Assessment of Treatment-Associated Changes in Behavior and Cholinergic Therapy of Neuropsychiatric Symptoms in Alzheimer's Disease

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Alzheimer's disease affects multiple domains of human brain function and has neuropsychological, neuropsychiatric, and neurologic manifestations. Behavioral changes should be assessed as part of a comprehensive evaluation of the effects of cholinergic treatment of Alzheimer's disease. The psychometric properties, origin, source of behavioral information, content, and administration requirements of tools used to assess behavior in Alzheimer's disease affect the type of information garnered and the conclusions that can be derived. Assessment of drug-related behavioral changes can be affected by spontaneous remission of neuropsychiatric symptoms, differing baseline severity of behavioral abnormalities, uncertain magnitude of expected treatment effects, and by the influence of disease stages, concurrent medications, and comorbid conditions. Cholinergic therapies ameliorate behavioral alteration in Alzheimer's disease, and changes in behavior should be monitored when such therapy is initiated. *(J Clin Psychiatry 1998;59[suppl 13]:23–30)*

Alzheimer's disease is a complex neurodegenerative disease with cognitive, behavioral, and neurologic manifestations.[1] Cognitive abnormalities include progressive disturbances in declarative memory, semantic comprehension and naming, visuospatial skills, and executive abilities.[2] Neuropsychiatric and behavioral disorders associated with Alzheimer's disease include psychosis (delusions, hallucinations), mood abnormalities (depression, euphoria, irritability, anxiety), alterations in personality (apathy, disinhibition), agitation, aggression, pacing, wandering, altered sexual behavior, changed sleep patterns, and disturbances of appetite.[3–5] Neurologic abnormalities are typically delayed until late in the course of Alzheimer's disease when incontinence, quadriparesis-in-flexion, and dysphagia supervene.[1] The cognitive, behavioral, and neurologic abnormalities reflect the progressive accumulation of amyloid, neuronal death, and transmitter depletion that constitute the pathophysiology of Alzheimer's disease.[6]

The ultimate goal of understanding the pathogenesis of Alzheimer's disease is to be able to devise treatments aimed at ameliorating the suffering of victims of the illness. This objective has been partially realized, and more effective therapies that delay the onset, slow the progression, and improve the symptoms of Alzheimer's disease promise to emerge from our improved understanding of the etiology and pathophysiology of the disease.[7]

Treatment efforts in Alzheimer's disease have focused almost exclusively on improving the cognitive deficits and memory abnormalities exhibited by the patients. The Alzheimer's Disease Assessment Scale, cognitive portion (ADAS-cog)[8] is the principal outcome measure of most clinical trials of anti–Alzheimer's disease agents, and improvement in cognition is the main factor required by the U.S. Food and Drug Administration (FDA) for approval of anti–Alzheimer's disease therapy. Assessment of the neuropsychiatric symptoms of Alzheimer's disease has received less attention than cognitive abnormalities, and study of treatment-related changes has been less systematic. However, since the neuropathologic processes of Alzheimer's disease become evident in several domains of function, it is important to assess the impact of therapy in each of these arenas. This review presents the importance of assessing the response of neuropsychiatric symptoms of Alzheimer's disease to treatment and describes the methodological challenges involved. The changes in neuropsy-

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Table 1. Attributes of Rating Scales Used to Assess Neuropsychiatric Symptoms in Dementia Patients*

Psychometric properties
Reliability
Validity
Source of information
Patient
Family caregiver
Professional caregiver
Clinician observer
Content
Psychiatric symptoms
Single
Multiple
Dementia-specific behaviors (eg, agitation)
Behavioral and cognitive symptoms
Global ratings
Total score (sum of item scores)
Frequency of symptoms
Severity of symptoms

*Based on reference 9.

chiatric symptoms produced by cholinergic agents and their assessment by neuropsychiatric rating scales are emphasized.

ASSESSING NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE

Systematic assessment of neuropsychiatric symptoms in Alzheimer's disease is a relatively recent research endeavor and poses many methodological dilemmas. The origin of the tools used, the sources of information about the patient's behavior, the contents of the instrument, psychometric properties of the scale, administration requirements, purpose of the assessment, and sensitivity to change must all be considered when choosing an evaluation tool (Table 1).[9]

Psychometric Properties

Reliability and validity are the essential properties of any assessment instrument and must be established before a tool can be applied confidently to the study of neuropsychiatric symptoms in Alzheimer's disease. Interrater, test-retest reliability, and internal consistency are the usual types of reliability that should be established. Determination of concurrent validity (comparison with an accepted standard) and construct validity (support of the instrument's results by information garnered through other approaches) is also critical.[10]

