**Clinical Review**

**Duration of Therapy with Acetylcholinesterase Inhibitors in Patients with Mild-to-Moderate Alzheimer’s Disease as Reported in the Literature**

Razan El Melik, Amanda Dubil, Melanie W. Pound

**OBJECTIVE:** To review the literature regarding the treatment duration of acetylcholinesterase inhibitor (AChEI) therapy for mild-to-moderate Alzheimer’s disease (AD) patients.

**DATA SOURCES:** A literature search was performed using MEDLINE/PubMed, Embase, International Pharmaceutical Abstracts, and Clinical Key (all through May 31, 2013) with the search terms Alzheimer’s disease, cholinesterase inhibitors, dementia, treatment and duration, with limits to human, clinical, and observational trials, and English studies; no limits were placed on publication dates.

**STUDY SELECTION AND DATA EXTRACTION:** Based on the study selection, 40 studies were identified. The criteria for studies reviewed focused on the duration of AChEIs in patients with mild or moderate AD for a minimum of one year.

**DATA SYNTHESIS:** Based on the selection criteria, five studies were reviewed. These studies evaluated the cognitive efficacy of AChEI after “long-term” (1.5 years) treatment in the clinical trial with follow-up noted in the observational studies of a maximum of “greater than 3 years” (up to 7 years). Cognitive decline was measured by changes in Mini-Mental State Exam scores or Alzheimer’s Disease Assessment Scale scores. There were no studies identified that suggested an optimal duration of AChEI therapy for AD patients.

**CONCLUSION:** Based on the trials reviewed, the duration for AChEI use is very patient-specific; therefore, risk versus benefit of therapy needs to be evaluated regularly in AD patients. The maximum mean duration of follow-up in the clinical study analyzed here was only 1.5 years and observational studies with follow-up “greater than 3 years.” Further long-term research is needed.

**KEY WORDS:** Alzheimer’s disease, Cholinesterase inhibitors, Dementia, Duration of treatment.

**ABBREVIATIONS:** AChEI = Acetylcholinesterase inhibitor, AD = Alzheimer’s disease, ADAS-Cog = Alzheimer’s Disease Assessment Scale-Cognitive Subscale, ADCS/ADL = Alzheimer’s Disease Cooperative Study of the Activities of Daily Living, APA = American Psychiatric Association, BNHI = Bureau of National Health Insurance, CDR = Clinical Dementia Rating, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory.

**Vignette**

An 88-year-old white male presented with his daughter for medication therapy management with a geriatric clinical pharmacist. Patient has a three-year history of Alzheimer’s disease (AD) and has been taking donepezil 10 mg daily for the past three years. Patient’s daughter reports primary reason for the consultation visit was to enquire about optimal duration of AD medication in patients like her father with mild-to-moderate disease.

**Background**

Alzheimer’s disease (AD) is a type of irreversible dementia that interferes with memory, cognition, and behavior that affects one in eight Americans. Alzheimer’s dementia is associated with significant costs with annual payments for care, nearing $200 billion in 2012 in the United States alone. Although AD places a significant burden on society, there are no known treatments that reverse AD, with current pharmacologic therapies observed that only retard the progressive decline of cognitive function. Two classes of medications are used for treating the cognitive effects of AD: acetylcholinesterase inhibitors (AChEIs) (donepezil, rivastigmine, galantamine, tacrine) and the N-methyl d-aspartate antagonist, memantine. In general, AChEIs are considered first-line agents for treatment of mild-to-moderate AD; in addition, donepezil and rivastigmine are also approved for severe AD. As disease progression continues, memantine is recommended as an add-on agent for moderate-to-severe AD. Common side effects of AChEIs include transient nausea (11%-25%) and vomiting (5%-19%), diarrhea (9%-10%), and weight loss.
(3%-8%), with more severe, yet rarer side effects (1.2%-2%) including bradycardia (relative contraindication) and syncope; therefore, the benefit versus risk of therapy must be continually assessed in AD patients.3-6

