A Systematic Review of Assessment and Treatment of Moderate to Severe Alzheimer's Disease

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Objective: The systematic, large-scale study of therapies for moderate to severe Alzheimer's disease (AD) is a relatively recent advancement in the field. This review describes for the general practitioner the characterization of moderate to severe AD, discusses the development of metrics sensitive to the constellation of symptoms in these patients, and critically evaluates the use of those measures in moderate to severe AD clinical trials.

Data Sources: Published clinical trials obtained by MEDLINE searches used the following key words: *moderate AD, severe AD, donepezil, rivastigmine, galantamine, memantine,* and *antidementia agents*. Clinical trials were limited by language (English), study type (clinical trial), and publication dates (1990–2005).

Study Selection: Nine clinical trials comprise the studies conducted to date in moderate to severe AD and include 5 prospective randomized clinical trials (3 for memantine, 2 for donepezil) and 4 retrospective subanalyses (2 for galantamine, 2 for rivastigmine) of primary datasets.

Data Extraction: Clinical trials are summarized and major findings are reviewed.

Data Synthesis: The data reviewed support the decision to initiate and maintain treatment in moderate to severe AD patients.

Conclusions: The development and implementation of improved metrics for moderate to severe AD patients has revealed that meaningful benefits are attainable in this patient population by treatment with the *N*-methyl-D-aspartate receptor antagonist memantine. Evidence also indicates a benefit from cholinesterase inhibitor treatment, although further study of these agents in this patient population is warranted.

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It has been estimated that over one half of community-dwelling patients diagnosed with Alzheimer's disease (AD) are in the moderate to severe stages of the disease,[1] and almost 90% of institutionalized patients with AD have been graded as moderate or severe.[2] Despite the large proportion of patients estimated to be in the moderate and severe stages of AD (31% moderate and 21% severe),[1] most clinical trials have examined antidementia drug effects earlier in the disease, leading to the approval of the cholinesterase inhibitors (ChEIs) for patients with mild or moderate AD. Given the inevitable decline of the AD patient from mild to moderate and ultimately to severe stages of the disease, clinicians are faced not only with the challenge of determining the proper treatment regimen for their individual AD patients but also with the responsibility of effectively communicating realistic short- and long-term treatment expectations to the patient and/or caregiver.

Previously, a lack of metrics capable of detecting therapeutic efficacy in more advanced AD contributed to the perception that clinical benefit of an antidementia agent was unlikely, or at best immeasurable, in patients with moderate to severe AD. Over the past several years, instruments have been developed and existing tools have been modified, allowing for the accurate characterization and tracking of patients beyond the mild stages of the

disease. Incorporation of these tools into clinical trials has provided meaningful data and expanded the study of AD beyond mild to moderate severity, as demonstrated by the positive results of prospective clinical trials examining the efficacy of the ChEI donepezil[3] and the moderate affinity *N*-methyl-D-aspartate receptor antagonist memantine in moderate to severe AD.[4,5] The 2003 Food and Drug Administration (FDA) approval of memantine made available for the first time a treatment indicated specifically for moderate to severe stages of AD, and the data supporting this decision utilized rating scales and outcome measures specific to a patient population with more advanced AD.

This review describes for the general practitioner the concept of advanced AD, discusses the development of metrics sensitive to the range of symptoms seen in these patients, and critically evaluates the use of such measures in clinical trials of antidementia agents in moderate to severe AD.

DISEASE PROGRESSION: MODERATE TO SEVERE ALZHEIMER'S DISEASE

The clinical spectrum of AD resides on a continuum whereby the initial signs may be barely detectable and the later symptoms are both obvious and complex.[6–8] AD disease progression is not a uniform process; rates of decline vary widely, and there is an enormous range of disability that is largely dependent on the stage of severity.

Early clinical manifestations may present as memory loss, progressing to language and communication impairments, deteriorating executive function, and social withdrawal. Unlike the cognitive impairment that dominates early stage AD, patients with advanced AD are beset by multiple, heterogeneous deficits that complicate the clinical picture. Increasing cognitive loss is accompanied by progressive functional deficits and eroding motor skills. Most sources agree that about 90% of patients will develop various behavioral and psychological symptoms at some point in the illness.[9–12] Anxiety, delusions, depression, restlessness, aggression, and pacing have been shown to be prevalent in the later stages of AD.[7,13]

STAGING TOOLS FOR DETERMINING ALZHEIMER'S DISEASE SEVERITY

A number of longitudinal AD studies have been used as the basis for developing staging systems.[8,14] Staging tools delineate the course of AD and provide a means whereby an individual with AD may be placed along a continuum of decline. Because multiple domains are affected by AD, a variety of staging tools have been developed; some evaluate cognition, others assess global severity, and others focus on functional status.[15] While staging the severity of AD does not necessarily assist with a prediction of future disease course (e.g., the rate of decline), assessing severity might aid a physician in understanding what particular groups of symptoms can be expected.

Clinical trials in AD use staging tools as inclusion criteria to define the severity of the patient population to be studied. The tools most commonly used in AD clinical trials include the Mini-Mental State Examination (MMSE),[16] probably the most widely used assessment of cognitive function employed in both clinical practice and clinical trials; the Clinical Dementia Rating Scale (CDR)[17,18]; the Global Deterioration Scale (GDS)[19]; and the Functional Assessment Staging Scale (FAST).[20] Brief descriptions of the utility and limitations of each of these tools are provided in Table 1.

