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Use of Pharmacotherapy in the Treatment of Aphasia

Delaina Walker-Batson

Aphasia Center, Texas Woman's University, Dallas

Over the past century the treatment of acquired aphasia has focused on behavioral and environmental interventions. Consideration of physiologic events surrounding brain injury, manipulation of neurotransmitter systems, and a fuller understanding of mechanisms of learning will be combined to define a neurologically based approach to rehabilitation, including aphasia in the new century.

Following cortical ischemic lesions it has been shown that the excitability of brain areas surrounding the lesion is increased and that these changes may increase the susceptibility of the lesioned brain for adaptive changes and recovery. In animals, a *use dependent* reorganization has been described that is a dynamic self-organizing process (Merzenich et al., 1983). Advantage is given to those behaviors that arrive first in the to-be-reorganized territory. More recent investigations also suggest that both lesion-induced plasticity and timely training are required for amplification of network plasticity (Hagemann et al., 1998). However, the timing of treatment is not clear, as animal studies have found detrimental effects, at least in motor recovery, when forced use (without pharmacotherapy) is applied during the acute period post injury (Kozlowsky et al., 1996).

Explorations of various neurotransmitters in central nervous system (CNS) recovery processes provide growing evidence for cortical reorganization on a structural as well as functional level. There is a growing body of literature exploring the use of pharmacotherapy to facilitate recovery of patients with neurological impairments including language disorders (Goldstein, 1998). The clinical application of pharmacotherapy extends work from the basic science laboratory that assesses the potential impact of specific neurotransmitter systems on recovery processes. The complexities of physiologic

Address correspondence and reprint requests to Delaina Walker-Batson, Ph.D., Texas Woman's University, Aphasia Center, 1810 Inwood Road, Dallas, TX 75235. E-mail: DWalkerBatson@twu.edu.

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events following brain injury complicate the timing for administration of various agents. For example, drugs that are effective in the very acute or subacute period following injury may be ineffective or even detrimental at later recovery periods. The end point of this work is the development of effective rehabilitation pharmacotherapies.

The role of norepinephrine in CNS recovery processes has received much attention, particularly by Feeney and his colleagues (Feeney, 1987). In a series of studies, noradrenergic agonists such as amphetamine have been used to facilitate recovery of sensory, motor, and visual deficits in cats and rats when paired with relevant experience. Feeney has suggested that amphetamine works by resolving a remote functional depression. Others have suggested that amphetamine-mediated release of neuromodulators such as norepinephrine may cause a condition of increased cortical excitability that permits circuit modification in the postinjury state when paired with task-specific practice (Deitrich et al., 1990). Mechanisms of learning could also be affected since amphetamine has been shown to affect long-term potentiation (Gold et al., 1984).

Over the past decade our group has been exploring the long-term effects of amphetamine on speech and language function (Walker-Batson, 1998) as well as hemiplegia (Walker-Batson et al., 1995). An ongoing clinical trial in aphasia is designed to compare subjects who receive 10 mg of dextro-amphetamine 30 minutes before language therapy to subjects who receive a placebo. Subjects are entered between day 16 and day 40 post onset and are followed across 12 months. Thus far, our results suggest that amphetamine accelerates the rate and in some patients the extent of recovery from aphasia independent of amount of tissue loss (Walker-Batson, 1998). Further studies will help to define potential responders, optimal amount of drug treatment and timing effects. Physiologic imaging with direct visualization of cortical denervation of specific neurotransmitters may determine individual response in the near future (Szabo et al., 1994). Our experience suggests that the timing of pharmacotherapy is very important and that the subacute period up to 90 days post onset may be a critical window when the lesioned brain is most malleable to pharmacologic modulation (Walker-Batson, April 1999). Other groups currently exploring the use of pharmacotherapy in aphasia are focusing on drugs that act as agonists for dopamine (Albert et al., 1988; Sabe et al., 1995) or nootropic agents that improve cognition through cholinergic and excitatory amine neurotransmission (Huber, 1997).

In the new century perhaps treatment for aphasia will be divided into three distinct phases that are qualitatively different in rationales and approaches. During Phase 1 (up to 14 days post-onset) no direct behavioral treatment would occur other than informal sessions such as bedside social conversations or reading aloud to the patient; i.e., a use it, but use it gently approach (Kozlowsky et al., 1996). Phase 2 (15 to 90 days post onset, depending on the medical stability of the patient) would be the period of pharmacotherapy

paired with intensive impairment level treatment. Drugs with specificity for particular cognitive or linguistic deficits may be employed. In Phase 3 (after 90 days post onset) behavioral intervention (including group treatment) would provide opportunities to practice over a long time in real life contexts.

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