



REVIEW

Effective Pharmacologic Management of Alzheimer's Disease

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ABSTRACT

In order to assist physicians in the effective pharmacologic management of this challenging population, evidence-based pharmacologic treatment algorithms for the different stages of Alzheimer's disease have been developed. Evidence-based guidelines outlining pharmacotherapeutic strategies can be systematically implemented to optimize outcomes for patients in different stages of Alzheimer's disease. The first step toward the best possible long-term management is early diagnosis of Alzheimer's disease, thereby facilitating early initiation of cholinesterase inhibitor treatment, which may stabilize/reduce the rate of symptomatic cognitive and functional decline. Cholinesterase inhibitor therapy with rivastigmine, donepezil, or galantamine is endorsed as standard first-line therapy in patients with mild-to-moderate Alzheimer's disease. The N-methyl-D-aspartate receptor-antagonist, memantine, may be used as monotherapy or in combination with a cholinesterase inhibitor for patients with moderate Alzheimer's disease, and as monotherapy for patients with severe Alzheimer's disease. During treatment, cognitive and functional status should be monitored over 6-month intervals, and pharmacologic therapy should ideally be continued until there are no meaningful social interactions and quality of life has irreversibly deteriorated. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Alzheimer's disease; Cholinesterase inhibitor; Donepezil; Galantamine; Management; Memantine; Pharmacotherapy; Rivastigmine

Over the past decade, substantial advances have been made in the pharmacologic treatment of Alzheimer's disease, and several drugs have proven to be useful for the treatment of cognitive and functional decline during the various stages of the disease. The cholinesterase inhibitors (ChEIs), rivastigmine, donepezil, and galantamine, and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, are the core treatments approved by the United States Food and Drug Administration (FDA) and are available for use in patients with Alzheimer's disease.

As the population ages, primary care physicians increasingly play a key role in diagnosing and treating patients with Alzheimer's disease.¹ A number of consensus statements and guidelines for the diagnosis and treatment of Alzheimer's

disease are now available to assist physicians in the effective management of patients with Alzheimer's disease.²⁻⁶ The most recently published guidelines are from the Alzheimer's Disease Management Council (ADMC) Clinical Consensus Panel,⁷ comprised of national leaders in neurology, psychiatry, geriatric medicine, primary care, and geriatric nursing. The aim of the current report is to provide physicians with updated, evidence-based guidelines outlining pharmacotherapeutic strategies that can be systematically implemented to optimize outcomes for patients in different stages of Alzheimer's disease.

RECOGNIZING EARLY SIGNS OF ALZHEIMER'S DISEASE

The benefits of ChEI therapy may be diminished when treatment is delayed,⁸⁻¹¹ and affording patients the opportunity to maintain the highest levels of cognitive and functional ability possible requires early diagnosis and treatment

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of Alzheimer's disease.¹ Diagnostic criteria should identify early-stage patients, and toward this end, the ADMC endorses the simplicity and easy applicability of the *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV)*¹² diagnostic criteria for Alzheimer's disease. In the absence of other conditions that are known to cause deficits in memory and cognition, DSM-IV states that Alzheimer's disease is characterized by impaired memory and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, and disturbed executive function. The cognitive abnormalities must represent a change from a previous higher level of function, be progressive, impair functioning, and not be present exclusively during a period of delirium. The gradual, progressive cognitive decline and impaired functional status that occur with Alzheimer's disease are not consistent with normal aging (Table 1).

PHARMACOLOGIC TREATMENT

Treatment Goals

In the absence of a cure for Alzheimer's disease, goals of drug therapy include temporary improvement, stabilization, or less-than-expected decline of cognitive, functional, and behavioral symptoms. Accomplishing these goals may reduce caregiver burden and delay institutionalization. It is important that physicians explain to patients and their caregivers that clinical improvements may not always be evident and emphasize that

drug therapy is intended to delay symptomatic decline. This is a worthwhile outcome considering the inevitably progressive nature of Alzheimer's disease.