The ideal definitions of moderate and severe AD would encompass the domains of cognition, function, behavior, global status, and caregiver burden. However, the heterogeneous nature of symptoms associated with AD, coupled with limitations inherent to staging tools (e.g., variability, ceiling and floor effects), argues against narrowly defining discrete stages in disease progression. Illustrating this point, Figure 1 highlights the variability in the range of MMSE scores for levels of severity globally determined by clinicians (based on the CDR).[18] In spite of these challenges, broad operational definitions of AD progression using staging tools as surrogate markers of disease severity are summarized in Table 2.

EVALUATING TREATMENT EFFICACY IN ADVANCED ALZHEIMER'S DISEASE

Subsequent to concerns regarding the insufficient testing of putative antidementia agents, the FDA proposed draft guidelines in 1990 for establishing whether a drug possessed antidementia efficacy.[29] As cognitive impairment is a core feature of AD, it was reasoned that a putative agent must demonstrate efficacy by improving cognition or retarding its deterioration. The FDA also requested that a clinically meaningful (global) measure be included as a second primary outcome to ensure that changes in cognitive test results are mirrored by clinical changes detectable by a physician, independently of psychometric tests. This established the dual-outcome criteria that were to become the de facto standard subsequent to the marketing approval of tacrine in the United States in 1996. The guidelines were limited, however, in their failure to recognize that improvement in behavior or function alone may be legitimate therapeutic goals, particularly in advanced AD patients who are unable to perform standard cognitive tests. Thus, the FDA requirements have guided the development of assessment tools, including those specific for advanced AD.[30]

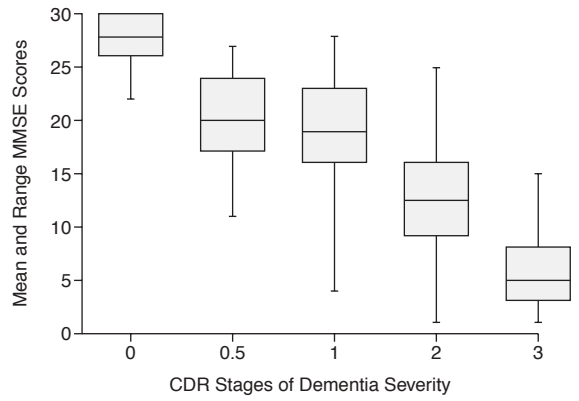
The development of metrics appropriate for patients with moderate to severe AD has made it possible to define and evaluate the cognitive, functional, and behavioral status in more advanced patients. Incorporation of these

Table 1. Staging Tools in Dementia

Staging Tool	Domains Assessed	Score Range	Administration	Comments
Mini-Mental State Examination (MMSE)[16]	Cognition: briefly evaluates orientation, memory, attention, recall, language, and constructional praxis	30 points from normal (30) to severe impairment (0)	Clinician to patient	The MMSE is an assessment of cognitive function employed in both clinical practice and clinical trials. Scores may be impacted by a number of factors including education, cultural background, and literacy.[21–23] Less sensitive to the earliest signs of cognitive decline; floor effect in severe patients[22,24]
Clinical Dementia Rating (CDR and CDR-Sum of Boxes)[17,18]	Global status: scores 6 domains (memory, orientation, judgment and problem-solving, community affairs, home/hobbies, and personal care) based upon a semistructured interview with patient and caregiver	5-point ordinal scale ranging from 0 = no impairment; 0.5 = questionable or very mild impairment; mild, moderate, and severe impairment are scored as 1, 2, and 3, respectively	Clinician to patient or caregiver	The CDR tracks early stages of AD best; it has autopsy validity and is used mainly by academic clinics to track patients over time.[25,26] In clinical trials, the CDR has also been used as a more quantitative sum-of-the-boxes numerical score of outcome. In this case, each domain is scored from 0–3 and the ratings from each domain summed yielding a total sum-of-boxes score range of 0–18
Global Deterioration Scale (GDS)[19]	Global status: clinicians with access to all sources of information pertinent to a patient assess the progressive cognitive, functional, and behavioral decline and place the patient on one of the 7 levels of severity on the basis of the clinical descriptions provided for each stage	Detailed clinical descriptions of 7 potential levels of AD severity, ranging from normality (1) to the most severe dementia (7)	Clinician to patient and caregiver	The GDS is used in the clinical trial setting and is limited in the detail it provides on more severe patients
Functional Assessment Staging (FAST)[20]	Function: the ability of patients to perform basic and instrumental activities of daily living (ADLs)	The FAST is also divided into 7 major stages ranging from normality (1) to the most severe dementia (7); however, these stages are delineated by the ability of the patient to perform ADLs	Clinician to patient and caregiver	Like the GDS, the FAST is divided into 7 major stages. Stages 6 and 7 are further divided into 11 substages, thereby extending the utility of the GDS, with more detail in advanced AD

Abbreviation: AD = Alzheimer's disease.