Origin of the Instrument

Tools to assess Alzheimer's disease have been imported from psychiatry, adapted from application to other neurologic disorders, and developed primarily for use with dementia patients. Initially, instruments used to measure similar behavioral and psychiatric phenomena in idiopathic psychiatric disorders were adopted for use in patients with Alzheimer's disease. Thus, the Hamilton Rating Scale for Depression (HAM-D)[11] is commonly used to measure mood symptoms in Alzheimer's disease. This strategy has several potential shortcomings, including the possibility that the phenomenology of depression in Alzheimer's disease may differ from that of idiopathic depression, and symptoms produced by depression—such as sleep changes, appetite disturbances, agitation, retardation, cognitive abnormalities, and paranoia—may occur in Alzheimer's type dementias without mood changes, resulting in an artificial elevation of depression scores. The Brief Psychiatric Rating Scale (BPRS)[12] is another example of a tool imported directly from psychiatric studies into the assessment of dementia patients. The BPRS captures many of the behavioral changes of Alzheimer's disease, but some items such as "thought disorganization" are difficult to apply to patients with dementia.

The Cornell Scale for Depression in Dementia (CDD)[13] has adapted items from the HAM-D for application to dementia patients. Similarly, the Neurobehavior Rating Scale (NRS)[14] is an adaptation of the BPRS for application to patients with neurologic conditions. The NRS was originally applied to patients with head trauma before it was used in dementia research.[15] Likewise, the personality inventory of Brooks and McKinlay[16] was also developed and applied in the assessment of head trauma prior to its application to dementia patients.[17]

The Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD),[18] Cohen-Mansfield Agitation Inventory,[19] and Neuropsychiatric Inventory (NPI)[20] are examples of tools originally developed for evaluation of dementia patients. The Behavior Rating Scale for Dementia (BRSD),[21] developed by the Consortium to Establish a Registry for Alzheimer's disease (CERAD), has items from the HAM-D and the BEHAVE-AD.[18] Dementia specific tools may be more sensitive to behavioral changes unique to dementia, but they make comparison of symptom complexes in patients with and without dementia more difficult.

Each of these assessment strategies has strengths and weaknesses. Use of instruments developed for idiopathic disorders allows direct comparison of symptoms in Alzheimer's disease to those of idiopathic depression, schizophrenia, or other conditions. On the other hand, these scales do not reveal symptoms unique to Alzheimer's disease, and their application to patients with cognitive impairment and dementia-related neurovegetative disorders may result in inflated rating scale scores. Adapting rating scales that have been developed for other disorders—or developing new scales specifically for use in patients with Alzheimer's disease—may provide information that is more relevant to Alzheimer's disease and its management. These tools, however, have been infrequently used, and their psychometric properties and clinical utility are correspondingly less thoroughly established.

Source of Information

Behavioral ratings may be derived from 1 or more of 4 sources: family caregivers, professional caregivers, observation by clinicians, and patient self-report. Different sources of information may result in different conclusions regarding the frequency of behavioral disturbances in Alzheimer's disease patients. For example, Burns et al.[22] reported that of 178 patients with Alzheimer's disease, 63% reported at least 1 symptom of depression, 43% were considered depressed by a family caregiver, 24% were rated as depressed by an observer, and none met the criteria for major depressive disorder. Similarly, Cummings and colleagues[23] found that 30% of patients with Alzheimer's disease had depressive symptoms on the ADAS noncognitive portion (ADAS-Noncog),[8] 12% had mild depression and 3% had moderate depression on the HAM-D,[11] and 6% met criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,[24] for major depression. Thus, the frequency of depressive symptoms varied considerably depending on how mood changes were assessed.

Family caregivers are intimately familiar with the behavior of patients and well positioned to report behavioral data. Observations, however, may be biased by caregiver mood, the lack of sophistication of the caregiver as an observer, or the previous relationship of the patient and caregiver. The BEHAVE-AD[18] and NPI[20] are examples of caregiver-based assessment instruments. The BEHAVE-AD is rated by the clinician on the basis of information obtained from the caregiver; the NPI requires the caregiver to rate the severity and frequency of behavior using defined anchor points for each rating.

Professional caregivers can provide information for rating scales, particularly for patients who are hospitalized or institutionalized. Members of the nursing staff are the usual reporters and have the advantage of being more experienced in behavioral observation. This approach has the disadvantage of deriving data from individuals who observed the patient during only one shift of work. Scales of this type include the Nurses' Observation Scale for Inpatient Evaluation,[25] the Ward Daily Behaviour Scale,[26] the NPI-Nursing Home version (NPI-NH),[27] and the Multidimensional Observation Scale for Elderly Subjects.[28] Many nurses' aides providing care in nursing homes have only modest training and are often not fluent in the English language; these issues must be considered if valid and reliable information is to be obtained.

Direct observation of patients by clinicians is another source of behavioral information. This approach has the advantage of using highly skilled observers and the disadvantage of capturing only the behaviors observed during a limited observation period. The NRS[14,15] is an example of a direct observation tool. Instruments of this type may be especially relevant for the assessment of acute changes in behavior produced by rapid-acting interventions or of behavioral states present while a metabolic or electrophysiologic measure is being taken.

