>Reverses deficit if coupled with vision experience</td>
<td>26</td>
</tr>
</tbody>
</table>

IP indicates intraperitoneal. Studies are organized by pharmacologic agent and cerebral system it was aimed at treating (ie, motor, cerebellar, or visual). Dose of drug and method of infusion are listed as are brief summaries of study results.

After experimental stroke, there was widespread cerebral cortical depression of glucose utilization, which could be accelerated by prior ablation of the locus ceruleus. d-Amphetamine could reverse this metabolic depression, which was exacerbated by haloperidol administration, and reverse the effects of locus ceruleus damage.

Animal models thus suggest that endogenous and exogenous catecholamines, particularly norepinephrine, acting through α-receptors, play an important role in recovery from stroke. These data also suggest that the effect of catecholamine augmentation therapy depends on concomitant experience. Thus motor recovery after stroke, while facilitated by pharmacotherapy, depended on the presence of motor practice, just as visual recovery depended on visual experience.

**Human Studies**

Pharmacotherapeutic studies of aphasia have employed a variety of agents. The theoretical motivations for use of these particular agents are diverse and range from purely clinical rationales (eg, people who are anxious do not speak as well) to clinically correlated neurobiological facts (eg, tissue catecholamines are decreased hemispherically after infarction). In these studies, the measures of outcome are linguistic or communicative, and even when formal evaluations have been made, they have been completely behavioral in nature.

The very nature of aphasia complicates the problem. Group studies in aphasia are difficult because of the fundamental heterogeneity of patients along functional and anatomic lines. Furthermore, while current static and dynamic imaging techniques have increased the precision of neurobiological evaluations, behavioral assessment remains a complex art. In studies of therapeutic efficacy, such as those described here, there has consequently been minimal correlation between outcome measures and pathophysiology.

Existing studies of aphasia pharmacotherapy are summarized in Table 3 and reviewed in this section. For historical purposes, the section begins with a review of the early case reports and empirically motivated studies, which no longer have tremendous relevance, and proceeds to examine the recent theoretically motivated studies of catecholamines.

**Early Studies and Case Reports**

Because hypertension is an important risk factor for cerebrovascular disease, patients with stroke frequently require medications to reduce blood pressure. Some of these agents, particularly catecholamine antagonists, might be expected to disturb stroke recovery. A retrospective review of the medications of 32 patients presenting for language evaluation after stroke showed that the 19 patients taking medicines performed significantly worse on the Porch Index of Communicative Ability (PICA) than the 13 patients not taking medicines. (The PICA has been standardized to provide a percentile score that compares the performance of a particular patient to a statistical norm.) Patients taking thiazide diuretics and haloperidol performed particu-
TABLE 3. Studies of Aphasia Rehabilitation Pharmacotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Subjects (n)/Lesion</th>
<th>Time</th>
<th>Tasks</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium amytal</td>
<td>(2) Neoplasm, vascular</td>
<td>Unstated</td>
<td>Informal test of naming, task description, and Goldstein-Sheerer block test</td>
<td>Improvement in fluency, time, attention</td>
<td>34</td>
</tr>
<tr>
<td>Sodium amytal</td>
<td>(27) Vascular, neoplastic, degenerative, metabolic, infectious</td>
<td>Unstated (variable)</td>
<td>Orientation, body part identification, body part naming, naming, naming, commands, singing and sound recognition, days of week, calculation, spelling, reading, picture-word matching, symbol recognition, writing, copying, time</td>
<td>No benefit</td>
<td>38</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>(29) Vascular</td>
<td>&gt;6 mo (19/29), &lt;6 mo (10/29)</td>
<td>Eisonson's aphasia exam, Language Progress Rating Scale, Progressive Matrices, Block Design and Object Assembly tests</td>
<td>No benefit</td>
<td>39</td>
</tr>
<tr>
<td>Hyperbaric oxygen</td>
<td>(16) Vascular</td>
<td>&gt;3 mo and &lt;108 mo</td>
<td>Token Test, Functional Communication Profile</td>
<td>No benefit</td>
<td>40</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>(14) Traumatic, vascular</td>
<td>&gt;21 d</td>
<td>PICA, Word Fluency Test</td>
<td>No benefit</td>
<td>49</td>
</tr>
<tr>
<td>Chlormiazepoxide</td>
<td>(14) Traumatic, vascular</td>
<td>&gt;21 d</td>
<td>PICA, Word Fluency Test</td>
<td>No benefit</td>
<td>49</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>(32) Vascular</td>
<td>Unstated (variable)</td>
<td>PICA</td>
<td>Degradation</td>
<td>31</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>(32) Vascular</td>
<td>Unstated (variable)</td>
<td>PICA</td>
<td>Degradation</td>
<td>31</td>
</tr>
<tr>
<td>Propranolol</td>
<td>(32) Vascular</td>
<td>Unstated (variable)</td>
<td>PICA</td>
<td>Improvement</td>
<td>31</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>(32) Vascular</td>
<td>Unstated (variable)</td>
<td>PICA</td>
<td>Degradation</td>
<td>31</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>(1) Vascular</td>
<td>3½ y</td>
<td>BDAE</td>
<td>Improvement</td>
<td>42,43</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>(1) Vascular</td>
<td>4 y</td>
<td>Visual reaction time test, Token Test, BNT, Word and category fluency, Description of the Cookie Theft Picture (BDAE)</td>
<td>No benefit</td>
<td>44</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>(2) Ischemic, vascular</td>
<td>&gt;18 mo</td>
<td>BDAE, BNT, speech fluency and speech content in spontaneous speech</td>
<td>Improvement in fluency</td>
<td>45</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>(7) Ischemic, vascular</td>
<td>&gt;1 y</td>
<td>Western Aphasia Battery</td>
<td>Improvement</td>
<td>46</td>
</tr>
<tr>
<td>d-Amphetamine</td>
<td>(6) Ischemic, vascular</td>
<td>&gt;10 d and &lt;30 d</td>
<td>PICA</td>
<td>Improvement</td>
<td>50,64,65</td>
</tr>
</tbody>
</table>

