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. 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. The most recently published guidelines are from the Alzheimer’s Disease Management Council (ADMC) Clinical Consensus Panel, 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 and affording patients the opportunity to maintain the highest levels of cognitive and functional ability possible requires early diagnosis and treatment.
of Alzheimer’s disease. 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) 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

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. ChEIs reduce cholinesterase-induced hydrolysis of ACh and potentiate cholinergic transmission in affected cerebral areas. 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. Both AChE and BuChE may constitute rational targets for the treatment of Alzheimer’s disease. Selective inhibition of AChE occurs with donepezil. Rivastigmine 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, and the NMDA receptor antagonist mechanism of action of memantine may mediate the therapeutic benefit observed with this agent.

#### 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). Placebo-controlled trials...
Clinical Benefits of Cholinesterase Inhibitors in Patients with Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Benefit</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent decline of cognitive function</td>
<td>10, 19, 22, 25</td>
</tr>
<tr>
<td>Improve or delay, the decline of cognition</td>
<td>10-22</td>
</tr>
<tr>
<td>Improve global function</td>
<td>10-22</td>
</tr>
<tr>
<td>Stabilize/improve ADAS-cog and MMSE</td>
<td>10-24</td>
</tr>
<tr>
<td>Reduce the decline in basic and instrumental activities of daily living</td>
<td>10-24</td>
</tr>
<tr>
<td>Reduce caregiver burden</td>
<td>30-31</td>
</tr>
<tr>
<td>Delay nursing home placement</td>
<td>32-34</td>
</tr>
<tr>
<td>Reduce psychotropic medications</td>
<td>29</td>
</tr>
<tr>
<td>Preserve functional ability</td>
<td></td>
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<tr>
<td>Minimize behavioral problems</td>
<td></td>
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<tr>
<td>Minimize adverse events on caregivers</td>
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<td>Minimize caregiver burden</td>
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ADAS-cog = Alzheimer’s Disease Assessment Scale-cognitive sub-scale (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.

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. An open-label extension trial reported that the efficacy and safety of memantine was maintained for an additional 24 weeks. 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, behavioral, activities of daily living, and caregiver burden have been observed in studies of patients with more advanced disease. 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.

### 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. 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>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Events</th>
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<tbody>
<tr>
<td>Donepezil (Aricept)</td>
<td>Nausea, vomiting, diarrhea, anorexia, insomnia, muscle cramps, fatigue, syncope</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>Nausea, vomiting, anorexia, weight loss, dyspepsia, asthenia, dizziness, fatigue, diarrhea</td>
</tr>
<tr>
<td>Galantamine (Razadyne, Razadyne ER)</td>
<td>Nausea, vomiting, anorexia, weight loss, dyspepsia, fatigue, dizziness, diarrhea</td>
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Table 3 Common Adverse Events Associated with Cholinesterase Inhibitors

(6-12 month duration) and open-label extension studies suggest that these effects are sustained during observation periods of 12 to 60 months. 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.

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. 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.
was not associated with drug-drug interactions. Significantly drug-drug interactions with ChEIs are rare.

No serious safety issues have been identified in association with memantine. 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. 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;

<table>
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<tr>
<th><strong>Agents Approved for Alzheimer’s Disease: Dosing and Administration</strong></th>
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<tr>
<td><strong>Donepezil:</strong> (Aricept)</td>
</tr>
<tr>
<td><strong>Rivastigmine:</strong> (Exelon)</td>
</tr>
<tr>
<td><strong>Galantamine:</strong> (Razadyne, Razadyne ER)</td>
</tr>
<tr>
<td><strong>Memantine:</strong> (Namenda)</td>
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</table>

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

**Concomitant Therapy with Alternative Drugs or Supplements**

Many patients with Alzheimer’s disease are treated with alternative drugs, biologicals, or supplements. Gingko biloba is safe and has previously shown some evidence of efficacy; however, recent studies show inconsistent results or are inconclusive. An agent with some supporting data suggesting efficacy is cytidinediphosphocholine. Vitamin E has been efficacious in some studies and not in others. Agents for which supportive data are limited or suggest no effect include vitamin C, hormone replacement therapy, non-steroidal anti-inflammatory drugs, lecithin, acetyl-l-carnitine, melatonin, vitamin B12, vitamin B6. 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).

As also recommended by the American Academy of Neurology, 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.
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. 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 management 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
Mini-Mental State Examination\textsuperscript{72} and the Instrumental Activities of Daily Living Scale,\textsuperscript{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-

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**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.\textsuperscript{7}
Diagnosis of severe, previously treated Alzheimer’s disease (AD)

FIRST-LINE THERAPY
NMDA Antagonism with Memantine
Titrate to target dose

Are there acceptable clinical benefits: stabilization and/or improvements in cognitive, functional behavioral impairments?

No
Yes
Maintain on therapy and monitor

Consider combination therapy for patients with poor response to memantine
Memantine + a Cholinesterase Inhibitor
Note that cholinesterase inhibitors are currently not FDA-approved for patients with severe AD

Does the patient manifest behavioral disturbances of severe AD?
Treatment triggers include aggression, psychosis, hallucinations, paranoia, delusions, delirium

Yes
No
Maintain on therapy and monitor

Agents that may be considered for management of behavioral disturbances include atypical antipsychotics, anticonvulsants, anti-depressants

Clinical judgment and ongoing clinical assessment will determine optimal drug selection and modification approaches -- titration, switching, adding, withdrawal -- for the individual patient

Treatment failure/lack of clinical benefits despite maximization of medical therapy

Yes
No
Maintain on therapy and monitor

Withdrawal of Cholinesterase Inhibitor and/or Memantine therapy

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
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.

ACKNOWLEDGMENT

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References


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

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Mini-Mental State Examination</td>
<td>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 year.</td>
</tr>
<tr>
<td>Clinician’s Interview-Based Impression of Change-plus caregiver input (CIBIC-plus)</td>
<td>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.</td>
</tr>
<tr>
<td>Function Activities Questionnaire</td>
<td>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.</td>
</tr>
<tr>
<td>Physical Self-Maintenance Scale and Instrumental Activities of Daily Living</td>
<td>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.</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory-Questionnaire</td>
<td>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.</td>
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</tbody>
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