Patient report is typically useful only in the early phases of a dementing illness, since insight is often compromised and the patients cannot reliably report on any but their immediate circumstances. Nevertheless, self-reports of mood changes have been used in some studies applying the Geriatric Depression Scale,[29] a self-rated depression instrument.

Each of the potential information sources for rating scales has advantages and disadvantages. The conclusions derived from any tool must be conditioned by understanding the strengths and limitations of the information sources involved.

Content of Behavioral Scales

Behavioral rating scales may assess individual neuropsychiatric symptoms (psychosis, mood changes, anxiety), evaluate multiple neuropsychiatric symptoms, provide global scores of behavioral disturbances, utilize additive total scores, or measure both behavior and cognitive abnormalities. The CDD[13] and the Columbia University Scale for Psychopathology in Alzheimer's Disease[30] are examples of behavioral rating scales that assess mood and psychosis, respectively. The Pittsburgh Agitation Scale[31] and the Cohen-Mansfield Agitation Inventory[19] concentrate on assessing agitation. The BEHAVE-AD[18] and NPI[20] provide both rating scale scores for individual neuropsychiatric symptoms and a global or total behavioral disturbance score. The BRSD[21] and NRS[15] utilize factor scores derived from a combination of items and a total behavioral abnormality score.

Rating scales may also assess combinations of psychopathology and other abnormalities. Behavioral and cognitive changes are included in the NRS,[14,15] the Gottfries-Brane-Steen Scale,[32] and the Revised Memory and Behavior Checklist.[33] The ADAS-Noncog[8] sums behavior changes, weight alterations, and tremor. The Caretaker Obstreperous-Behavior Rating Assessment[34] scale evaluates aggression, personality, mechanical skills, and vegetative functions. Caregiver distress associated with behavioral changes is assessed by the Revised Memory and Behavior Problems Checklist[33] and the NPI.[20]

No single scale or assessment strategy is necessarily superior to another. Mixed-component assessments may give an overall impression of the patient in a single score but may be insensitive to individual behaviors, whereas highly focused tools provide precise information on one specific behavioral attribute but do not reflect the entire spectrum of behaviors exhibited by a patient. Multidimensional instruments provide information on many symptoms but lack the depth of assessment typical of focused scales. Treatment of behavioral disturbances focuses on specific behaviors rather than global or cognitive improvement, and treatment outcome assessment requires

the use of instruments that measure changes in individual behaviors. Multidimensional instruments with subscale scores facilitate the detection and characterization of multiple treatment effects and side effects.

Administration Issues

A variety of decisions must be made regarding the administration of an instrument, and each decision will impact the type of information harvested and the statistical analyses that can be applied to the data. Behaviors may be judged to be present or absent by using a checklist approach. Scales may rate both the frequency and severity of behavior. Severity may be rated with a fixed-interval scale—such as mild = 1, moderate = 2, severe = 3, as used in the Revised Memory and Behavior Problem Checklist[33] and the NPI[20]—or an analogue scale in which the patient or caregiver chooses a point between 2 polar extremes (e.g., happy and sad) that best characterizes the patient's behavior.[35]

Tools may be comprehensive, as in the BRSD,[21] and require substantial administration time or they may be relatively brief, devoting only a few questions to each behavioral domain, as in the ADAS-Noncog.[8] The NPI[20] uses a screening methodology: if screening questions are positive, more extended questioning is pursued; if they are negative, the domain is not explored in depth.

Sensitivity to Change

Measurement of change in behavior as a product of drug treatment is difficult. Among the issues that must be considered are treatment response as distinguished from spontaneous remission; the influence of differing severity and frequency of behaviors at baseline; the emergence of new behavioral symptoms in the course of the disease; the potential range of scores available from different instruments; the amount of change in an instrument's score that is acceptable as clinically meaningful; the determination of the specific criterion symptoms on which drug effects will be assessed; the interaction of cognitive and behavioral symptoms with treatment; the presence of comorbid medical or cerebral conditions (e.g., white matter changes on magnetic resonance imaging); concomitant treatment with other medications, particularly psychotropic agents; differences in drug efficacy relative to the stage of disease; and the potential influence of nonbiological events such as increasing caregiver distress, change in residence (e.g., to a nursing home), or other environmental effects.

Most of the instruments used in Alzheimer's disease research were designed for cross-sectional studies to identify specific behaviors, and little information is available on their utility for longitudinal tracking of behaviors or their sensitivity to behavioral changes produced by specific interventions. There is substantial literature on the use of the HAM-D[11] in studies of antidepressant responses, and the ADAS[8] (including the noncognitive portion) has been used extensively in clinical trials of antidementia drugs. One study has demonstrated that the NPI is sensitive to behavioral changes associated with tacrine in the treatment of Alzheimer's disease.[36]

Analysis of Scale Scores

The analysis chosen will depend on the purpose of the study. When assessing treatment response, the analysis should be focused on the specific criterion symptoms hypothesized to be responsive to the therapy. Global and total scores are of secondary interest; no treatment is likely to affect all the behaviors reflected in total or global scores. Factor scores have been derived for some instruments (BRSD, NRS) and can be used instead of item analysis. Correlational analyses are appropriate to investigate relationships of behavior to demographic variables and relationships among behaviors. Matching patients for baseline severity of behaviors is often important before assessing a treatment response. New behaviors emerge in the course of Alzheimer's disease, and the suppression of emergent symptoms as well as the reduction of symptoms present at the time treatment was started should be assessed.