PICA indicates Porch Index of Communicative Ability; BDAE, Boston Diagnostic Aphasia Examination; and BNT, Boston Naming Test. The pharmacologic agent administered to patients, the nature of brain lesions, how many subjects were treated, time from brain injury to treatment, tasks used to test patients, and results are listed for each study.

In an early case report, Linn describes two aphasic patients with language disorders from traumatic brain injuries. The patients had language testing before and after the injection of intravenous amobarbital sodium. Although language performance of the first patient improved, Linn attributed the result to improved attention and “energy.” The second patient went from a state of near mutism to a markedly improved state, but it lasted only as long as the drug was administered, and the patient eventually developed tolerance to the drug. The article concludes that sodium amytal may help with the “psychological component” present in organic disease. The most realistic explanation for improvement in these patients with traumatic brain lesions concerns the short-acting anticonvulsant properties of amobarbital.
One could speculate that the beneficial effect of this drug in the alleviation of aphasia after brain trauma was the direct result of stopping ongoing partial seizures in the left temporal lobe. Aphasic seizures constitute a well-documented form of partial epilepsy, and it would be interesting to re-examine Dr Linn’s patients with this in mind.

Furthermore, a carefully controlled clinical study involving 27 hospitalized patients with aphasia failed to replicate Dr Linn’s finding. Comprehensive language and cognitive testing of these patients before and after administration of intravenous amobarbital found that while many patients felt that they were more fluent during the amobarbital infusion, no patient showed objective improvement in function.

West and Stockel selected 29 patients with right hemiparesis and aphasia from stroke for a double-blind, placebo-controlled crossover study of meprobamate therapy combined with behavioral speech therapy. In each 6-month cycle, a patient had one 3-month period of meprobamate plus speech therapy and another of placebo plus speech therapy. General physical and neurological examinations, laboratory evaluations, and comprehensive language and cognitive measures were performed before and after four such cycles. After careful statistical analysis, the authors determined that the medication did not produce better results than speech therapy alone. While this double-blind crossover study produced valid results for a subpopulation of patients with aphasia, eligibility required a right hemiparesis, excluding many patients with aphasia.

Sarno et al studied the effects of hyperbaric oxygen on 16 chronic aphasic patients with left hemisphere cerebral damage from a cerebrovascular cause, with right hemiplegia and aphasia. Comprehensive neurological and cognitive evaluation before and after treatment with hyperbaric air or hyperbaric oxygen failed to show improvement in auditory comprehension or functional communication during or after therapy.

Augmentation of Brain Dopamine

The studies of brain catecholamines after stroke in animals led to an analogous study in humans. In this study, it was found that the concentration of catecholamines in human cerebrospinal fluid is decreased after cerebral cortical infarction. This theoretical motivation and a number of empirical speculations have led to studies aimed at augmenting these transmitters in the brain of patients after stroke.

Several studies have examined the role of dopamine. Albert and his colleagues described a case suggesting that the dopamine agonist bromocriptine helped restore speech fluency in a patient with transcortical motor aphasia from stroke. The patient was tested before treatment with bromocriptine, during treatment, and then after cessation of treatment. Fluency improved when the patient was taking bromocriptine and evaporated after cessation of the drug. This case is particularly difficult to interpret, given the lack of many specific neurological details and of careful controls on the evaluation process. The absence of an underlying basal ganglia disorder was never documented, and the possibility of a placebo effect or performance variability was not discussed.