Figure 1. Mean and Range of MMSE Scores (box plot) for Levels of Impairment Defined by CDR Stages of Dementia Severity[a]



[a]Data shown are from the entry evaluations of normal, aged controls and persons with dementia enrolled in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) data set.
Abbreviations: CDR = Clinical Dementia Rating, MMSE = Mini-Mental State Examination.

tools into clinical trials has resulted in the quantification of treatment benefits that previously went undetected. Since the choice of assessment tools in clinical trials and the variability of symptoms in more advanced AD patients can affect both the interpretation of trial data and the ability of primary care physicians to apply trial results to the clinic, it is important to gain an understanding of currently employed assessment tools.

The scales that have been developed or modified for use in moderate to severe AD clinical trials include the Severe Impairment Battery (SIB),[31] the Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory modified for Severe Patients (ADCS-ADL$_{19}$),[32] the modified Instrumental Activities of Daily Living (IADL+),[33] the modified Physical Self-Maintenance Scale (PSMS+),[33] and the Disability Assessment in Dementia (DAD).[34] Details of each scale are summarized in Table 3.

Although the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) has been the most commonly used outcome measure of cognitive function in antidementia clinical trials,[42] it was specifically developed to assess treatment effects in mild to moderate AD patients.[43,44] As AD progresses and patients experience a dissolution of expressive and receptive language skills, performance on measures like the MMSE or ADAS-cog may be subject to floor effects, making it difficult to quantify and assess change in patients with moderate to severe AD.

For this reason, the SIB was designed for use in patients with more advanced dementia[31] and provides an accurate assessment of change in cognition over time in patients with MMSE scores below 15. Due to the limited comprehension and language skills of this patient

Table 2. Operational Definitions of Alzheimer's Disease (AD) Stages

Operational Category	Incipient or Questionable AD	Mild AD	Moderate AD	Severe AD	Profound AD
Estimated MMSE	25–30	18–24	12–18	≤ 12	< 5; often MMSE = 0
Activities	Essentially preserved ADLs	IADLs begin to decline	Increasing losses of ADLs	Despite losses, many retained activities; some IADLs/ADLs intact	Engages in almost no activities
Communication	Communication preserved; memory impairment may be noticed by others	Dissolution of expressive and receptive language skills	Becoming difficult to engage in conversation	Communication with variable success	Unable to verbally communicate; may retain some words
Awareness	Aware of others; aware of memory deficit	Aware of others; capable of interaction	Aware of others; capable of interaction	Aware of others; capable of interaction	No response to others or simple visual awareness
CDR stage	0.5	1	2	3	4,5[27,28]
GDS stage	3	4	5	6	7
FAST	2–3	4	5	6	7

Abbreviations: ADLs = activities of daily living, CDR = Clinical Dementia Rating, FAST = Functional Assessment Staging, GDS = Global Deterioration Scale, IADLs = instrumental activities of daily living, MMSE = Mini-Mental State Examination.

Table 3. Rating Scales Used in Moderate to Severe Alzheimer's Disease (AD) Trials

Rating Scale	Domains Assessed	Score Range	Administration	Comments
Severe Impairment Battery (SIB)[31]	Cognition: 6 subscales including attention, orientation, language, memory, visual perception, and construction. There are also brief assessments of social skills, praxis, and response to name	Most widely used version has a range of 1–100: 63 or less is considered very severely impaired; higher scores indicate less impairment	Clinician or trained interviewer to patient	Measures a range of cognitive functioning in patients who are unable to complete existing neuropsychological measures such as the MMSE[16] and ADAS-cog.[43] Patients are scored by what they know or can do instead of scoring by errors. Scoring allows credit for nonverbal and partially correct responses, important features given the extent of comprehension and language deficits seen in these patients. The SIB was included in the Alzheimer's Disease Cooperative Study (ADCS) instrument protocol,[30,35] and the validity, reliability, and sensitivity of the SIB to longitudinal change have been established[35–37]
Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+)[38,39]	Global status: 4 areas of patient function including general, cognitive, behavioral, and ADLs	Range 1–7: 1 indicates marked improvement; 4 indicates no change; 7 indicates markedly worse	Clinician to patient and caregiver (this scale administered without caregiver input is referred to simply as the CIBIC)	There are several forms of the CIBIC+. The NYU version of the CIBIC+ uses the usual 7-point scale but importantly provides standardized guidelines for assessing change. The high interrater variability of the CIBIC+ and CIBIC makes it difficult to compare this measure across drug studies
Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory ($ADCS\text{-}ADL_{19}$)[4,32]	Function: 19 ADLs demonstrated to be appropriate for assessing patients with moderate to severe AD[40]	0–54: lower scores indicate more impairment	Clinician or trained interviewer to caregiver or informant	This is a modified version of the ADCS-ADL inventory developed to gauge functional performance in patients over a wide range of AD severity; 19 of the original 24 items were retained
Modified Instrumental Activities of Daily Living (IADL+)[33]	Function: ADLs including the use of household appliances, managing personal mail, the ability to get around inside/outside the home, hobbies/leisure activities, and grasping situations or explanations	4–30: lower scores indicate less impairment	Clinician or trained interviewer to caregiver or informant	The IADL scale has 8 items that assess those abilities lost earlier in the course of dementia. The modified version removed the laundering item and added selected items more applicable to moderate-severe AD[3,41]
Modified Physical Self-Maintenance Scale (PSMS+)[33]	Function: basic ADLs and 3 items important for the provision of care in advanced patients: loss of recognition of immediate caregiver, impaired ambulation, and wandering	6–30: lower scores indicate less impairment	Clinician or trained interviewer to caregiver or informant	The PSMS is a 6-item scale that was modified to include 3 additional items that were believed to be important for the provision of basic ADL care in moderate to severe patients[3,41]
Disability Assessment in Dementia (DAD)[34]	Function: initiation, planning, organization, and performance of ADLs, IADLs, and leisure activities	0–100: lower scores indicate more impairment	Clinician or trained interviewer to caregiver or informant	The DAD was specifically developed for patients with AD

Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, ADLs = activities of daily living, IADLs = instrumental activities of daily living, MMSE = Mini-Mental State Examination, NYU = New York University.

population, the assessment employs simple verbal commands accompanied by gestures.[45] In addition, credit for nonverbal and partially correct responses is given, which allows for a finer assessment of cognitive function in this highly impaired group. For example, an 85-year-old man with an 8-year history of AD obtained an MMSE score of 5 based on repetition of 3 objects and orientation to city and state (note that only 17% of the MMSE remains to describe disease progression). However, when the SIB is obtained, his score is a 74. The SIB subscales reveal that his primary areas of dysfunction are in praxis (25% completed), orientation (50% correct), memory (71%), and language (76%), with essentially no impairments in basic skills of attention, social interaction, and simple constructions. Given his ability to function on the SIB, and given the wide range of skills identified by the SIB items, cognition can be tracked more carefully in response to treatment and disease progression. Similar to the use of the ADAS-cog in pivotal trials of mild to moderate AD, the SIB has become the de facto standard for assessing cognition in trials of moderate to severe AD.

The PSMS and IADL were among the first scales developed to evaluate function in elderly patients and are validated measures for the assessment of basic (i.e., personal care activities such as walking, feeding, and toileting) and instrumental (i.e., more complicated tasks such as handling finances, shopping, and food preparation) activities of daily living (ADLs), respectively.[33] These scales have been modified to enhance their sensitivity for use in clinical trials of moderate to severe AD (IADL+ and PSMS+).[3,41] As reported by Feldman et al.,[41] these modified instruments are sufficiently sensitive to measure drug treatment effects in moderate to severe AD patients; however, notable limitations of these scales include coarse rating increments that impede their sensitivity to change and the need for concurrent use of both scales to obtain information on basic and instrumental ADLs.[46] Other limitations of these and other available assessments of function include the use of gender-specific items, subjective questioning, and inclusion of behavioral as well as functional information.

In response to the limitations, the ADCS-ADL[32] and DAD[34] were developed to assess the performance of both basic and instrumental ADLs in AD patients. The ADCS-ADL was further modified, and the resulting 19-item version, the ADCS-ADL$_{sev}$ (referred to as the ADCS-ADL$_{19}$ in this article), was shown to be appropriate for the assessment of functional change in clinical trials of patients with moderate to severe dementia.[40]

CLINICAL TRIALS IN MODERATE TO SEVERE ALZHEIMER'S DISEASE

Published clinical trials obtained by MEDLINE searches used the following key words: *moderate AD, severe AD, donepezil, rivastigmine, galantamine, memantine,* and *antidementia agents*. Clinical trials were limited by language (English), study type (clinical trial), and publication dates (1990–2005).

Clinical trial results published to date with memantine, the ChEIs, or both in moderate to severe AD patients are summarized in Tables 4 and 5 and are described in detail below.

Efficacy of Memantine in Moderate to Severe Alzheimer's Disease

Cholinesterase inhibitors have been used for AD treatment for about a decade. Memantine is the first treatment from a new class of compounds that has been approved for use in patients with AD. Memantine represents a new approach to AD therapy and offers the first approved treatment option for those patients in the moderate to severe stages of the disease. The safety and efficacy of memantine in moderate to severe AD were supported by 3 pivotal trials, and the developmental history of memantine mirrors the advances in outcome measures over the last decade.

The first large-scale placebo-controlled trial of memantine in dementia was initiated in the early 1990s. It was designed to investigate the clinical efficacy and safety of memantine (10 mg/day) over the course of 12 weeks in nursing home patients with severe dementia of the Alzheimer's type or vascular dementia.[47] This population was of interest as there were no therapies approved or in development for this patient population. At the time the study was initiated, the primary outcome measures of interest that could be reliably tested were related to patient function and global performance: the care dependency subscale of the Behavioral Rating Scale for Geriatric Patients (BGP-care) and the Clinical Global Impressions of Change (CGI-C) scale. The BGP was adapted from the Stockton Geriatric Rating scale,[52] an investigator-rated scale that provides an objective behavioral assessment of geriatric patients. The BGP has been used in Europe since 1971 and has good reliability and the ability to measure longitudinal change.[53] The superiority of treatment with memantine over placebo demonstrated on both the BGP-care and CGI-C became the "proof-of-principle" that initiated further investigation of memantine efficacy in patients with later stages of AD.