Pharmacologic Approaches to Alzheimer's Disease

Disease

The cholinergic hypothesis of Alzheimer's disease concludes that the cognitive deterioration that occurs with the disease is associated in part with progressive loss of cholinergic neurons and decreasing acetylcholine (ACh) levels in the brain.¹³ ChEIs reduce cholinesterase-induced hydrolysis of ACh and potentiate cholinergic transmission in affected cerebral areas.¹⁴ Initial cholinergic research focused on inhibition of acetylcholinesterase (AChE), but recently it has been demonstrated that butyrylcholinesterase (BuChE) also plays an important role in the degradation of ACh in normal and Alzheimer's disease brains.¹⁵ Both AChE and BuChE may constitute rational targets for the treatment of Alzheimer's disease.^{15,16} Selective inhibition of AChE occurs with donepezil. Riv-

astigmine inhibits both AChE and BuChE, and galantamine selectively inhibits AChE and also modulates nicotinic ACh receptors. The clinical significance of these additional mechanisms of action has yet to be determined. It has been suggested that glutamate-mediated toxicity may play a role in neurodegeneration in Alzheimer's disease,¹⁷ and the NMDA receptor antagonist mechanism of action of memantine may mediate the therapeutic benefit observed with this agent.¹⁸

Clinical Trials

For the FDA to approve a drug for use in Alzheimer's disease, the drug must exert a beneficial effect on a performance-based cognitive instrument and a global measure of functioning or an assessment of activities of daily living in at least 2 well-conducted Alzheimer's disease trials. On the basis of the results of double-blind, randomized, placebo-controlled trials, rivastigmine, donepezil, and galantamine are approved for first-line use in patients with mild-to-moderate Alzheimer's disease, and memantine is approved for use in patients with moderate-to-severe Alzheimer's disease. Tacrine will not be considered in this review because, although approved, it is no longer marketed or widely used in the US.

Pivotal 6-month, placebo-controlled trials have shown that ChEIs have beneficial effects on the cognitive and global functioning of patients with mild-to-moderate Alzheimer's disease (Table 2).^{10,19-24} Placebo-controlled trials

CLINICAL SIGNIFICANCE

- In Alzheimer's patients, cognitive abnormalities represent a change from a previous higher level of function, are progressive, impair functioning, and are not associated with impaired alertness or delirium.
- Early diagnosis and drug treatment of Alzheimer's disease allows patients to maintain the highest levels of cognitive and functional ability possible.
- The overall benefits of cholinesterase inhibitor therapy might be diminished if treatment is delayed. Early treatment may stabilize or reduce the rate of symptomatic decline.

Table 1 Changes in Cognition, Behavior and Global Functioning that are Consistent with Normal Aging or with Alzheimer's Disease

Normal Aging	Alzheimer's Disease
Retrieval deficit type memory impairment (responds well to clues and multiple choice questions)	Amnesic type memory impairment (benefits little from clues and multiple choice questions)
Insight retained	Insight loss
No change in activities of daily living	Activities of daily living compromised
Minor delay in word finding	Anomia
Visuospatial function retained	Visuospatial function impaired (eg, clock drawing)
Social engagement retained	Apathy, withdrawal

Table 2 Clinical Benefits of Cholinesterase Inhibitors in Patients with Alzheimer's Disease

<p>Improve, or delay, the decline of cognition 21- to 26-week trials showed statistically significant benefits in ADAS-cog and MMSE^{10,19-24} Cognitive benefits sustained over 3 to 5 years^{9-11,25,26} compared with projected rates of decline expected of untreated patients with Alzheimer's disease</p> <p>Improve global function 24- to 26-week trials showed improvement in about 20% to 40% of patients^{10,19,20,22-24} 21- to 26-week trials showed stabilization/improvement in 64-70% of patients^{10,21,22}</p> <p>Preserve functional ability Reduce the decline in basic and instrumental activities of daily living over treatment periods of 6 months to at least 1 year^{10,19,22,25}</p> <p>Improve disturbed behaviors or reduce the emergence of new behavioral symptoms^{21,27-29}</p> <p>May reduce need for psychotropic medications²⁹</p> <p>Reduce caregiver burden^{30,31} Delay nursing home placement³²⁻³⁴ Pharmacoeconomic benefits demonstrated³⁴</p>

ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale (scale used in clinical trials; not suitable for use in clinical practice); MMSE = Mini-Mental State Examination (scale suitable for use in clinical practice).