NEUROBIOLOGICAL CORRELATES OF NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE

The measurement of behavior is relevant to understanding the neurobiology and treatment of behavioral symptoms in patients who have Alzheimer's disease. There are neurobiological differences between Alzheimer patients with and without neuropsychiatric symptoms. They have distinguishing demographic features, profiles of neuropsychological function, patterns of cerebral metabolism and perfusion, electroencephalographic findings, and brain pathology. Alzheimer patients with delusions, for example, have more rapid cognitive decline than those without delusions.[37–39] Patients with behavioral disturbances have more marked deficits in executive function on neuropsychological testing than Alzheimer patients without major behavioral alterations.[40] Alzheimer patients with delusions have more marked abnormalities of glucose metabolism and regional perfusion in the frontal and temporal lobes,[41–46] and those with agitation and elation have greater frontal lobe dysfunction.[46,47] Alzheimer patients with apathy have reduced medial frontal perfusion in a pattern different from that observed in Alzheimer patients with psychosis.[48] Electroencephalographic abnormalities are more severe in Alzheimer patients with psychosis than in patients with Alzheimer's disease of similar severity without psychosis.[49] Zubenko and coworkers[50,51] found differences in senile plaque and neurofibrillary tangle densities in the frontal and temporal lobes in patients with Alzheimer's disease as well as different neurochemical

profiles in psychotic compared to nonpsychotic Alzheimer patients and in depressed compared to nondepressed Alzheimer patients. Thus, there are neurobiological differences between Alzheimer patients with and without neuropsychiatric disturbances, and the patterns are specific to each type of behavioral abnormality (e.g., regions of perfusion abnormalities differ among various behavioral syndromes). These studies validate the findings from rating scale studies and have important implications for understanding the pathophysiology of the neuropsychiatric symptoms.

Neurobiological determinants of neuropsychiatric symptoms are also evident when behavioral profiles are studied in different disease states. Distinctive NPI profiles have been shown in Alzheimer's disease, frontotemporal dementias, and progressive supranuclear palsy.[5,52,53] These diseases affect different brain regions, produce differing neuropathologic and neurochemical changes, and have contrasting neuropsychiatric manifestations.

IMPORTANCE OF ASSESSING TREATMENT OF NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE

Neuropsychiatric symptoms in Alzheimer's disease are important targets of treatment because of the distress that is associated with persecutory delusions, anxiety, agitation, apathy, and depression. In addition, neuropsychiatric symptoms have important consequences for both patients and caregivers. Demented patients with delusions are more aggressive than those without delusions.[54,55] Delusional demented patients are also noisier, more restless, and more likely to wander than nondelusional patients.[56]

Aggressive and delusional patients are often abused by caregivers,[57] and dementia patients with behavioral disturbances are more likely to be admitted to nursing homes than nondelusional dementia patients.[58–61] Delusional patients are treated with psychotropic medications including neuroleptics, antidepressants, and anxiolytics. They are also often restrained and likely to be hospitalized in a psychiatric unit.[56,59,62] Once admitted to a nursing home, agitated and aggressive patients require greater staff supervision than patients without behavioral disturbances.

Rabins and colleagues[63] showed that families find the behavioral disturbances of dementia patients to be a major problem. Physical violence, catastrophic reactions, delusions, and accusatory behavior were described as problematic for over 80% of families reporting the occurrence of these behaviors. Behavioral problems in patients with dementia have been found to correlate with increased caregiver depression, burden, and sacrifice of social life.[64]

Measurement of behavioral changes in Alzheimer's disease is important from a clinical trials perspective to allow study of the contribution of neuropsychiatric symptoms to global ratings. Alterations in behavior (beneficial or deleterious) will be reflected in global change scales such as the Clinician Interview–Based Impression of Change (CIBIC),[65] and assessment of the contribution of these alterations is necessary to interpret the changes in global scores.