Another case report failed to find a similar benefit from bromocriptine in a man with transcortical motor aphasia from ischemic stroke. Both multiple baselines for testing and withdrawal periods were used to study this patient, who showed no improvement in language performance despite his perception to the contrary. The authors concluded that a placebo effect may be responsible for the apparent improvement in language function seen in some patients.

Recently, two patients with left frontoparietal infarcts and nonfluent aphasia were treated with bromocriptine for 3 months in an escalating dose and underwent comprehensive language testing before therapy and monthly during therapy. Both patients improved markedly in speech fluency but not in other aspects of language function. The presence of multiple baselines, with lack of improvement in language measures other than fluency, gives this study some weight. However, its value is limited by certain design flaws, including the inability to rule out placebo effects and lack of any withdrawal phase.

A prospective open-label trial of bromocriptine in treatment of nonfluent aphasia studied seven patients with left frontal ischemic infarctions and a nonfluent aphasia. Every 2 weeks, the dose of bromocriptine was escalated and then de-escalated, with language and neuropsychological testing before and during treatment. Statistical analysis of behavioral measures correlated improvement with escalating doses and deterioration with declining doses of the drug in patients with moderate aphasia. Severely impaired patients did not improve. The open-label nature of this study, with few controls, no withdrawal periods, and improvement in all baselines, diminishes the generalizability of these results.

Augmentation of Brain Catecholamines With Amphetamine

In a study of rehabilitation from human motor cortical injury, 88 elderly patients who had been classified as “rehabilitation failures” because of poor progress in physical therapy were given d-amphetamine as an adjunct to physical therapy. Patients with dementia or depression were excluded from the study. The dose schedule was increased from 2.5 mg twice daily to a maximum of 10 mg twice daily as tolerated. With some dramatic cases among them, a full 55% of all subjects improved, and 58% of these were able to leave the hospital. Of those who experienced limiting side effects (26% of all patients) or did not improve (19% of all patients), only 23% were able to leave the hospital. The improvement was particularly evident in the younger group (66 to 84 years old) compared with the older group (85 to 94 years old).

These data are enticing, given the dramatic nature of the functional outcome measure (ie, some patients left the hospital and others could not). However, many problems limit the degree to which this optimistic interpretation is justified, including the role of placebo effects, the possibility of better care being given to patients receiving medicine, and the consistency of motor testing, particularly without blinding of the tester.

A double-blind, placebo-controlled study attempted to replicate this beneficial effect of d-amphetamine in motor stroke rehabilitation. One group of four patients received d-amphetamine and physical therapy,
and another group of four patients received placebo and physical therapy. Neurological evaluations conducted on the days immediately before and after therapy demonstrated a positive effect of the drug on motor functioning after ischemic stroke. The results of this study coupled with its careful design provide some degree of optimism for amphetamine pharmacotherapy in stroke rehabilitation.

An early study of aphasia pharmacotherapy focused on the amphetamine-related drug methylphenidate and the benzodiazepine chlordiazepoxide. In this double-blind, placebo-controlled crossover study, a language battery was performed 1 hour after drug (or placebo) administration. Statistical analysis of the data revealed no difference in language performance between any of the conditions for the patients as a group.

Recently, Walker-Batson et al reported a study of six patients with ischemic cerebral infarction, all in the distribution of the left middle cerebral artery. All patients were aphasic and were evaluated by the PICA. Each patient took d-amphetamine every 4 days, approximately 1 hour before a session of speech and language therapy, for a total of 10 sessions. When evaluated after this period, the patients were significantly over 100% of their expected levels, according to the PICA norms. Of potential significance, the two studies showing beneficial effects of d-amphetamine, ie, this study and the controlled study of motor rehabilitation, share the common feature of evaluating the drug as an enhancement to behavioral or physical therapy, rather than as a monotherapeutic panacea.

Summary and Conclusions

Pharmacotherapy of aphasia has been tried intermittently for many years. The early studies, motivated by intuitive behavioral and physiological rationales, demonstrated little success. The first concept was that “patients with aphasia speak more easily when they are relaxed,” leading to studies of the barbiturates. Although this therapy was reported to work in one or two patients, possibly due to the anticonvulsant properties of amobarbital, prospective studies have yielded little. A similar rationale “to condition [aphasic patients] physiologically and psychologically” with meprobamate yielded similar results.

Another therapeutic rationale, motivated by the many aphasic patients with cerebrovascular disease, concerned cerebral perfusion and blood oxygenation. Investigators postulated that decreased tissue oxygen from vascular thrombosis or embolism might exacerbate language recovery, and that hyperbaric oxygen therapy might improve aphasia rehabilitation. This theory did not hold up to a carefully designed study.

