Developing Treatment Guidelines for Alzheimer's Disease and Other Dementias

Peter V. Rabins, M.D.

Escalating health care costs and evidence that there is widespread variation in medical practice have led to the formation of more than 1800 consensus conferences in the past 10 years. These conferences seek to review the evidence that existing treatments have demonstrable efficacy; to determine if evidence favors one form of therapy over another; to review the guidelines for implementation, continuation, and discontinuation of the therapy; and to identify currently used treatments for which no benefit can be documented. This is a review of the process used by the American Psychiatric Association Task Force on Developing Treatment Guidelines for Alzheimer's Disease and Other Dementias, still in process at the time of this presentation. *(J Clin Psychiatry 1998;59[suppl 11]:17–19)*

Escalating health care costs and evidence of widespread variation in medical practice have led to more than 1800 consensus conferences in the past 10 years. The development of treatment guidelines is a multistep process. Consensus conferences seek to review the evidence that existing treatments have demonstrable efficacy; to determine if evidence favors one form of therapy over another; to review the guidelines for implementation, continuation, and discontinuation of the therapy; and to identify currently used treatments for which no benefit can be documented. The American Psychiatric Association appointed a committee of individuals, all of whom have expertise in geriatric psychiatry and in dementia, to develop treatment guidelines for Alzheimer's disease and other dementias. Additional committee members include liaison members from the American Psychiatric Association committee overseeing all guideline development and members in training.

OVERVIEW OF PROGRESS

Initially, the committee identified broad types of treatment and then set the standard of evidence for reviewing treatment in each of these areas. Ideally, all treatments would meet the same standards and recommendations would be based on the randomized, controlled trials. The initial criteria for studies to be included for review were that subjects be randomly assigned to treatment or control; those performing the assignment, treatment, and assessment be blind to treatment status; and the primary outcome or outcomes be chosen during study design. In assessing treatments for dementia, the committee concluded that this standard could be met for assessing pharmacologic therapy. The committee also decided to review pharmacologic studies that did not meet these criteria, for example, case series, since some pharmacotherapies currently in use have not been subjected to randomized, controlled trials. This decision was made so that the treatment guidelines could address the strength of evidence upon which such treatments are based. After an initial review revealed that many nonpharmacologic therapies in widespread use have not undergone randomized, controlled trials, the committee chose a lower standard for nonpharmacologic treatments. This standard required that the treatment be compared to a group that was untreated or treated with a different method, that outcome be blindly assessed, and that the outcome be chosen during study design. The committee chose to do so because in some instances, randomized, controlled trials would be difficult, if not impossible, to design. Single case studies were not chosen for inclusion because of the inability to generalize from them.

Clearly, the compromises made during this design phase of the guideline process can influence output. Had the committee chosen to require that two randomized, controlled trials be available before a treatment could be recommended, then most of the recommended treatments would have been pharmacologic in nature. One of the committee's recommendations is that randomized control trial methodology be used as much as possible in designing studies of treatment efficacy in the future.

From the Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, School of Medicine, Baltimore, Md.

Presented in part at the symposium "Alzheimer's Disease: From Research to Practice," held May 4, 1996, New York, N.Y., during the 149th annual meeting of the American Psychiatric Association and supported by unrestricted educational grants from Pfizer Inc and Eisai Inc.

Reprint requests to: Peter V. Rabins, M.D., Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287.

The second step in developing guidelines is to identify databases from which articles are sought. This requires work with knowledgeable medical librarians, and assistance was provided by the American Psychiatric Association librarian and by librarians at the institutions at which committee members were working. In addition to MEDLINE, other databases emphasizing psychological therapies and psychosocial studies were included. Studies were also obtained by searching reference lists. Studies known to individual investigators were sent to the committee during its review process and were also examined.

The next stage was to perform a meta-analysis. Each committee member was assigned a specific area to review. The first step in this meta-analysis was to develop a table that included all review studies and specific information including number of subjects, whether or not subjects were randomized, whether assessment was blind, and specific outcomes and findings. Meta-analyses can be carried out mathematically, and formulas exist by which the results of studies can be combined. This committee chose not to use this method because for many treatments only one or two studies were available, design often varied greatly among studies, and there was a lack of agreement among experts that such an approach is valid. Rather, the committee developed an evidence table for each treatment approach, reviewed it, and came to consensus as to whether the available data supported its use. The strength of their recommendation was based on the appropriateness of the study design, the number of times a finding was replicated, an assessment of the quality of the studies, and the number of subjects studied.

The final set of steps included writing the results of the review and circulating results among committee members and then among a selected group of approximately 80 national experts in dementia. This was followed by distribution of results to all district branches of the American Psychiatric Association and then to a much wider set of national experts. Finally, preliminary presentations at the American Psychiatric Association were given to encourage widespread review and contribution.

RESULTS AND RECOMMENDATIONS

The committee concluded that available evidence supported the use of cholinergic enhancers for treating cognitive impairment and that these have modest efficacy. The committee also concluded that no other class of drugs targeting cognitive enhancement could yet be recommended, based on available evidence, although studies of other agents are expected to be released soon.