CHANGES IN NEUROPSYCHIATRIC SYMPTOMS WITH CHOLINERGIC TREATMENT

Cholinergic agents were developed for the treatment of cognitive abnormalities linked to the well-established deficiency of acetylcholine in Alzheimer's disease.[66] Cholinesterase inhibitors are the most commonly used agents, and 2 drugs in this class—donepezil and tacrine—have been approved by the FDA for the treatment of mild-to-moderate Alzheimer's disease. Direct cholinergic receptor agonist agents that interact with the postsynaptic acetylcholine receptor are also being developed. Cognitive improvement has been documented following administration of drugs from both of these classes.[67–71]

Very few studies have addressed the responses of neuropsychiatric symptoms to cholinergic treatment. Preliminary information suggests that both cholinesterase inhibitors and cholinergic receptor agonists ameliorate behavioral abnormalities with few adverse behavioral effects. Cummings and coworkers[72,73] observed reductions in both delusions and agitation in Alzheimer's disease patients treated with physostigmine, a cholinesterase inhibitor. The magnitude of the reported responses was similar to that produced by haloperidol. Similarly, tacrine, another cholinesterase inhibitor, was reported to reduce apathy, disinhibition, pacing, and hallucinations,[74] and preliminary observations of patients treated with donepezil suggest that it has comparable psychotropic effects. Xanomeline, a receptor agonist, also has been shown to ameliorate behavioral disturbances in Alzheimer's disease. In a double-blind, placebo-controlled clinical trial of xanomeline, Bodick et al.[67] observed in the treated group significant reductions in vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, fearfulness, compulsiveness, tearfulness, mood swings, and threatening behavior. Likewise, Hollander and colleagues[75] noted improvement in behavior in 7 of 12 patients treated with RS 86, another muscarinic cholinergic receptor agonist.

Thus, preliminary observations suggest that cholinergic agents have beneficial psychotropic effects. The implication of these studies is that the cholinergic deficiency of Alzheimer's disease contributes to the pathophysiology of the behavioral as well as the cognitive abnormalities that accompany the disease and that enhancement of cholinergic function ameliorates the cholinergically based neuropsychiatric symptoms.[9,40] Improvement has been reported in response to treatment with both cholinesterase inhibitors and cholinergic receptor agonists and may be a general property of cholinergic therapy.

These investigations indicate that cholinergic agents are unique disease-specific, mechanism-based psychotropic agents that exert beneficial effects on several types of cholinergically mediated symptoms. They demonstrate that assessment of behavioral changes with cholinergic therapy is warranted.

COMMENT

Alzheimer's disease is evidenced by changes in cognition, behavior, and neurologic function. The studies reviewed here demonstrate that changes in both behavior and cognition may benefit from cholinergic treatment. Standardized assessment of the changes in neuropsychiatric symptoms associated with cholinergic therapy is imperative to document the range of beneficial effects exerted by these drugs, to determine the extent to which behavioral changes are responsible for improvements in global ratings observed in clinical trials of cholinomimetic treatment, and to suggest clinical circumstances in which cholinergic agents may offer alternatives to conventional psychotropic treatment.

Multidimensional neuropsychiatric assessment is critical to characterizing the range of behavioral responses to cholinergic therapy. Available observations indicate that cholinomimetic therapy has beneficial effects on psychosis, agitation, apathy, disinhibition, and aberrant motor behavior (e.g., pacing, wandering, rummaging). Other symptoms may also be responsive to this therapy, and changes can be documented as secondary outcomes in treatment studies. Behavioral side effects can also be posited with cholinergic therapy, and multidimensional behavioral scales will help ensure that these are detected and characterized.

Cholinergic agents have beneficial behavioral as well as cognitive effects. These agents would be expected to be effective primarily in diseases with cholinergic disturbances. While Alzheimer's disease is the most common condition with a cholinergic deficiency, it is not the only such disorder; other diseases with cholinergic abnormalities include Parkinson's disease and dementia, Down syndrome with dementia, dementia with Lewy bodies, some cases of Creutzfeldt-Jakob disease, mixed vascular–Alzheimer's disease dementias, Parkinsonism-dementia complex of Guam, and dementia pugilistica.[76] Cholinergic agents may also be expected to exert beneficial psychotropic effects in these disorders.

Differences among cholinergic agents in their psychotropic effects can be anticipated. Cholinesterase inhibitors have differences in pharmacodynamic and pharmacokinetic profiles, drug interactions, administration regimens, effects on hepatic microenzyme systems, side effects, enzyme selectivity (acetylcholinesterase, butyrylcholinesterase) and physiologic interactions with acetylcholinesterase (reversible vs. irreversible, competitive vs. noncompetitive), noncholinergic effects, and the degree to which they interact with muscarinic and nicotinic systems. These distinguishing features may produce differences in the psychotropic effects of different cholinergic compounds.

There have been surprisingly few controlled trials of conventional psychotropic agents in patients with Alzheimer's disease. Antipsychotic drugs, antidepressants, and anxiolytics have been administered to these patients because of the similarity of delusions, mood changes, and anxiety symptoms in Alzheimer's disease to those of idiopathic illnesses for which these agents were developed. These symptoms, however, may have different or only partially overlapping pathophysiologies in Alzheimer's disease and idiopathic disorders, and treatment responses cannot be confidently extrapolated from one condition to another. A meta-analysis of conventional psychotropic agents showed that these drugs offer only modest benefit over placebo in the treatment of agitation and psychosis in Alzheimer's disease.[77]

Conventional psychotropic drugs were developed and tested in patients with intact cholinergic systems (e.g., schizophrenia), and their efficacy may depend on intact cholinergic function. The cholinergic abnormalities may account for the apparently diminished utility of conventional psychotropics in Alzheimer's disease, and improvement of cholinergic function with cholinergic agents may facilitate their use for treatment of residual behavioral symptoms after cholinergic therapy has been initiated.