The studies involving the AChEIs and AD generally determine efficacy based on several cognitive, behavior, or functional scales. These scales are described further in Table 1. AD progression is usually characterized by an annual three- to four-point decrease in Mini-Mental State Examination (MMSE) scores in patients that are untreated; treatment with AChEI has been shown to attenuate this decrease.7 A Cochrane review of 10 randomized, double-blind, placebo-controlled trials of AChEI showed a treatment effect from a 2.3- to 3.0-point improvement at six months with respect to the Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog).8 While statistically significant, in patients with mild-to-moderate dementia, a change of at least three to four points is considered clinically significant.8,9 This three- to four-point difference is also the decline in the ADAS-Cog at six months in untreated patients.8 Although the majority of AChEI trials were for a duration of 26 weeks or fewer, many patients are continued on therapy for much longer time periods.8 The guidelines from the American Psychiatric Association (APA) published in 2007 state “the decision whether to continue treatment with cholinesterase inhibitors is a highly individualized one.”3 In addition, the AD and dementia guidelines from the European Federation of Neurological Societies, as well as the American College of Physicians/American Academy of Family Physicians, respectively, both comment on the insufficient data to determine optimal treatment duration

<table>
<thead>
<tr>
<th>Scale</th>
<th>Scale Range (points)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0-30</td>
<td>• Normal: MMSE score of 27-30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mild-moderate AD: MMSE score of 10-27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe AD: MMSE score less than 10</td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td>0-70</td>
<td>• ADAS-Cog has 11 items</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Each item has a different score range</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severity of AD depends on performance of these 11 items</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Higher scores indicate worsened AD impairment</td>
</tr>
<tr>
<td>ADCS/ADL</td>
<td>0-54</td>
<td>• ADCS/ADL has 19 items</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Higher scores indicate less AD impairment</td>
</tr>
<tr>
<td>CDR</td>
<td>0-3</td>
<td>• No cognitive impairment: CDR-0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Very mild dementia: CDR-0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mild dementia: CDR-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Moderate dementia: CDR-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe dementia: CDR-3</td>
</tr>
<tr>
<td>NPI</td>
<td>0-144</td>
<td>• NPI has 12 symptom-based items (12-point-scale per item)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Higher scores indicate worsened AD impairment</td>
</tr>
</tbody>
</table>

**Table 1. Summary of Scales Commonly Utilized in Alzheimer’s Disease Studies**

**Abbreviations:** ADAS-Cog = Alzheimer’s Disease Assessment Scale-Cognitive Subscale, ADCS/ADL = Alzheimer’s Disease Cooperative Study/Activities of Daily Living, CDR = Clinical Dementia Rating, MMSE = Mini-Mental State Exam, NPI = Neuropsychiatric Inventory.

**Source:** References 17-19.
Clinical Review

of AChEIs. Several patient-specific parameters need to be considered, such as adverse effects, patient motivation, therapeutic effectiveness, and affordability. APA guidelines recommend discontinuing AChEIs in patients who have rapid disease progression despite therapy with AChEIs, therefore being labeled a “medication nonresponder.” Because AChEIs slow, but do not reverse, cognitive decline, the question arises as to when these agents should be discontinued and at what point does the patient no longer receive benefit from this class of medications.

Literature Review
A literature search was performed using MEDLINE/ PubMed, Embase, International Pharmaceutical Abstracts, and Clinical Key (all through May 31, 2013) with the search terms dementia, Alzheimer’s disease, cholinesterase inhibitors, treatment, and duration, with limits to human, clinical, and observational trials written in English, and no limits were placed on publication dates. Each author performed an independent search. This search yielded 40 returns. The criteria for studies reviewed focus on the effective duration of AChEIs treatment in patients with mild or moderate Alzheimer’s dementia. Mild-to-moderate Alzheimer’s dementia was defined based on validated assessment tools used in the inclusion criteria for each study. A total of 10 articles met the general criteria, but only 1 clinical trial evaluated AChEIs’ duration in AD patients exclusively, and 4 studies were considered observational. Based on these criteria, a total of 35 articles were excluded, and 5 articles are included for discussion below (Figure 1 provides details of the search criteria). Of these 5 trials, study duration ranged from 1.0 to 1.5 years, with a maximum follow-up to 7 years (Table 2). None of the studies identified suggested an optimal duration for AChEI therapy.