Adapted with permission from Alzheimer's disease: risk stratification, patient evaluation, and outcome-effective pharmacologic therapy—year 2004 clinical update.⁷

(6-12 month duration) and open-label extension studies suggest that these effects are sustained during observation periods of 12 to 60 months.^{9-11,25,26} These trials provide evidence that patients receiving ChEI therapy can be maintained near pretreatment baseline levels for at least 1 year of therapy and then decline, but then appear to maintain higher levels of function than expected if untreated. Beneficial effects of ChEIs on activities of daily living and behavioral scales have been demonstrated in patients with mild-to-moderate Alzheimer's disease.^{10,19,21,22,25,27}

If patients are progressing or have adverse effects with one ChEI, they may benefit by changing medications. An open-label study suggests that over 50% of patients with mild-to-moderate disease experiencing lack of efficacy or tolerability problems with one agent benefit from switching to another.³⁵ Treatment benefits obtained with ChEIs, such as maintenance of cognition, preservation of function, and minimization of behavioral problems, may translate into reduced demands on caregiver time and delayed nursing home placement.³⁰⁻³³

The NMDA receptor antagonist, memantine, slowed the rate of cognitive and functional decline in patients with moderate-to-severe Alzheimer's disease in 2 placebo-controlled 6-month trials.^{36,37} An open-label extension trial reported that the efficacy and safety of memantine was maintained for an additional 24 weeks.³⁸ Although ChEIs are primarily used in patients with mild-to-moderate Alzheimer's disease and are approved only for use in this group, beneficial effects on measures of cognition, behavior, activities of daily living, and caregiver burden have been observed in studies of patients with more advanced disease.^{28,39-42} The addition of memantine to stable doses of donepezil in patients with moderate-to-severe Alzheimer's disease resulted in significantly better outcomes than donepezil plus placebo on measures of cognition, activities of daily living, global outcome, and behavior in a 6-month trial.⁴³

Adverse Events, Titration, and Dosing

The most frequently reported adverse events for ChEIs are listed in Table 3. Cholinergic adverse effects, such as mild-to-moderate nausea, vomiting, and diarrhea, are transient and occur most frequently during dose titration. Patients and caregivers should be informed of potential side effects with ChEIs and reassured that these usually resolve with continued therapy. Patients also should be advised to take rivastigmine or galantamine with food to minimize the gastrointestinal adverse events associated with these drugs. Patients receiving rivastigmine should be monitored for weight loss. Specific dosing recommendations are presented in Table 4.

The potential risk of adverse events occurring as a result of pharmacokinetic drug interactions is relatively high in elderly patients, as they are likely to receive a variety of concomitant medications. Donepezil and galantamine are both metabolized by hepatic cytochrome P450 isoenzymes; rivastigmine is primarily hydrolyzed by brain esterases.⁴⁸ Donepezil or galantamine may interact with other drugs known to affect P450 isoenzymes. Treatment with rivastigmine in patients receiving concomitant medications (22 different therapeutic classes) for common comorbidities

Table 3 Common Adverse Events Associated with Cholinesterase Inhibitors⁴⁴⁻⁴⁷

Drug	Adverse Events
Donepezil (Aricept)	Nausea, vomiting, diarrhea, anorexia, insomnia, muscle cramps, fatigue, syncope
Rivastigmine (Exelon)	Nausea, vomiting, anorexia, weight loss, dyspepsia, asthenia, dizziness, fatigue, diarrhea
Galantamine (Razadyne, Razadyne ER)	Nausea, vomiting, anorexia, weight loss, syncope, fatigue, dizziness, dyspepsia, diarrhea

Table 4 Agents Approved for Alzheimer's Disease: Dosing and Administration^{7,37,44-47}

Donepezil: (Aricept)	Initiate once daily oral therapy at 5 mg/day, at bedtime with or without food, and, after 4-6 weeks, 10 mg/day dosing (maximum) may be initiated if tolerated. The minimum therapeutic dose for donepezil is 5 mg/day.
Rivastigmine: (Exelon)	Initiate twice daily oral therapy at 3 mg/day, taken with full meals in the morning and evening, with stepwise increments to 6 mg/day, 9 mg/day, and 12 mg/day (maximum) after ≥ 4 weeks of well-tolerated therapy at each previous dose. The minimum therapeutic dose is 6 mg/day. If treatment is interrupted for more than several days, the lowest dose should be reinitiated and titration repeated.
Galantamine: (Razadyne, Razadyne ER)	For Razadyne, initiate twice daily oral therapy at 8 mg/day, taken with full meals in the morning and evening, with stepwise increments to 16 mg/day and 24 mg/day (maximum) after ≥ 4 weeks of well-tolerated therapy at each previous dose. The minimum therapeutic dose is 16 mg/day. If treatment is interrupted for >1 week, the lowest dose should be reinitiated and the titration repeated. Razadyne ER is administered once daily in the morning, preferably with food.
Memantine: (Namenda)	The recommended starting dose for memantine is 5 mg/day (once daily), with or without food. The recommended target dose is 20 mg/day. At 1-week intervals, the dose should be titrated in 5-mg increments to 10 mg/day (5 mg twice daily), 15 mg/day (separate 5-mg and 10-mg doses), and 20 mg/day (10 mg twice daily).