Neuroleptic agents are the drugs most commonly used to control psychosis and reduce agitation in Alzheimer's disease. These medications have many side effects, including akathisia, parkinsonism, tardive dyskinesia, and postural hypotension. These side effects are more common in elderly patients such as those with Alzheimer's disease than in younger patients with other types of psychosis. Many cholinergic agents have fewer side effects than neuroleptics and offer a safer means of reducing neuropsychiatric symptoms. Confirmation of the behavioral effects of cholinergic therapy will establish their role as alternative and possibly safer treatments for neuropsychiatric symptoms in Alzheimer's disease.

The pathogenesis of Alzheimer's disease is increasingly well understood, and the sequential steps in the cascade of events leading to neuronal death and neurotransmitter deficiencies offer well-defined targets for therapeutic trials. Antioxidants have been shown to slow the progression of Alzheimer's disease,[78] and accumulating evidence suggests that antiinflammatory agents and estrogens may also be beneficial in delaying the onset or slowing the decline of Alzheimer's disease.[79,80] The principal effect of cholinergic therapies is to improve existing symptoms by enhancing cholinergic transmission. Thus, a combination of disease-modifying treatment (antiamyloid drugs, antioxidants, and other neuroprotective agents) and

cholinergic agents used to improve current symptoms will comprise the expected Alzheimer's disease treatment regimen. Disease-modifying compounds may reduce the emergence of new behavioral disturbances in the course of the illness,[78] and cholinergic drugs may relieve existing neuropsychiatric symptoms as well as suppress those emergent symptoms.

CONCLUSIONS

Alzheimer's disease has multiple manifestations and produces cognitive, behavioral, and neurologic abnormalities. Cholinergic abnormalities contribute to both cognitive deficits and neuropsychiatric symptoms. Cholinergic therapies have beneficial effects on cognition and reduce several types of aberrant behavior including psychosis, agitation, disinhibition, apathy, and motor excesses. Changes in neuropsychiatric symptoms should be measured when new cholinergic agents are developed, and the psychometric properties, content, and purpose of the assessment instruments used must be considered when selecting a tool for evaluation of psychotropic properties of cholinergic agents.

Drug names: donepezil (Aricept), haloperidol (Haldol and others), tacrine (Cognex).