Clinical Trials
Lyketsos et al. conducted an extension study that was a follow-up to a double-blind, placebo-controlled trial evaluating galantamine immediate-release 24 mg/day (12 mg twice daily, maximum recommended dose) for an extended duration of therapy in terms of safety and efficacy in the treatment of mild-to-moderate AD (MMSE 10-22 and ADAS Cog/11 ≥ 18). Patients first participated...
### Table 2. Summary of Alzheimer’s Disease Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Study Groups</th>
<th>Outcome</th>
<th>Duration</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyketsos et al.</td>
<td>Clinical</td>
<td>Galantamine Placebo</td>
<td>Change in ADAS-Cog score from baseline</td>
<td>18.5 months</td>
<td>Continuous galantamine ADAS-Cog change from baseline was 2.28, $P = 0.002$ Subgroup analysis demonstrated cognitive function maintained $x$ 14 months with galantamine</td>
</tr>
<tr>
<td>Doody et al.</td>
<td>Observational</td>
<td>Treated Donepezil Tacrine Other Untreated</td>
<td>Annualized MMSE score change</td>
<td>12 months-14.3 months</td>
<td>Annualized MMSE score change: Treated (-2.5) versus untreated (-3.7); $P = 0.05$ Donepezil (-1.5) versus untreated (-3.7); $P = 0.007$ Tacrine (-2.8) versus untreated (-3.7); $P = 0.33$</td>
</tr>
<tr>
<td>Kavanaugh et al.</td>
<td>Observational</td>
<td>Galantamine Untreated</td>
<td>MMSE score change per year</td>
<td>Up to 7 years</td>
<td>MMSE score change (no $P$ values): Patients who continued AChEI (-2.4 per year) Patients who discontinued AChEI (-4.5 per year) Patients who switched to different AChEI (-2.6 per year)</td>
</tr>
<tr>
<td>Sun et al.</td>
<td>Observational</td>
<td>AChEI Donepezil Rivastigmine Galantamine</td>
<td>Treatment duration*</td>
<td>Mean – 14 months</td>
<td>Percent taking AChEI at: &lt; 1 year: 56% 1-3 years: 34% &gt; 3 years: 10%</td>
</tr>
<tr>
<td>Lopez et al.</td>
<td>Observational</td>
<td>AChEI Untreated</td>
<td>Classification of “slow progressor” at 1 year**</td>
<td>1 year</td>
<td>Slow progressors: AChEI (60%) versus untreated (39%); $P = 0.001$</td>
</tr>
</tbody>
</table>

*Therapy discontinued when MMSE score declined by more than 2 points in 6 months.

**Slow progressor defined as ≤ 2 point decline in MMSE at 1 year.

**Abbreviations:** AChEI = Acetylcholinesterase inhibitor, ADAS-Cog = Alzheimer’s Disease Assessment Scale-Cognitive Subscale, MMSE = Mini-Mental State Examination.
in an earlier five-month randomized controlled study of galantamine. Of the patients \( n = 799 \) who completed the original trial, 723 (90%) were enrolled to participate in a galantamine withdrawal study (six weeks’ duration), with 687 (95%) completing the study. Of these patients, 681 were enrolled in the final study in addition to 18 patients who completed the original five-month study, but did not participate in the six-week withdrawal phase. A total of 699 patients were treated for 12 months beyond the initial 6.5 months. Thus, total treatment was 18.5 months (5 months double-blind, followed by 6 weeks withdrawal, followed by 12 months open-label) for the combined study duration.\(^7\) The patients were analyzed in one of three groups according to the treatment they received during each treatment phase (treatment phases: initial double-blind 5-month phase/6-week withdrawal phase/12-month open-label extension phase, respectively): 1) placebo/placebo/galantamine, 2) galantamine/galantamine/galantamine, 3) galantamine/placebo/galantamine.\(^12\)

The primary efficacy endpoint was change in the ADAS-Cog score from baseline to the end of study (18.5 months). Additional outcomes included total scores on the Alzheimer’s Disease Cooperative Study of the Activities of Daily Living (ADCS/ADL) and the Neuropsychiatric Inventory (NPI). Safety was also evaluated through monitoring of adverse events.\(^12\)

The mean age at baseline was 77 years of age, with white (93%), and female (66%) patients representing the majority. At baseline, the mean ADAS-Cog score was 29.1 overall, with the mean MMSE, NPI, and ADCS/ADL scores of 18, 10.7, and 53.9, respectively. Of the 699 who began the open-label extension phase study, only 468 (67%) completed the study. The primary reasons for treatment discontinuation were adverse effects (agitation, nausea, and depression) and withdrawal of consent (13.7% and 7.2%, respectively). The results demonstrated that the group with galantamine treatment throughout the study had a mean ADAS-Cog score change of 2.28 from baseline after 18.5 months of follow-up, indicating cognitive deterioration \( P = 0.0002 \). The initial placebo/placebo/galantamine showed a mean change from baseline in the ADAS-Cog score of 3.39 (no \( P \)-values reported). However, the between-group comparison of galantamine/galantamine/galantamine versus placebo/placebo/galantamine change in ADAS-Cog scores did not show a statistical difference \( P = 0.268 \). The nonstatistical finding could be a result of an inadequate sample size (power was not stated in the trial) or simply a true lack of effect of the AChEI. Subgroup analysis demonstrated that cognitive function was maintained up to 14 months among patients who had continuous galantamine therapy (18.5 months), although cognitive deterioration did continue after that time period (mean ADAS-Cog score change from baseline 2.28). Most common side effects reported with galantamine treatment were agitation (20%), nausea (17%), and depression (13.4%).\(^12\)