Adapted with permission from Alzheimer's disease: risk stratification, patient evaluation, and outcome-effective pharmacologic therapy—year 2004 clinical update.⁷

was not associated with drug-drug interactions.⁴⁹ Significant drug-drug interactions with ChEIs are rare.

No serious safety issues have been identified in association with memantine.³⁷ Confusion may be observed during the titration phase and is usually transient. The primary reasons for discontinuation of the drug are somnolence, falls, headache, and confusion.

Use of ChEIs in Early Alzheimer's Disease

Although many clinical trials suggest the utility of treatment with ChEIs in all phases of Alzheimer's disease, some review articles challenge the scientific basis for recommending them for the treatment of Alzheimer's disease.⁵⁰ A further question is whether ChEIs have a place in the treatment of patients in the early stages of dementia. Several studies suggest that ChEIs may have some efficacy in patients with mild cognitive impairment (MCI), who may then progress to develop Alzheimer's disease;^{51,52} however, other studies report negative results.⁵³ Based on pharmacoeconomic analyses, the National Institute for Clinical Excellence (NICE) is revising their recommendations on the use of drugs to treat Alzheimer's disease in the UK.⁵⁴ NICE will recommend that ChEIs be used only in patients with Alzheimer's disease of moderate severity (Mini-Mental State Examination scores between 10 and 20) and that memantine not be used in any patients except as part of clinical studies. Numerous patient advocacy groups are protesting this decision and recommend that NICE include mild Alzheimer's disease in their treatment guidelines for ChEIs, as well as including memantine as an option for patients who fail to respond to ChEIs or who subsequently develop moderate-to-severe Alzheimer's disease. Patients and caregivers greatly value the cognitive, functional, and behavioral benefits of these agents.

Concomitant Therapy with Alternative Drugs or Supplements

Many patients with Alzheimer's disease are treated with alternative drugs, biologicals, or supplements.^{55,56} Ginkgo biloba is safe and has previously shown some evidence of efficacy;⁵⁷ however, recent studies show inconsistent results or are inconclusive.⁵⁸ An agent with some supporting data suggesting efficacy is cytidinediphosphocholine.⁵⁹ Vitamin E has been efficacious in some studies⁶⁰ and not in others.⁶¹ Agents for which supportive data are limited or suggest no effect include vitamin C,⁶¹ hormone replacement therapy,^{62,63} non-steroidal anti-inflammatory drugs,^{64,65} lecithin,⁶⁶ acetyl-L-carnitine,⁶⁷ melatonin,⁶⁸ vitamin B12,⁶⁹ and vitamin B6.⁷⁰ This is an area in which further research is needed.

TREATMENT ALGORITHMS

First-Line Treatment Pathways

The ADMC Clinical Consensus Panel has developed evidence-based, expert-endorsed treatment algorithms outlining strategies for outcome-effective pharmacologic management of patients with mild-to-moderate Alzheimer's disease, patients with moderate-to-severe disease, and patients with severe disease (Figures 1-3, respectively).⁷

As also recommended by the American Academy of Neurology,⁴ the ADMC Panel supports ChEIs as standard first-line treatment in patients with mild-to-moderate Alzheimer's disease. In order to obtain the maximum benefits achievable with these agents, it is important to slowly titrate to the maximum dose tolerated by individual patients within the therapeutic dose range of the ChEI in use. If a dose within the therapeutic range of the initially prescribed ChEI cannot be reached, titration of another ChEI should be attempted.