In the next trial designed to assess the clinical efficacy and safety of memantine in patients with moderate to severe AD, Reisberg and colleagues performed a 28-week, randomized, double-blind, placebo-controlled trial in 252 AD patients.[4] At the time the trial was conducted, the SIB and the ADCS-ADL$_{19}$ had been validated by the ADCS. Primary outcome measures included a global measure, the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+), and a modified functional measure (ADCS-ADL$_{19}$). Secondary outcomes included

Table 4. Memantine in Moderate to Severe Alzheimer's Disease (AD)

Study	Design	Duration/ Patient Residence	N	Diagnosis/ Inclusion Criteria	Baseline Cognition	Primary Outcomes	Secondary Outcomes
Winblad and Poritis[47]	Multicenter Randomized DBPCT, PG	12 weeks Nursing home	166	AD/VaD MMSE < 10 GDS 5–7 CGI-S 5–7	MMSE scores: PBO = 6.1 MEM = 6.6	CGI-C BGP-care dependency	BGP-total BGP-cog D-test
Reisberg et al[4]	Multicenter Randomized DBPCT, PG	28 weeks Community dwelling	252	Moderate to severe AD MMSE 3–14 GDS 5–6 FAST ≥ 6a	MMSE scores: PBO = 8.05 MEM = 7.72	CIBIC+ ADCS-ADL$_{19}$	SIB NPI RUD MMSE FAST GDS
Tariot et al[5]	Multicenter Randomized DBPCT, PG	24 weeks Community dwelling	404	Moderate to severe AD MMSE 5–14 Patients stabilized on donepezil (minimum of 6 months)	MMSE scores: PBO = 10.2 MEM = 9.9	SIB ADCS-ADL$_{19}$	CIBIC+ NPI RUD MMSE FAST GDS BGP-care

Abbreviations: ADCS-ADL$_{19}$ = Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory, BGP = Behavioral Rating Scale for Geriatric Patients, CGI-C = Clinical Global Impressions of Change scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CIBIC+ = Clinician's Interview-Based Impression of Change Plus Caregiver Input, D-test = Luria-based D-Test Battery, DBPCT = double-blind placebo-controlled trial, FAST = Functional Assessment Staging, GDS = Global Deterioration Scale, MEM = memantine, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, PBO = placebo, PG = parallel group, RUD = resource utilization, SIB = Severe Impairment Battery, VaD = vascular dementia.

a cognitive measure (assessed by the SIB and MMSE), a behavioral measure (Neuropsychiatric Inventory [NPI]),[54] and additional functional ratings (FAST, GDS) by the clinicians. The benefits of memantine (10 mg b.i.d.) over placebo in patients with moderate to severe AD were clinically meaningful as determined by the CIBIC+ ($p = .03$ for observed cases [OC]; $p = .06$ for last observation carried forward [LOCF]) with 45% of memantine-treated patients either improving or not changing, compared with only 27% of patients receiving placebo. Patients treated with memantine also had better preservation of cognition (as measured by the SIB; $p < .001$, LOCF; $p < .002$, OC), especially in the areas of memory and visuospatial activity. Functional preservation was greater with memantine (ADCS-ADL$_{19}$; $p = .02$, LOCF; $p = .03$, OC) compared with placebo, including improvements in conversing. Finally, the effect of memantine on behavioral outcome (as measured by the NPI) was superior to placebo treatment over the study period, reaching statistical significance at week 12.[55]

In a more recent trial, Tariot and colleagues published the first prospective, double-blind, placebo-controlled trial examining the benefits of memantine in patients with moderate to severe AD who also were receiving a stable dose of the ChEI donepezil.[5] Prior to study initiation, patients had been taking donepezil for an average of 2 years (minimum of 6 months). Primary outcome assessments in this 24-week trial included the SIB and the ADCS-ADL$_{19}$; secondary outcome measures included the CIBIC+, FAST, NPI, and BGP. This trial randomly assigned 403 patients to memantine 10 mg b.i.d. ($N = 202$) or placebo ($N = 201$). Significantly more memantine-treated patients (85% vs. 75%) completed the trial ($p = .01$). At week 24, patients treated with memantine/donepezil showed statistically significant improvement ($p < .001$) in cognitive function (SIB) compared to patients treated with placebo/donepezil, notably in the areas of memory, language, and praxis. Furthermore, memantine-treated patients displayed significantly less decline ($p = .028$) in daily function (ADCS-ADL$_{19}$), and additional analyses showed the maintenance of higher-level functions such as grooming, finding belongings, and turning faucets/lights on and off.[56] A significant difference in favor of memantine/donepezil was also seen on the CIBIC+ ($p = .027$), NPI ($p = .002$), and BGP-care ($p = .001$). Taken together, these data suggest that treatment with memantine in patients stabilized on donepezil is superior to donepezil alone.

In addition, a recently completed phase 3 trial of similar design to the monotherapy study by Reisberg and colleagues[4] did not demonstrate statistical significance at trial end-point on primary outcomes (data on file, Forest Laboratories, New York, N.Y.).[57] Potential confounding factors included less than normal rates of disease progression with placebo treatment and nonnormal distribution of outcome scores. Nevertheless, numerical superiority of memantine was seen over placebo on all outcomes (data on file, Forest Laboratories, New York, N.Y.).[57] While these data support the safety and efficacy of memantine treatment in moderate to severe AD, further analyses are underway to fully understand the implications of the findings of this trial. Additional investigations with memantine in mild to moderate AD patients have provided evidence that memantine may be

Table 5. Cholinesterase Inhibitors in Moderate to Severe Alzheimer's Disease (AD)