This study suggested that the group of AD patients treated with galantamine throughout the study remained stable (change in ADAS-Cog score improved initially and then declined to baseline) for up to 14 months. However, all groups showed worsening cognition beyond this time period. Another limitation is the duration of the placebo group was not consistent throughout the study period. By the last portion of the study, all participants were receiving galantamine, so no comparison of treatment to placebo could be determined. This study provided limited information about long-term effects of AD. Benefits of galantamine treatment have been previously verified, but long-term effectiveness and benefit beyond 14 months are still questionable.

**Observational Studies**

Doody et al. conducted a retrospective cohort study comparing rates of cognitive decline between probable AD patients treated with a long duration (defined as three months or more) of AChEIs with patients who remained untreated.\(^13\) The primary endpoint was not clearly stated, although change in MMSE score at one year was reported as an “outcome.” There were a total of 423 patients; 205 (48%) AChEI patients (tacrine \( n = 128 \), donepezil \( n = 53 \), other \( n = 24 \)), and 218 (51.5%) untreated patients were included in the study. The mean age was 70 years, with most patients (98%) living in the community. There were more untreated patients residing in
a noncommunity dwelling compared with the donepezil or tacrine groups (8% vs. 0%, or 3%, respectively). The baseline mean MMSE score was 17 in the untreated and tacrine groups and 19 in the donepezil group.¹³

The length of time (i.e., duration of follow-up) between MMSE scores significantly differed between the groups with 365 days of follow-up with the treated group compared with 436 days for the untreated group ($P < 0.001$). As for the change in MMSE score outcome, there was a significant difference noted in the yearly MMSE score change from donepezil compared with the untreated group, with noted mean changes of -1.5 and -3.7, respectively ($P = 0.007$). When the yearly MMSE change for all AChEIs (mean score -2.5) was compared with the untreated MMSE mean, borderline significance was noted ($P = 0.05$). There was no difference noted between tacrine (yearly MMSE change mean -2.8) and the untreated group ($P = 0.33$).¹³

This study concluded that donepezil is efficacious for at least the first year of therapy. The small sample size is a limitation of the study, especially when evaluating the individual AChEIs (donepezil, n = 53 and tacrine, n = 128); a type 2 statistical error may have contributed to the nonsignificant difference noted. One limitation to this study is that most of the patients were taking tacrine as the AChEI, which is widely unused in current practice; thus extrapolating the results of this study may be limited. Since this article focused on the MMSE score differences, a longer duration of follow-up would be beneficial to determine the average annual rate of decline. In addition, as the disease severity worsens, the rate of MMSE change may also contribute to the effectiveness, or lack thereof, of the medication. Another major limitation to this study is the difference in the duration of follow-up between the treated (365 days) and the untreated (436 days) groups. This 71-day difference could have resulted in a worsened MMSE score change in the untreated group. Further studies beyond one year are needed to fully assess efficacy in this patient population.¹³

Kavanaugh et al. retrospectively reviewed the medical charts of mild-to-moderate (MMSE scores 9-24) AD patients who had previously participated in three clinical trials with galantamine.$^{14}$ This study evaluated the observed change in MMSE scores for these patients with up to seven years of AChEI therapy. Of the 1,728 patients in the original studies, only 258 were analyzed for this study. Patients were analyzed based on their time of exposure to galantamine: none (n = 11), 0-< 6 months (n = 53), 6-12 months (n = 21), > 1-2 years (n = 30), > 2-3 years (n = 37), and > 3 years (n = 106). Of these patients, the mean baseline MMSE scores ranged from 16.8 (> 1-2 year group) to 20.2 (no-treatment group). The mean duration of follow-up for all patients was not stated. For the patients who received AChEI treatment, the average MMSE decline per year was 2.4 points; however, among patients who discontinued AChEI treatment, the average MMSE decline per year was 4.5 points. Those who switched to a different AChEI had an average MMSE decline per year of 2.6 points.$^{14}$