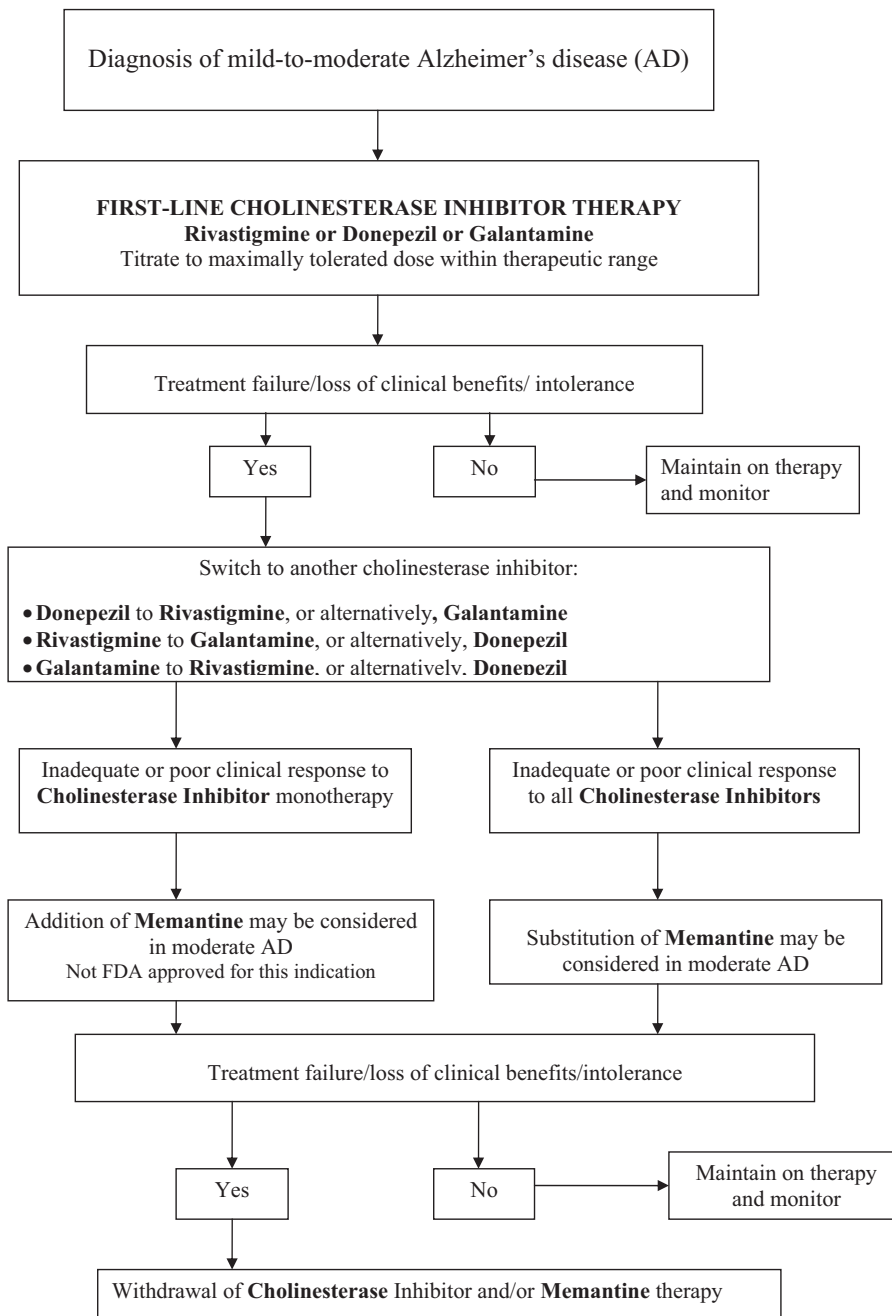


Figure 1 Alzheimer's Disease Management Council Clinical Consensus Panel-endorsed treatment algorithm for patients with mild-to-moderate Alzheimer's disease. Adapted with permission from Alzheimer's disease: risk stratification, patient evaluation, and outcome-effective pharmacologic therapy—year 2004 clinical update.⁷

Memantine may be used as monotherapy or in combination with a ChEI for patients with moderate Alzheimer's disease. It is the only agent approved for treatment in patients with severe Alzheimer's disease. In patients with mild-to-moderate Alzheimer's disease, memantine has modest effect sizes and is used mostly in combination with ChEIs in this patient population.⁷¹ Optimal quality of care during the early and middle phases of Alzheimer's disease requires the identification of triggers for implementation of ChEIs, monitoring of patient response in order to detect triggers for switching drugs/combination therapy, and man-

agement of patient and caregiver expectations. During the later stages of Alzheimer's disease, maintenance of function, control of disturbed behavior, family support, and patient comfort are the primary clinical objectives.

