# Treatment of Acute Ischemic Stroke: Does It Impact Neuropsychiatric Outcome?

**C. Alan Anderson, M.D.**
**David B. Arciniegas, M.D.**
**Christopher M. Filley, M.D.**

*Stroke is a leading cause of disability globally. Although neuropsychiatric symptoms are produced by stroke and adversely effect stroke outcome, it is unclear whether neuropsychiatric outcome can be improved by acute stroke treatment. The authors reviewed published acute ischemic stroke treatment trials to determine whether neuropsychiatric outcome measures were employed. Of the 190 trials reviewed, only seven included specific measures of neuropsychiatric outcome, usually a short test of cognition or mood. Further studies are needed to determine the potential benefits of acute stroke treatment on both poststroke neuropsychiatric symptoms and the relationship between such symptoms and stroke outcome.*

(The Journal of Neuropsychiatry and Clinical Neurosciences 2005; 17:486–488)

Stroke is the third most common cause of death in the U.S. and the leading cause of major disability.[1] More than 750,000 new ischemic strokes occur each year, and more than 4 million Americans are living with the residual effects of stroke.[2] The treatment of acute ischemic stroke has been the focus of a major clinical research initiative in the United States and elsewhere.[3] An enormous amount of investigator and patient time, funding, and effort has produced only modest improvements in the treatment of this disorder. To illustrate, among all the interventions studied, only the thrombolytic agents rTPA and prourokinase, the defibrinogenating agent ancrod, and the antiplatelet drug aspirin have been effective in improving outcome.[4] Among these agents, only r-TPA and aspirin have been incorporated into widespread clinical practice.[4]

Neuropsychiatric sequelae of ischemic stroke are common and produce significant morbidity.[5] Cognitive impairment and behavioral disturbances after stroke are associated with poor outcome, including decreased functional capacity, lower quality of life, reduced independence, and a greater likelihood of complications.[5,6] Because ischemic stroke often damages brain regions re-

Received June 8, 2004; revised September 7, 2004; accepted September 13, 2004. From the Department of Neurology, University of Colorado School of Medicine, Denver, Colorado; Denver Veterans Affairs Medical Center, Denver, Colorado; the Department of Psychiatry, University of Colorado School of Medicine, Denver, Colorado. Address correspondence to Dr. Anderson, Neurology B-182, University of Colorado Health Sciences Center, 4200 E. 9th Ave., Denver, CO; al.anderson@UCHSC.edu (E-mail).

quired for normal cognition and behavior, measures of neuropsychiatric (i.e., cognitive, emotional, and behavioral) status may add to the dimensions of outcome following acute stroke intervention. In this study, we attempted to evaluate the impact of acute stroke therapies on neuropsychiatric outcome. As a first step, it was necessary to identify clinical stroke trials in which appropriate measures for this aspect of outcome were employed.

## METHOD

A detailed literature review of acute stroke clinical trials was conducted to determine the frequency with which neuropsychiatric outcome measures were included in the studies. This review was limited to trials of acute intervention for ischemic stroke that were published in English from 1976 through 2003. A MEDLINE search was performed using the search terms "stroke" and "cerebrovascular accident." The Cochrane Database of Systematic Reviews for acute interventions in ischemic stroke was also surveyed. Treatment trials were reviewed for the inclusion of cognitive, behavioral, and other neuropsychiatric measures. Small case series, case reports, and small open-label clinical studies were excluded from the analysis. The therapeutic agents tested in these trials included anticoagulants, antiplatelet drugs, calcium channel antagonists, excitatory amino acid antagonists, gangliosides, pentoxifylline, prostacyclin and analogs, vasoactive drugs, thrombolytic agents, and a small number of other miscellaneous interventions.

## RESULTS

Of the 190 published acute stroke trials reviewed, one employed a battery of neuropsychiatric outcome measures, including the Trail Making Test, Boston Naming Test, the Visual Form Discrimination Test, and the Line Cancellation Test.[7] Two others included a standard cognitive measure, the Mini-Mental State Examination (MMSE).[8] Depression was assessed in four trials, using the Zung Self-Rating Depression[9] or Hamilton Depression Rating Scales.[9,10] The most common outcome measures used in these trials were the Modified Rankin Scale, the Barthel Index, the National Institutes of Health Stroke Scale, the Canadian Stroke Scale, and the Scandinavian Stroke Scale.[11] None of these instruments, as well as other assessment tools that were sometimes employed, include more than a minimal assessment of cognition, typically brief measures of level of consciousness, language, or sensory neglect. As such, the focus of these assessments has been the measurement of elemental neurological function and not cognition and behavior.[11] There were no cognitive or behavioral benefits demonstrated in the trials that used the neuropsychiatric measures. However, the number of trials employing measures sensitive to cognitive and behavioral impairments is so small that no firm conclusions can be drawn regarding the effects of acute stroke intervention on poststroke neuropsychiatric symptoms.