Sun et al. evaluated the duration of AChEI among patients in Taiwan with mild-to-moderate (MMSE scores 10-26 and Clinical Dementia Rating 1 or 2) AD.$^{15}$ In Taiwan, treatment with AChEI (donepezil, rivastigmine, or galantamine) for AD is covered by the Bureau of National Health Insurance (BNHI). However, therapy is discontinued if the MMSE score declines by more than 2 points in six months or if the CDR shows worsening of disease in six months by a change in 1 grade. Data were gathered for this trial using the BNHI database, and a total of 9,877 patients were assessed. The majority of patients were taking donepezil (61.3%), followed by rivastigmine (36.9%) and galantamine (1.75%), and the average age was 75 years. Approximately 56%, 34%, and 10% utilized AChEI therapy for less than one year, one to three years, and more than three years, respectively. Overall, the mean AChEI treatment duration was 14 months.$^{15}$

Lopez et al. evaluated community-dwelling patients (baseline mean MMSE scores 17.8-19.5) who were already being studied by the University of Pittsburgh Alzheimer’s Disease Research Center.$^{16}$ Of these 270 patients, 135 were prescribed AChEI therapy and were matched with 135 patients who were not receiving this therapy. Matching was based on age, symptom duration prior to therapy initiation, level of education, and MMSE score at baseline.
Overall, 34% of the patients included were female and the mean age was 72 years. At 12 months of follow-up, those patients classified as “slow-progressors” (defined as ≤ 2 point decline in MMSE at 1 year), were more likely to have utilized AChEI therapy compared with those who did not ($P = 0.001$). At 2 years of follow-up, 16% and 1% of the untreated and treated patients, respectively, were admitted to a long-term care facility ($P = 0.001$), while at 3 years, 50% and 11% of untreated and treated patients, respectively, were admitted ($P < 0.001$).\textsuperscript{16}

Overall, these studies are limited by their observational design and retrospective nature.\textsuperscript{14-16} Despite attempts to control for confounding, this type of study design often does not always account for differences at baseline or with other disease states and drug-class effects, especially those that were unknown at the time of initiation of the studies. Thus, it is impossible to determine direct cause and effect from these studies, and at best an association between AChEI therapy and benefit with duration of treatment can be inferred.

**Conclusion**

No clinical evidence has been published suggesting the optimal duration of AChEI therapy in patients with AD. The maximum duration of therapy evaluated in these trials is an average of 1.5 years for clinical data and more than 3 years for the observational data. Certainly, in any progressive disease state, the patient reaches a point in the disease where certain medications would be considered inappropriate. For mild-to-moderate AD patients, the question of duration of treatment with AChEIs still remains unanswered. According to the current available literature, it appears that further long-term, well-designed trials with inferential statistics are needed to determine whether AChEI therapy continues to have beneficial effects over longer periods of time. Unfortunately, these types of trials would be expensive and time-consuming and require a large number of patients. At this time, the optimal duration of AChEI therapy in patients with AD remains unclear, and risks and benefits of therapy must be assessed for each patient.

Razan El Melik, PharmD, is assistant professor of pharmacy practice, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia. Amanda Dubil, PharmD, is pharmacist II-internal medicine, New Hanover Regional Medical Center, Wilmington, North Carolina. Melanie W. Pound, PharmD, BCPS, is associate professor of pharmacy practice, Campbell University College of Pharmacy & Health Sciences, Buies Creek, North Carolina, and is affiliated with New Hanover Regional Medical Center, Wilmington, North Carolina.

For correspondence: Melanie W. Pound, PharmD, BCPS, Campbell University, PO Box 1090, Buies Creek, NC 27506; Phone: 910-343-4500; Fax: 910-815-5186; E-mail: melanie.pound@nhrmc.org.

Acknowledgments: A special thanks to Brad Elliott, PharmD, BCPS, BCOP, for his technical corrections and edits.

Disclosure: No funding was received for the development of this manuscript. None of the authors have potential conflicts of interests.

© 2014 American Society of Consultant Pharmacists, Inc. All rights reserved.

Doi:10.4140/TCP.n.2014.400.
Therapy with AChEI Inhibitors in Patients with Alzheimer’s Disease

References