Study	Design	Duration/ Patient Residence	N	Diagnosis/ Inclusion Criteria	Baseline Cognition	Primary Outcomes	Secondary Outcomes
Donepezil							
Feldman et al[3]	Multicenter Randomized DBPCT, PG Flex-dose	24 weeks Reside in community/ assisted living	290	Moderate to severe AD MMSE 5–17 FAST ≤ 6	MMSE scores: PBO = 11.97 DON = 11.72	CIBIC+	MMSE SIB DAD IADL+ PSMS+ NPI FRS
Tariot et al[48]	Multicenter Randomized DBPCT, PG Flex-dose	24 weeks Nursing home	208	Mild to moderately severe AD MMSE 5–26 NPI-NH item frequency score 3–4 on at least 1 domain	MMSE scores: PBO = 14.4 DON = 14.4	NPI-NH	MMSE CDR-SB PSMS+
Rivastigmine							
Doraiswamy et al[49]	Post hoc analysis of a randomized, DBPCT, PG, flex-dose range and the open-label extension	52 weeks Reside in community	159	Retrospectively defined "moderately severe" patients as defined by GDS ≥ 5 from a trial of mild-moderately severe AD (MMSE 10–26)	MMSE scores: PBO = 16.4 RIV = 16.1 RIV = 16.5	ADAS-cog	
Galantamine							
Wilkinson et al[50]	Retrospective subanalysis of a pooled dataset of 4 registration trials in mild-moderate AD	Trials ranged from 3–6 months in duration	626	Retrospectively defined "advanced moderate" patients as defined by either: ADAS-cog > 30 or MMSE ≤ 12	Patients defined by ADAS-cog score: 15.4 Patients defined by MMSE score: 11.2	ADAS-cog ADCS-ADL NPI CIBIC+ DAD	Responder analyses
Blesa et al[51]	Retrospective subanalysis of a subset of patients who participated in one of 4 registration trials of mild-moderate AD and subsequent open-label extensions	Trials ranged from 3–12 months in duration	1003, of which 237 met criteria for post hoc analysis	Retrospectively defined "advanced moderate" patients as defined by either: ADAS-cog > 30 or MMSE ≤ 14	Patients defined by ADAS-cog score: 15.9 Patients defined by MMSE score: 12.5	ADAS-cog DAD	Responder analyses

Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory, ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, CDR-SB = Clinical Dementia Rating-Sum of the Boxes, CIBIC+ = Clinician's Interview-Based Impression of Change Plus Caregiver Input, DAD = Disability Assessment in Dementia, DBPCT = double-blind placebo-controlled trial, DON = donepezil, FAST = Functional Assessment Staging, FRS = Functional Rating Scale, GDS = Global Deterioration Scale, IADL+ = Modified Instrumental Activities of Daily Living, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, NPI-NH = Neuropsychiatric Inventory-Nursing Home, PBO = placebo, PG = parallel group, PSMS+ = Modified Physical Self-Maintenance Scale, RIV = rivastigmine, SIB = Severe Impairment Battery.

efficacious across the full spectrum of AD (data on file, Forest Laboratories, New York, N.Y.).[57]

Efficacy of Cholinesterase Inhibitors in Moderate to Severe Alzheimer's Disease

Cholinesterase inhibitors were the first evidence-based treatments available for patients with AD. Although they currently are indicated for the treatment of mild to moderate AD, several lines of evidence support the hypothesis that ChEIs would be beneficial across a wider spectrum of AD, including moderate to severe AD.[58,59] The clinical trials of ChEIs conducted in moderate to severe AD patients have varied in design, duration, patient status, inclusion criteria, and outcome measures, reflecting the lack of standardized approaches to the study of this patient population.

The first trial to evaluate a currently available ChEI in more advanced AD investigated the safety and efficacy of donepezil in patients with moderate to severe AD.[3] This study was a prospective, randomized, double-blind, placebo-controlled trial in which 290 patients with moderate to severe AD received donepezil 10 mg/day (after 28 days of 5 mg/day) for a 6-month period. The majority of the patients resided in the community (≈87%), with the remainder in assisted living situations (≈13%). The CIBIC+

was selected as the primary outcome measure as there were reservations concerning the perceived clinical relevance of a small but significant change on a cognitive outcome measure at this stage of the disease. Secondary outcome measures, with the exception of the modified standardized MMSE, were selected for their utility in advanced AD in hopes of avoiding floor effects. These secondary measures included assessments of cognition with the SIB; function as measured by the DAD, the IADL+, and the PSMS+; behavioral symptoms as evaluated by using the NPI; and an additional global assessment with an instrument known as the Functional Rating Scale (FRS).[60]

Patients receiving donepezil demonstrated significant, clinically meaningful benefits as determined by the CIBIC+ compared with placebo at all visits up to week 24 ($p < .001$). All other secondary measures (including MMSE, SIB, DAD, IADL+, PSMS+, FRS, and NPI) showed significant differences between the groups in favor of donepezil at week 24 ($p < .05$). Of particular interest to the study of moderate to severe patients were the findings on the 2 cognitive measures, the SIB and the MMSE. The SIB demonstrated a significant sensitivity to change in either direction, allowing for a detection of both a decline from baseline in the placebo group and an improvement from baseline in the donepezil group. This contrasts with the MMSE results, which exhibited floor effects in the placebo group. Together, these results underscore the utility of the SIB and its sensitivity as a measure of cognition with this advanced population and demonstrate the impact of instrument selection on the evaluation of AD treatment outcomes.