Studies of ergoloid mesylates[1] and selegiline[2] suggest modest efficacy in improving noncognitive measures. Studies are underway to determine whether selegiline has beneficial effects on cognition or delays the rate of decline, but such data are not currently available.

For the pharmacologic treatment of noncognitive symptoms of dementia, the neuroleptic drugs have been best studied. The committee concluded that neuroleptic drugs are modestly effective in treating the behaviors described as agitation. The committee could not locate adequate evidence to support the use of other classes of drugs in treating noncognitive symptoms but did find that there was an extensive literature suggesting that anticonvulsants, antianxiety drugs, and several other classes of agents might be effective in treating specific noncognitive behavioral disorders. Data on the treatment of depression coexisting with dementia are mixed. Several recent studies support the efficacy of antidepressants for treating depression in patients with depression,[3] but several earlier studies either did not find a benefit beyond that provided by placebo or did not meet the criterion of randomized, controlled trials.[4]

The committee reviewed a variety of nonpharmacologic therapies such as pet therapy, music therapy, and environmentally focused behavior therapy. Taken together, these studies suggest that such therapies are modestly effective in increasing activity and diminishing behavioral disorder. However, one recently published, well-designed study[5] demonstrated that a combination of psychiatric assessment and activity therapy was beneficial in diminishing behavior disorder among persons with Alzheimer's disease. There is no evidence demonstrating better efficacy of one type of therapy over another. The committee concluded that such therapies are modestly effective and that their benefit most likely results from factors that are common across these treatments rather than specific to any one form of therapy. The evidence supporting behavior therapy rests on single or small case series, and generally such studies are not blinded. There is some evidence that memory-retraining approaches are transiently effective but no evidence that any gain persists after the training session.[6]

A number of well-designed studies[7] support the efficacy of interventions focused at improving caregiver well-being, and the committee concluded that such interventions are moderately effective in decreasing caregiver emotional morbidity and increasing caregiver knowledge. There is some evidence that emotion-focused caregiver interventions are more effective than educational interventions and weak evidence that the combination is the most effective approach.

STRENGTHS OF THE GUIDELINE DEVELOPMENT PROCESS

This process has several strengths. It provides for the review of a large body of published data on the efficacy of particular treatments. As such, it can provide a guide to clinicians in choosing among available treatments. Furthermore, it theoretically should lead to improved care of

persons suffering from dementia since the guidelines would support the use of effective therapies and circumstances in which they might not be instituted.

Another strength is that this review can also highlight areas in which knowledge is lacking or in which clinical practice is based more on experience than on available data. Identifying such areas highlights interventions that require further study and may constrain the faddish use of treatments for which evidence of efficacy is lacking.

On the other hand, the treatment guideline development approach has clear limitations. While "evidence-based" clinical practice is an ideal, the care of patients is an art as well as a science, and the review process can not capture many elements of the patient-clinician interaction. By focusing only on specific therapies, the important role that the relationship between clinician and patient, clinician and family, and clinician and other caregivers plays is ignored. In addition, not all treatments have been subjected to careful study. The lack of evidence supporting efficacy or effectiveness can not be used to deny that a treatment is efficacious. The only statement that can be made is whether evidence is available to support its use and the strength of that evidence. For example, the committee is unable to find evidence supporting the use of special or focused-care units in long-term care facilities. It is not clear that a randomized, controlled trial to this approach is practical, and yet such units are widespread. A review can be beneficial in tempering enthusiasm for such therapies that are unproved, but skepticism can be negative. It is important that a lack of evidence supporting specific approaches not be taken as suggesting that the treatments do not work.

Drug name: selegiline (Eldepryl).

Editor's Note: The treatment guideline discussed in this article has since been published:
American Psychiatric Association. Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias of Late Life. Am J Psychiatry Suppl 1997;154(5):1–39

REFERENCES

1. Schneider LS, Olin JT. Overview of clinical trials of Hydergine in dementia. Arch Neurol 1994;51:787–798
2. Tariot PN, Cohen RM, Sunderland T, et al. L-deprenyl in Alzheimer's disease: preliminary evidence for behavioral change with monoamine oxidase B inhibition. Arch Gen Psychiatry 1987;44:427–433
3. Gottfries CG, Karlson I, Nyth AL. Treatment of depression in elderly patients with and without dementia disorders. Int Clin Psychopharmacol 1992;6:55–64
4. Petracca G, Teson A, Chemerinski E, et al. A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1996;8(3):270–275
5. Rovner B, Steele C, Shmuely Y, et al. A randomized trial of dementia care in nursing homes. J Am Geriatr Soc 1996;44:7–13
6. Zarit SH, Zarit JM, Reever KE. Memory training for severe memory loss: effects on senile dementia patients and their families. Gerontologist 1982; 22:373–377
7. Rabins PV. Clinical interventions with Alzheimer's caregivers: a conceptual approach. In: Light E, Niederehe G, Leboqitz BD, eds. Stress Effects on Family Caregivers of Alzheimer's Patients. New York, NY: Springer Publishing Co; 1994:133–137