REFERENCES

1. Cummings JL, Benson DF. Dementia: A Clinical Approach. 2nd ed. Boston, Mass: Butterworth-Heinenmann; 1992
2. Zec RF. Neuropsychological function in Alzheimer's disease. In: Parks RW, Zec RF, Wilson RS, eds. Neuropsychology of Alzheimer's Disease and Other Dementias. New York, NY: Oxford University Press; 1993:3–80
3. Eastwood R, Reisberg B. Mood and behaviour. In: Gautheir S, ed. Clinical Diagnosis and Management of Alzheimer's Disease. London, England: Martin Dunitz; 1996:175–189
4. Gilley DW. Behavioral and affective disturbances in Alzheimer's disease. In: Parks RW, Zec RF, Wilson RS, eds. Neuropsychology of Alzheimer's Disease and Other Dementias. New York, NY: Oxford University Press; 1993:112–137
5. Mega M, Cummings JL, Fiorello T, et al. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996;46:130–135
6. Blass JP, Poirier J. Pathophysiology of the Alzheimer syndrome. In: Gautheir S, ed. Clinical Diagnosis and Management of Alzheimer's Disease. London: Martin Dunitz; 1996:17–31
7. Cummings JL, Mega M. Alzheimer's disease: etiologies and pathogenesis. Consultant Pharm 1996;11(suppl E):8–15
8. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364
9. Cummings JL, Kaufer DI. Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. Neurology 1996;47:876–883
10. De Vellis RF. Scale Development. Theory and Applications. London, England: Sage Publications; 1991
11. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Psychol 1967;6:278–296
12. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
13. Alexopoulos GS, Abrams RC, Young RC, et al. Cornell Scale for Depression in Dementia. Biol Psychiatry 1988;23:271–284
14. Levin HS, High WM, Goethe KE, et al. The Neurobehavior Rating Scale: assessment of the sequelae of head injury by the clinician. J Neurol Neurosurg Psychiatry 1987;50:183–193
15. Sultzer DL, Levin HS, Mahler ME, et al. Assessment of cognitive, psychiatric, and behavioral disturbances in patients with dementia: the Neurobehavior Rating Scale. J Am Geriatr Soc 1992;40:549–555
16. Brooks DN, McKinlay W. Personality and behavioural change after severe blunt head injury: a relative's view. J Neurol Neurosurg Psychiatry 1983; 46:189–198
17. Cummings JL, Petry S, Dian L, et al. Organic personality disorders in dementia syndromes: an inventory approach. J Neuropsychiatry Clin Neurosci 1990;2:261–267
18. Reisberg B, Borenstein J, Salob SP, et al. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry 1987;48 (5, suppl):9–15
19. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. J Gerontol 1989;44:M77–M84
20. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314
21. Tariot PN, Mack JL, Patterson MB, et al. The CERAD Behavior Rating Scale for Dementia (BRSD). Am J Psychiatry 1995;152:1349–1357
22. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease, III: disorders of mood. Br J Psychiatry 1990;157:81–86
23. Cummings JL, Ross W, Gornbein J, et al. Depressive symptoms in Alzheimer's disease: assessment and determinants. Alzheimer Dis Assoc Disord 1995;9:87–93
24. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
25. Honigfeld G, Klett CJ. The Nurses' Observation Scale for Inpatient Evaluation. J Clin Psychol 1965;21:65–71
26. Blunden J, Hodgkiss A, Klemperer F, et al. The Ward Daily Behaviour Scale. Br J Psychiatry 1994;165:87–93
27. Cummings JL. Theories behind existing rating scales for rating behavior in dementia. Int Psychogeriatr. In press
28. Helmes E, Csapo K, Short JA. Standardization and validation of the Multidimensional Observation Scale for Elderly Subjects (MOSES). J Gerontol 1987;42:395–405
29. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1983;17:37–49
30. Devanand DP, Miller L, Richards M, et al. The Columbia University Scale for Psychopathology in Alzheimer's disease. Arch Neurol 1992;49: 371–376
31. Rosen J, Burgio L, Kollar M, et al. The Pittsburgh Agitation Scale: a user friendly instrument for rating agitation in dementia patients. Am J Geriatr Psychiatry 1994;2:52–59
32. Gottfries CG, Brane G, Gullberg B, et al. A new rating scale for dementia symptoms. Arch Gerontol Geriatr 1982;1:311–330
33. Teri L, Truax P, Logsdon R, et al. Assessment of behavioral problems in dementia: the Revised Memory and Behavior Problems Checklist. Psychol Aging 1992;7:627–631
34. Drachman DS, Swearer JM, O'Donnell BF, et al. The Caretaker Obstreperous-Behavior Rating Assessment (COBRA) scale. J Am Geriatr Soc 1992; 40:463–480
35. Friedenberg D, Cummings JL. Parkinson's disease, depression, and the on-off phenomenon. Psychosomatics 1989;30:94–99
36. Kaufer DI, Cummings JL, Christine D. Effect of tacrine on behavioral symptoms in Alzheimer's disease: an open label study. J Geriatr Psychiatry Neurol 1996;9:1–6
37. Chui HC, Lyness SA, Sobel E, et al. Extrapyramidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer's disease. Arch Neurol 1994;51:676–681
38. Mortimer JA, Ebbitt B, Jun S-P, et al. Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. Neurology 1992;42:1689–1696
39. Stern Y, Brandt J, Jacobs DM, et al. Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer's disease: prospective analyses from the Predictors Study. Neurology 1994;44:2300–2307
40. Cummings JL, Back C. The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. Am J Geriatr Psychiatry. In press
41. Grady CL, Haxby JV, Schapiro MB, et al. Subgroups in dementia of the Alzheimer type identified using positron emission tomography. J Neuropsychiatry Clin Neurosci 1990;2:373–384
42. Kotrla KJ, Chacko RC, Harper RG, et al. SPECT findings on psychosis in