## DISCUSSION

Our study demonstrates that most acute stroke intervention studies have not attempted to assess neuropsychiatric function in a comprehensive manner. As a result, the effect of treatment on this aspect of outcome is almost entirely unknown. While the current study focuses exclusively on cognitive and neuropsychiatric measures, our findings are consistent with prior surveys of stroke outcome measures used in acute treatment trials.[12,13] Because substantial cognitive and behavioral benefits may result from acute stroke treatment, greater attention to the measurement of neuropsychiatric outcome after stroke treatment is warranted.

Ischemic stroke is a common event associated with enormous morbidity and mortality. Neuropsychiatric morbidity includes impairment of attention, motivation, mood, memory, language, visuospatial function, and executive function. Depression and anxiety occur in up to 50% of patients after their stroke.[14] Deficits such as these are associated with loss of independence and reduced quality of life.[15,16] Patients may report greater disability and reduction in quality of life from neuropsychiatric sequelae than from disturbances of strength, sensation, and coordination.

Separate assessment of neuropsychiatric sequelae in clinical stroke trials would provide a more thorough understanding of outcome after acute stroke treatment. To begin, there are many unanswered questions about the differential rate and extent of recovery between sensorimotor and neuropsychiatric function. It is also possible that individual treatment trials reporting no benefits on stroke outcome may have overlooked a beneficial effect

of the treatment by failing to assess neuropsychiatric outcome. Moreover, the lack of measures assessing neuropsychiatric outcome in this context prohibits formal meta-analytic statistical approaches to the study of this issue. Thus it is conceivable that the treatments may already be helping to improve neuropsychiatric function, but that these benefits are not apparent in the medical literature as a result of the unavailability of appropriate measures providing such evidence. Alternatively, there may be no current neuropsychiatric benefits of acute stroke treatment. In either case, inclusion of neuropsychiatric assessment measures could help capture these aspects of stroke morbidity and determine to what extent acute stroke treatment affords any benefits.

An obvious issue is the time investment necessary to gather cognitive and behavioral data in the setting of acute stroke. Because of the narrow time window from onset of symptoms to initiation of therapy for many of the studied interventions, there are practical limitations related to the time available for neuropsychiatric assessment. For this reason, we suggest the introduction of brief standardized measures that can be administered acutely and repeatedly during recovery. As a first step, the use of the MMSE[8] and a depression scale, such as the Beck Depression Inventory,[17] the Zung Self-Rating Depression Scale,[9] or the Hamilton Depression Rating Scale,[10] would provide global measures of cognition and mood that would greatly improve the ability to judge the effects of acute stroke treatment on neuropsychiatric outcome.

*This study was presented in part as a poster at the American Neuropsychiatric Association Annual Meeting, February 2004, Bal Harbour, FL.*

*This study was supported by the L.W. Frohlich Charitable Trust.*

**References**

1. Casper ML, Barnett E, Williams GI, et al: Atlas of Stroke Mortality: Racial, Ethnic, and Geographic Disparities in the United States. Atlanta, Ga, Department of Health and Human Services, Centers for Disease Control and Prevention, 2003
2. American Heart Association: Heart Diseases and Stroke Statistics, 2004
3. Fisher M, Brott TG: Emerging therapies for acute ischemic stroke: new therapies on trial. Stroke 2003; 34:359–361
4. Adams HP, Jr., Adams RJ, Brott T, et al: Guidelines for the early management of patients with ischemic stroke: A scientific statement from the stroke council of the American Stroke Association. Stroke 2003; 34:1056–1083
5. Moroz A, Bogey RA, Bryant PR, et al: Stroke and neurodegenerative disorders, 2: stroke: comorbidities and complications. Arch Phys Med Rehabil 2004; 85:S11–14
6. McLean DE: Medical complications experienced by a cohort of stroke survivors during inpatient, tertiary-level stroke rehabilitation. Arch Phys Med Rehabil 2004; 85:466–469
7. Lezak MD: Neuropsychological Assessment. New York, Oxford University Press, 1995
8. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198
9. Zung W: Self-rating depression scale. Arch Neurol 1965; 12: 63–70
10. Hamilton M: The development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967; 6:278–296
11. Lyden PD, Hantson L: Assessment scales for the evaluation of stroke patients. J Stroke Cerebrovasc Dis 1998; 7:113–127
12. Roberts L, Counsell C: Assessment of clinical outcomes in acute stroke trials. Stroke 1998; 29:986–991
13. Duncan PW, Jorgensen HS, Wade DT: Outcome measures in acute stroke trials: a systematic review and some recommendations to improve practice. Stroke 2000; 31:1429–1438
14. Kotila M, Numminen H, Waltimo O, et al: Post-stroke depression and functional recovery in a population-based stroke register: The Finn Stroke Study. Eur J Neurol 1999; 6:309–312
15. Patel MD, Coshall C, Rudd AG, Wolfe CD: Cognitive impairment after stroke: clinical determinants and its associations with long-term stroke outcomes. J Am Geriatr Soc 2002; 50:700–706
16. Herrmann N, Black SE, Lawrence J, et al: The Sunnybrook Stroke Study: a prospective study of depressive symptoms and functional outcome. Stroke 1998; 29:618–624
17. Beck A: Beck Depression Inventory. San Antonio, The Psychological Corporation, 1987