Monitoring Response

Tools used to evaluate the efficacy of Alzheimer's disease drugs in clinical trials are generally not suitable for use in the primary care practice setting. Assessments that can be used readily in clinical practice to monitor cognitive and functional response to pharmacological therapy include the

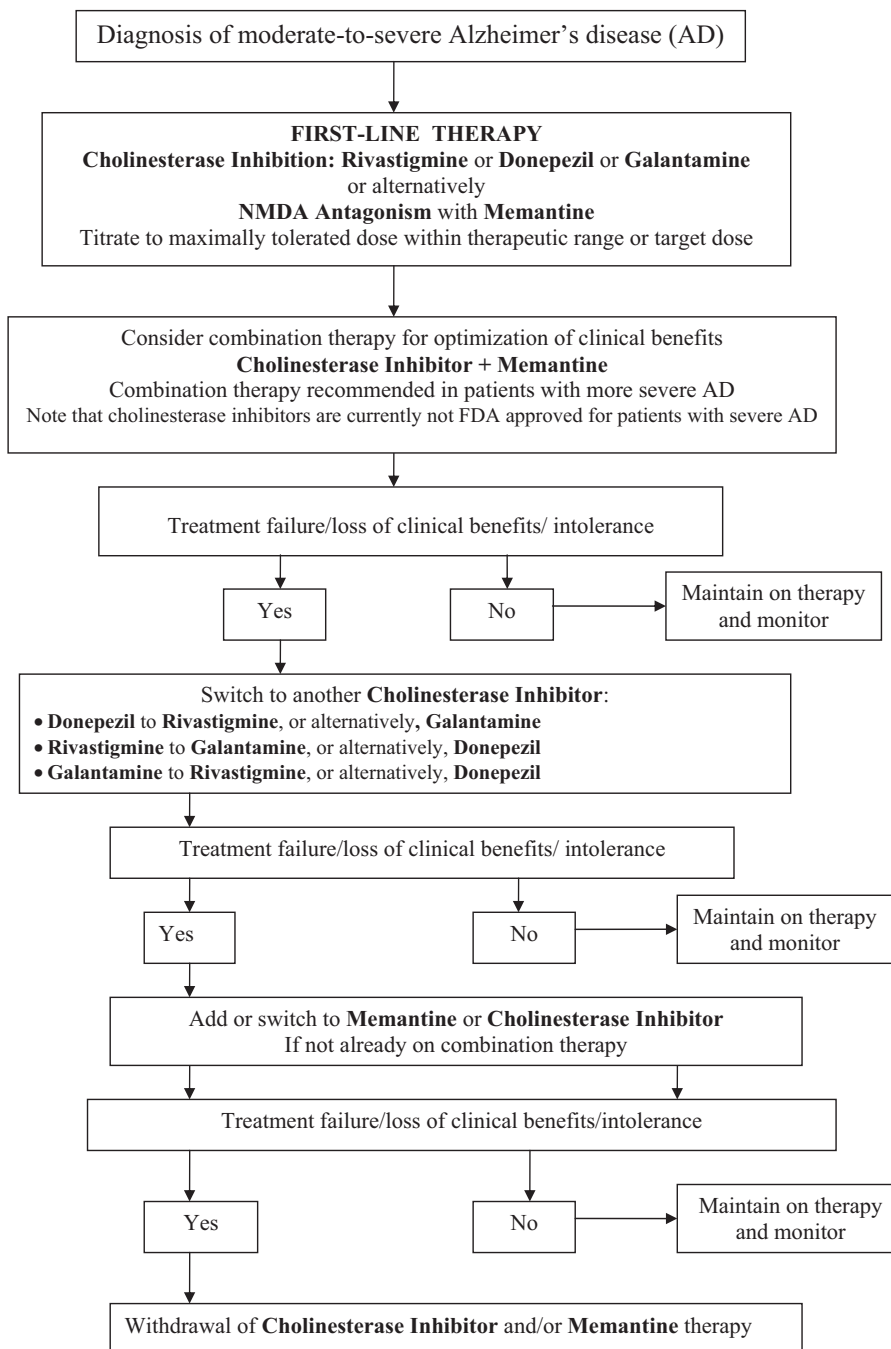


Figure 2 Alzheimer's Disease Management Council Clinical Consensus Panel-endorsed treatment algorithm for patients with moderate-to-severe Alzheimer's disease. Adapted with permission from Alzheimer's disease: risk stratification, patient evaluation, and outcome-effective pharmacologic therapy—year 2004 clinical update.⁷