Alzheimer's disease. Am J Psychiatry 1995;152:1470–1475
43. Mentis MJ, Weinstein EA, Horwitz B, et al. Abnormal brain glucose metabolism in the delusional misidentification syndromes: a positron emission tomography study in Alzheimer disease. Biol Psychiatry 1995;38: 438–449
44. Ponton MO, Darcourt J, Miller BL, et al. Psychometric and SPECT studies in Alzheimer's disease with and without delusions. Neuropsychiatry Neuropsychol Behav Neurol 1995;8:264–270
45. Starkstein SE, Vazquez S, Petracca G, et al. A SPECT study of delusions in Alzheimer's disease. Neurology 1994;44:2055–2059
46. Sultzer DL, Mahler ME, Mandelkern MA, et al. Psychiatric symptoms are associated with regional cortical metabolism in Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1995;7:476–484
47. Lebert F, Pasquier F, Danel T, et al. Psychiatric, neuropsychologic, and SPECT evidence of elated mood in dementia of the Alzheimer's type. Neuropsychiatry Neuropsychol Behav Neurol 1994;7:299–302
48. Craig AH, Cummings JL, Fairbanks L, et al. Cerebral blood flow correlates of apathy in Alzheimer's disease. Arch Neurol 1996;53:1116–1120
49. Lopez OL, Becker JT, Brenner RP, et al. Alzheimer's disease with delusions and hallucinations: neuropsychological and electroencephalophic correlates. Neurology 1991;41:906–912
50. Zubenko GS, Moossy J, Kopp U. Neurochemical correlates of major depression in primary dementia. Arch Neurol 1990;47:209–214
51. Zubenko GS, Moossy J, Martinez J, et al. Neuropathologic and neurochemical correlates of psychosis in primary dementia. Arch Neurol 1991;48:619–624
52. Levy ML, Miller BL, Cummings JL, et al. Alzheimer disease and frontotemporal dementias: behavioral distinctions. Arch Neurol 1996;53: 687–690
53. Litvan I, Mega M, Cummings JL, et al. Neuropsychiatric aspects of progressive supranuclear palsy. Neurology 1996;47:1184–1189
54. Deutsch LH, Bylsma FW, Rovner BW, et al. Psychosis and physical aggression in probable Alzheimer's disease. Am J Psychiatry 1991;148: 1159–1163
55. Flynn FG, Cummings JL, Gornbein J. Delusions in dementia syndromes: investigations of behavioral and neuropsychological correlates. J Neuropsychiatry Clin Neurosci 1991;3:364–377
56. Rovner BW, Steele CD, German P, et al. Psychiatric diagnosis and uncooperative behavior in nursing homes. J Geriatr Psychiatry Neurol 1992;5: 102–105
57. Ryden MB. Aggressive behavior in persons with dementia who live in the community. Alzheimer Dis Assoc Disord 1988;2:342–355
58. Martinson IM, Muwaswes M, Gilliss CL, et al. The frequency and troublesomeness of symptoms associated with Alzheimer's disease. J Community Health Nurs 1995;12:47–57
59. Morriss RK, Rovner BW, Folstein MF, et al. Delusions in newly admitted residents of nursing homes. Am J Psychiatry 1990;147:299–302
60. O'Donnell BF, Drachman DA, Barnes HJ, et al. Incontinence and troublesome behaviors predict institutionalization in dementia. J Geriatr Psychiatry Neurol 1992;5:45–52
61. Steele C, Rovner B, Chase GA, et al. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. Am J Psychiatry 1990;147:1049–1051
62. Malone ML, Thompson L, Godwin JS. Aggressive behaviors among the institutionalized elderly. J Am Geriatr Soc 1993;41:853–856
63. Rabins PV, Mace NL, Lucas MJ. The impact of dementia on the family. JAMA 1982;248:333–335
64. Pruchno RA, Resch NL. Aberrant behaviors and Alzheimer's disease: mental health effects on spouse caregivers. J Gerontol 1989;44:S177–S182
65. Olin JT, Schneider LS, Doody RS, et al. Clinical evaluation of global change in Alzheimer's disease: identifying consensus. J Geriatr Psychiatry Neurol 1996;9:176–180
66. Tariot PN, Schneider L. Contemporary treatment approaches to Alzheimer's disease. Consultant Pharm 1996;11(suppl E):16–24
67. Bodick N, Offen W, Levey AI, et al. Effects of xanomeline, a selective muscarinic agonist, on cognitive function and behavioral symptoms in Alzheimer's disease. Arch Neurol 1997;54:465–473
68. Davis KL, Thal LJ, Gamzu ER, et al. A double-blind placebo-controlled multicenter study of tacrine for Alzheimer's disease. N Engl J Med 1992; 327:1253–1259
69. Farlow M, Gracon SI, Hershey LA, et al. A controlled trial of tacrine in Alzheimer's disease. JAMA 1992;268:2523–2529
70. Knapp MJ, Knopman DS, Solomon PR, et al. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. JAMA 1994;271:985–991
71. Rogers SL, Friedhoff LT, and the Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicentre, randomized, double-blind, placebo-controlled trial. Dementia 1996;7:293–303
72. Cummings JL, Gorman DG, Shapira J. Physostigmine ameliorates the delusions of Alzheimer's disease. Biol Psychiatry 1993;33:536–541
73. Gorman DG, Read S, Cummings JL. Cholinergic therapy of behavioral disturbances in Alzheimer's disease. Neuropsychiatry Neuropsychol Behav Neurol 1993;6:229–234
74. Kaufer DI, Cummings JL, Christine D. Response of behavioral symptoms in Alzheimer's disease to tacrine. J Neuropsychiatry Clin Neurosci. In press
75. Hollander E, Davidson M, Mohs RC, et al. RS 86 in the treatment of Alzheimer's disease: cognitive and biological effects. Biol Psychiatry 1987; 22:1067–1078
76. Cummings JL, Benson DF. The role of the nucleus basalis of Meynert in dementia: review and reconsideration. Alzheimer Dis Assoc Disord 1987; 1:128–145
77. Schneider LS, Pollack VE, Lyness SA. A meta-analysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990;38:553–563
78. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. N Engl J Med 1997;336:1216–1222
79. Andersen K, Launer LJ, Ott A, et al. Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease? the Rotterdam study. Neurology 1995;45:1441–1445
80. Mortel KF, Meyer JS. Lack of postmenopausal estrogen replacement therapy and the risk of dementia. J Neuropsychiatry Clin Neurosci 1995;7: 334–337