Further analysis of this trial revealed a sensitivity of the modified metrics (IADL+, PSMS+, DAD) to detect a significantly slower decline associated with donepezil than placebo in both instrumental and basic ADLs.[41] Additional benefits of the delayed functional decline seen with donepezil treatment included less time spent in provision of care and lower levels of caregiver stress, thus extending the effects of donepezil in moderate to severe patients to include measurable effects on caregivers.

Tariot and colleagues[48] reported the results of a double-blind, randomized, placebo-controlled trial of donepezil in 208 nursing home patients with mild to moderately severe AD. The primary outcome measure, a modified version of the NPI adapted for nursing home settings, revealed no significant treatment effect on behavioral symptoms. The authors attributed the paucity of effect on the larger than expected placebo effect and high rate of concomitant psychotropic medication use. Perhaps most striking in this trial is the impact that wide ranges of symptom variability and disease severity have on AD trial outcomes, a reminder of the inherent difficulties involved in studying a disease with a high degree of heterogeneity. Although approximately one third of the patients had advanced AD (MMSE < 10), the study was not powered to focus specifically on this patient subgroup, warranting further study with this patient population in this setting.

Data regarding the efficacy of the other currently marketed ChEIs, rivastigmine and galantamine, are derived from post hoc analyses of pivotal clinical trials in patients with mild to moderate AD. In these analyses, data were extracted from patients who, at baseline, were at the more advanced end of the mild to moderate spectrum ("advanced-moderate" patients). While outcomes of these trials are encouraging and support the evidence for efficacy in moderate to severe AD, there are some inherent limitations to the scope of interpretation of these studies. These limitations typify the challenges of studying more advanced AD and will be discussed in detail below.

In the study reported by Wilkinson et al.,[50] data from 4 phase 3 pivotal trials[61–64] with galantamine in mild to moderate AD were pooled, and a post hoc analysis was performed on the subgroup of "advanced-moderate" patients. Once pooled, advanced-moderate patients were defined in one of 2 ways, resulting in 2 overlapping groups. Over a 6-month time period, galantamine (24 mg/day) had significant benefits over placebo on cognition (as measured by the ADAS-cog scale) in both subpopulations of advanced-moderate patients. Similar results were seen on measures of function (assessed by the ADCS-ADL) and behavior (measured by the NPI) in the subpopulation of advanced-moderate patients defined on the basis of ADAS-cog scores.

Blesa and colleagues[51] performed a similar post hoc analysis of the 4 pivotal trials with galantamine but also included data from the open-label extension trials to assess the longitudinal effects (1 year) of galantamine on advanced-moderate patients. Patients were required to fulfill one of 2 criteria for advanced-moderate AD: either a baseline ADAS-cog score greater than 30 or a baseline MMSE score below 15. Historical placebo data were obtained from similar subsets of patients in previous clinical trials with sabeluzole to model the placebo decline from 6–12 months, corresponding with the timing and duration of the open-label extension studies. Similar to the 6-month report, cognitive abilities (assessed using the ADAS-cog) of patients with advanced-moderate AD who received galantamine for 12 months were maintained at baseline levels after 12 months and were significantly better than those of the placebo group ($p < .001$). Responder analyses revealed that at 12 months, 51% of advanced-moderate patients with baseline ADAS-cog scores > 30 maintained or improved their ADAS-cog scores; similarly, 48% of the subgroup of patients with baseline MMSE scores ≤ 14 met this same criterion for response. Functional abilities, as measured by the DAD, also demonstrated significant benefits in galantamine-treated patients compared with placebo.

The long-term efficacy of 2 dosage groups of rivastigmine (1–4 or 6–12 mg/day) was assessed in a post hoc

analysis of a 26-week pivotal trial and subsequent 26-week open-label extension study.[49] The subset of moderately severe AD patients in this year-long study was chosen based upon a baseline GDS score of 5 or more. (Of note, only 3 of the 159 patients that completed the double-blind portion of the trial had a GDS score > 5). After 52 weeks, patients in both dosage groups experienced significantly smaller declines in ADAS-cog scores from baseline than the projected decline in the placebo group. Further analyses revealed benefits associated with earlier initiation of treatment.

These post hoc analyses were constrained by the criteria and outcomes originally defined in the mild to moderate AD trials. For example, considerable variation exists in defining criteria for "advanced-moderate" and "moderately severe" AD and in the outcome measures used (ADAS-cog and other metrics less specific for moderate to severe AD populations). Therefore, caution must be exercised when interpreting these data.

The length of 2 of the reports (1 year) raised the possibility that traditional efficacy measures of cognition (e.g., MMSE and ADAS-cog) may suffer from measurement effects, including floor effects resulting from eroding verbal capacity that affect the applicability of common metrics of cognition. Prior to the development of tools appropriate for more advanced AD, this lack of a valid and reliable measure represented one reason for the paucity of studies with this population.

Furthermore, longer-term trials, while useful in evaluating drug safety, often raise more questions than answers regarding efficacy, owing largely to the open-trial design, lack of randomization, and use of historical/projected placebo controls. The differences in the manner in which placebo controls were generated in the 2 yearlong analyses highlight this point; in the galantamine trial, historical placebo data from similar patients in another drug trial were used, whereas the rivastigmine analysis used placebo controls projected from the rate of decline by the placebo arm in the first 6 months of double-blind treatment.