Mini-Mental State Examination⁷² and the Instrumental Activities of Daily Living Scale,⁷³ respectively (Table 5). The sensitivity of these tools to drug-induced changes is low and asking the caregiver about recent changes provides valuable adjunctive information.

A minimum 6-month period, during which cognitive and functional status are monitored, should elapse before any definite decision regarding the efficacy of treatment is made. Response should not be judged on the basis of monitoring change in a

single domain. Cognition, activities of daily living, and behavior may respond to treatment with ChEIs or memantine.

Switching Cholinesterase Inhibitors

Failure to benefit from one ChEI does not mean that a patient will not have a favorable response to another. Similarly, intolerance to one ChEI does not preclude tolerance to another. Switching between ChEIs, identified by the ADMC Panel as an important concept in the management of Alzheimer's dis-

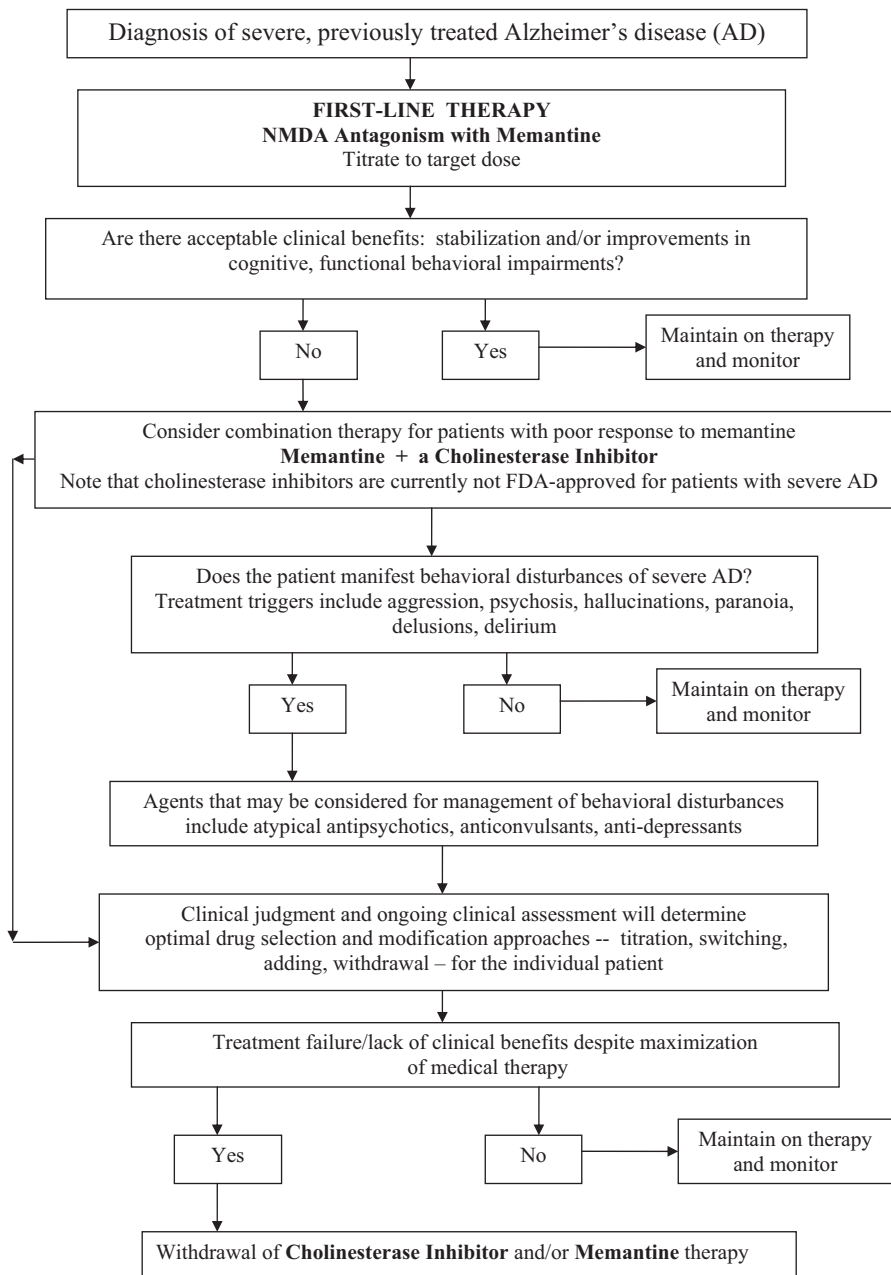


Figure 3 Alzheimer's Disease Management Council Clinical Consensus Panel-endorsed treatment algorithm for patients with severe Alzheimer's disease. Adapted with permission from Alzheimer's disease: risk stratification, patient evaluation, and outcome-effective pharmacologic therapy—year 2004 clinical update.⁷

ease, should be considered in patients who show an initial lack, or loss over time, of efficacy, or in patients who experience safety/tolerability issues with a particular drug. Before the decision to switch ChEIs is made, dose adjustment should be considered, ensuring that optimal therapy with the initial agent has been achieved.

Expert opinion suggests that switching from donepezil to rivastigmine or galantamine can be performed safely without a washout period if no safety or tolerability issues were present with the initial drug treatment. However, if the patient experienced adverse effects with the initial drug,

then a washout period (7 to 14 days) should be implemented.⁷⁸ Patients should be monitored carefully for cholinergic toxicity during any switch procedure. Rivastigmine and galantamine have shorter half-lives and a switch from one of the agents can occur after a one-day washout period.

Criteria for Therapy Changes or Withdrawal of Therapy

Add-on therapy or considering memantine monotherapy should be instigated in patients with moderate disease when no

Table 5 Scales and Evaluation Instruments Used to Monitor Response to Pharmacological Therapy in Clinical Practice