Recent animal studies of experimental stroke and stroke recovery, with functional injury to motor or visual system, have suggested that pharmacological augmentation of brain catecholamine concentrations can greatly accelerate the beneficial effects of practice. d-Amphetamine was the most successful agent used in these studies; it definitely helped motor recovery when coupled with exercise and visual recovery when accompanied by visual experience. A study of intraventricular norepinephrine and dopamine suggested that the beneficial effect of d-amphetamine was due to its ability to increase postsynaptic norepinephrine rather than dopamine.

These animal models provide a different sort of therapeutic rationale than has been present previously for the pharmacologic treatment of aphasia. In particular, these studies provide evidence that certain neurochemical defects are present after stroke, even in brain areas not thought to be injured during the acute event. These studies focused on the catecholamines and led to subsequent animal and human studies of stroke recovery, both physical and cognitive aspects, with exogenous augmentation of brain catecholamine concentrations.

The human studies of pharmacotherapy with d-amphetamine and bromocriptine are difficult to interpret for several reasons. Although not all studies fail on all counts, the studies as a whole are marked by a myriad of problems. First, the anatomic definitions of aphasia differ from one study to another and even from one patient to another within a single study. In many cases, imaging is either not available or not reported. Second, the functional definitions of aphasia are also inconsistent. Such classifications rely on behavioral assessment procedures that do not unambiguously and reproducibly test specific cognitive and linguistic abilities. In aphasia, these functions are not only difficult to define clearly, but are also subject to performance variability based on factors related to both the patient being tested and the tester. Third, there are serious problems with patient selection. These studies do not ensure that the patients do not have other concomitant neurological or psychiatric illnesses in addition to cerebral infarction. This is particularly important in the context of stroke recovery, in which spontaneous improvement can be mistaken for a beneficial effect of a drug.

Patient selection constitutes a particularly complex problem for these studies. Parkinson’s disease has three problematic characteristics: It is a common disease; it is dramatically improved by therapy with levodopa or dopamine agonists such as bromocriptine; and it manifests itself with speech fluency problems, precisely one of the measures thought to improve with pharmacotherapy of nonfluent aphasias.

Affective disorders constitute another problem for these studies. Depression is a well-documented sequela of stroke and constitutes a confounding factor in analyzing the therapeutic benefit of pharmacotherapy for motor and language rehabilitation. In particular, it may not be clear if a perceived therapeutic benefit derives from treatment of the primary deficit (eg, aphasia) or of the depression that accompanies it.

Available information suggests that depression is a much greater concomitant of infarction in the left hemisphere than the right, particularly anteriorly or in the basal ganglia. Patients with concomitant motor speech disorders and aphasia are thought to be particularly vulnerable. However, in patients with left hemi-
spheric lesions and aphasia, there seems to be no correlation between the severity of the aphasia and the presence of dysphoric mood or sleep disturbance. Each pharmacotherapy study of human stroke rehabilitation must be interpreted within the full clinical context of the patient, including premorbid illnesses and the full extent of stroke symptomatology.

Because they are marked by design problems that limit interpretation of the results, existing studies are ambiguous about the potential beneficial effect of increased CNS catecholamines on human motor recovery and aphasia rehabilitation. In the realm of motor system recovery, both human and animal studies suggest that d-amphetamine can facilitate recovery when combined with practice. Weaker evidence also suggests that when coupled with practice in oral communication, increasing brain norepinephrine and/or dopamine might facilitate improvement in speech and language impairments after stroke.

The role of aphasia pharmacotherapy lies in recognizing what it has potential to do and what it will never do. Can pharmacotherapy be used as a replacement for questionable effective speech therapy to ameliorate significantly the language and cognitive performance of patients with cerebral infarctions? The answer is certainly no. In each case where pharmacotherapy radically improved language functioning in people with aphasia, a confounding factor appears to be responsible (eg, seizures, Parkinson’s disease). On the other hand, can pharmacotherapy be used as an adjunct to behavioral rehabilitation to decrease the amount of performance variability and consequently improve mean performance in patients with mild to moderate language dysfunction from infarctions? In this case, the answer is probably yes. Only with carefully designed and well-controlled studies can this promise be rigorously evaluated.

Acknowledgments

This work was supported by the National Institute of Deafness and Other Communication Disorders (NIDCD) of the National Institutes of Health (NIH) under a clinical investigator development award (K08-DC-00054). I am indebted to several people for their help with the preparation of this review, particularly Margaret M. Forbes, Rock Heyman, Gloria E. Hoffman, Malcolm R. McNeil, and Oscar M. Reinmuth. I also thank the patients who participate in the Aphasia Center at the University of Pittsburgh Medical Center for their encouragement and support of this work.

References

Pharmacotherapy of aphasia. A critical review.
S L Small

Stroke. 1994;25:1282-1289
doi: 10.1161/01.STR.25.6.1282

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/6/1282

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/