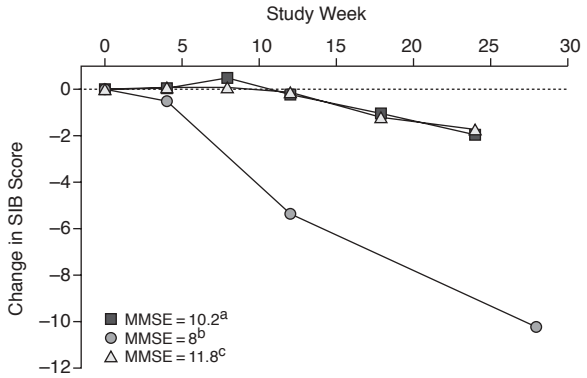
Results from such post hoc analyses need to be confirmed in prospective clinical investigations of sufficient power using inclusion criteria and outcome measures specific to the moderate to severe AD population. Nevertheless, the findings from these post hoc analyses are consistent with the positive results from the donepezil trial and further support the use of ChEIs in patients with moderate to severe AD.

LIMITATIONS OF ACROSS-TRIAL COMPARISONS

Review of the clinical trials performed in moderate to severe AD reveals a number of challenges as we move toward the future in the study of AD in severely demented individuals. The observation that patients prospectively described as moderate to severe differed in certain baseline characteristics underscores the importance of having a consensus on secondary staging tools. For example, although patients are described as "moderate to severe" in the Feldman donepezil trial (FAST ≤ 6),[3] they are quite different functionally from those in the Reisberg memantine trial (FAST ≥ 6a).[4] Furthermore, variation in baseline severity may influence the rate of progression in AD as measured by different instruments. For example, Figure 2 depicts the effect that baseline MMSE scores may have on the rates of decline in clinical trials. Despite the variability often seen with MMSE scores at different severity levels, lower mean baseline MMSE scores were associated with more obvious progression as reflected in SIB scores for the placebo group in the Reisberg trial compared with the Tariot and Feldman trials (Figure 2).

Secondly, patients with more advanced AD, such as those included in the reviewed studies, necessitate the use of specialized scales designed to detect changes as a result of treatment. The use of the ADAS-cog, for example, to track cognitive decline in more advanced patients has limitations, and the same limitations apply for other domains as well. Prior to the use of specialized scales, the tangible benefits patients experience with antidementia treatment may have been unrealized. Similarly, if outcomes are evaluated using modified scales, changes that are perhaps immeasurable in the "big picture" may have a large impact in this patient population. Clinically, relatively minor changes due to treatment may have a major impact on symptoms and function. Even small gains in day-to-day living capabilities can be clinically meaningful from the standpoint of quality of life for the patient

Figure 2. Impact of Baseline MMSE Scores on SIB Score Decline in Placebo Patients



[a]Data from Tariot et al.[5]
[b]Data from Reisberg et al.[4]
[c]Data from Feldman et al.[3] Data shown are least square mean change from baseline.
Abbreviations: MMSE = Mini-Mental State Examination, SIB = Severe Impairment Battery.

as well as the caregiver. For example, maintaining toileting skills can reduce caregiver stress and the need for supervision and can potentially reduce the need for nursing facility placement.

CONCLUSIONS

The clinical trial data reviewed above support the decision to initiate and maintain treatment in moderate to severe AD patients, with important, albeit modest, benefits observed across multiple domains. Indeed, the clinical value of treating a moderate to severe AD patient population was supported by the FDA with the October 2003 approval of memantine. Although similar conclusions for the ChEIs are currently limited by trial design heterogeneity, the data summarized above provide evidence to support their continued study in later stages of AD.

Preservation of cognitive and functional abilities as well as "suppression" of behavioral symptoms improves the quality of life for both patients and caregivers. Furthermore, functions that are preserved in advanced AD are just as important, if not more so, than those that are lost. Alzheimer's disease patients, even beyond the moderate stages of disease, usually have some abilities worth preserving, and a plan of care may be implemented that focuses on optimizing patient autonomy and quality of life. Both memantine and the ChEIs have demonstrated an ability to stabilize or slow the decline of key areas affected by AD. For the individual patient, it appears to be crucial to target behaviors, functions, and cognitive skills that the patient may still attempt independently (compare ADCS-ADL_{19} development[40]). Then, these behaviors and skills may be used to monitor treatment response.

For many years, it has been a popular opinion that patients with more advanced AD would not benefit from therapeutic interventions; however, the development and implementation of improved metrics for advanced AD over the last several years have revealed clinical evidence that meaningful benefits are attainable in moderate to severe AD. While efforts to identify preventative treatment offer hope for reducing incidence of or a potential cure for AD, no such therapies are currently available. Thus, continued efforts to improve metrics and conduct prospectively designed clinical trials across the spectrum of AD severity are warranted in order to provide additional information and to ensure that the treatment needs of this sizeable AD patient subset are not neglected.

Drug names: donepezil (Aricept), galantamine (Razadyne), memantine (Namenda), rivastigmine (Exelon), tacrine (Cognex).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, donepezil, galantamine, rivastigmine, and tacrine are not approved by the U.S. Food and Drug Administration for the treatment of severe Alzheimer's disease and memantine is not approved for the treatment of mild Alzheimer's disease.

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