<p>Mini-Mental State Examination⁷² Measures cognition Assesses orientation, registration, recall, language, and attention Uses a 30-point scale Requires approximately 5 to 10 minutes to complete Minimal training needed to administer in outpatient setting Administered by and useful for physicians and nurses Untreated disease typically deteriorates 3 points per year⁷⁴</p>
<p>Clinician's Interview-Based Impression of Change-plus caregiver input (CIBIC-plus)⁷⁵ Global assessment of functioning Overall assessment of behavior, general psychopathology, cognition, activities of daily living Overall scale of 1 (marked improvement) to 7 (marked deterioration) Based on simple interview with patient and caregiver</p>
<p>Function Activities Questionnaire⁷⁶ Intended to quantify level of disability Scores functional capacity on a scale of 1 (normal) to 7 (severely incapacitated) Requires 5 to 10 minutes to complete Filled out by caregiver</p>
<p>Physical Self-Maintenance Scale and Instrumental Activities of Daily Living⁷³ Evaluates patient's ability to perform basic and instrumental tasks Assesses 8 areas of higher function on a scale of 1 to 5, and 6 basic tasks that are fundamental to daily function Requires about 10 minutes to complete scale Very useful in clinical practice Minimal training required to administer Comment: Seldom used. Very easy to administer but has mainly been used in research setting</p>
<p>Neuropsychiatric Inventory-Questionnaire⁷⁷ Measures disturbed behaviors Assesses frequency and severity of 12 symptoms (agitation, irritability, depression, etc) Can be completed by the interviewer in 10 to 15 minutes</p>

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stabilization or reduction in the rate of cognitive and functional decline is observed during ChEI monotherapy despite dose optimization and switching strategies. If a patient deteriorates to the point that there is dependency in all basic activities of daily living, or in the opinion of family members and the physician, meaningful social interactions and quality of life benefits are no longer possible, pharmacologic treatment should be withdrawn. Deterioration in cognition, function, or behavior during withdrawal may indicate a continuing response and may suggest the agent should be continued.

Summary

In summary, optimal quality of care during the early and middle phases of Alzheimer's disease requires the identification of triggers for implementation of ChEIs and memantine, monitoring of patient response to detect triggers for switching drugs/add-on therapy, and management of patient and caregiver expectations. During the later stages of Alzheimer's disease, medication-based control of disturbed behavior, family support, and patient comfort are the primary clinical objectives.

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