Abstract
Despite growing recognition that Alzheimer’s disease (AD) represents a global public health and social care crisis, diagnosis is frequently slow and many patients still receive no treatment at all. Of those who do receive treatment, many remain on lower than recommended doses. The Alzheimer’s disease International Global Charter promotes awareness and understanding of AD, stressing the importance of optimal treatment. However, the definition of “optimal treatment” is unclear. Since cholinesterase inhibitors became available nearly 20 years ago, clinicians have developed a variety of protocols on the basis of clinical experiences. This review considers what is optimal for several aspects of cholinesterase inhibitor therapy, taking into account initiation strategies, dosages, modes of drug delivery (e.g., oral vs. transdermal), and treatment durations. Regardless of management approach, individuals with AD, their families, and caregivers have a right to a timely diagnosis and access to best available treatment.

Keywords: Alzheimer’s disease; Cholinesterase inhibitors; Treatment

1. Introduction
Thanks in part to advances in medical technology, people throughout the world are living longer. This means that a higher proportion of individuals are reaching the age of increased risk for Alzheimer’s disease (AD), which is being increasingly recognized as a global public health and social care challenge. The reach of this progressive, debilitating condition is projected to expand, placing increasing demand on families, caregivers, and healthcare providers. In 2006, an estimated 26.6 million people suffered from AD, and this number is expected to quadruple by 2050 to in excess of 100 million living with the disease [1].

Despite rising incidence rates and forecasts reported for AD, diagnosis is frequently delayed, many patients still receive no treatment at all and, of those who do receive it, many are on inadequate doses of medication [2,3]. In 2008, Alzheimer’s Disease International launched a Global Alzheimer’s Disease Charter to promote awareness and better understanding of AD; to provide people with AD, their families, and caregivers with additional support; and to stress the importance of early diagnosis and optimal treatment. Yet the precise definition of “optimal” treatment remains controversial.

Cholinesterase inhibitors are widely used for the treatment of AD [4]. Since their first availability over a decade ago, experienced physicians have developed their own treatment protocols on the basis of clinical experience and preferences. For example, the recommended titration phase for rivastigmine capsules, once in 2 weeks, was extended to 4 weeks on the basis of their wider experience [5]. Although instructions for use are provided in product labels for cholinesterase inhibitors, in practice, individual clinicians vary in their approach.

The objective of this article was to consider what constitutes “optimal” AD treatment with cholinesterase inhibitors. This topic formed the basis for discussion during a debate-style symposium at the Alzheimer’s Association International Conference on Alzheimer’s Disease in Vienna, Austria, July 2009. The proceedings of this symposium are reported in this study for physicians’ information in light of their own AD management strategies.
2. Early diagnosis

Practice guidelines encourage timely detection and diagnosis of dementia, and subsequently treatment initiation [4,6]. Many clinicians treat in the early stages of dementia (i.e., mild to moderate), thinking that it has the greatest potential to improve long-term outcomes overall, by preserving functional levels while cognitive symptoms and impairment of activities of daily living are still mild [7].

Despite general recognition of the merits of early diagnosis and intervention, this strategy can be a challenge. An estimated 50% of primary care patients with dementia who are aged >65 years are not diagnosed by their primary care physicians [8]. Among the patients who are diagnosed, most have reached moderate stages [9]. Numerous factors contribute to the delayed diagnosis of AD. A general lack of understanding and awareness of AD is largely responsible. Cognitive decline is still overlooked by many as part of the normal aging process. Furthermore, patients, families, and physicians seem reluctant to recognize and to diagnose dementia—a serious, progressive condition without a cure, which continues to be associated with stigma [2,10]. Despite such challenges, appropriate care can improve quality of life for patients with AD and for their families.

3. Optimal treatment initiation

The direct consequence of no or late AD diagnosis is that treatment initiation is delayed or is never started. Treatment rates—that is, percentages of patients with AD treated with any pharmacotherapy—vary considerably across countries. However, in 2004 in Europe, they were estimated to average around 30% [2]. Thus, a nihilistic approach (the belief that “nothing can help”) to AD treatment appears to exist, although evidence suggests that this attitude may be on the decline [11].

No cure for AD has yet been discovered, although available treatment options offer symptomatic improvements and offer meaningful benefits for patients and their families. Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) have been widely approved for the treatment of mild to moderate AD [4]. As a class, cholinesterase inhibitors have proven efficacy in 3 major domains: activities of daily living, behavior, and cognitive function [12–14]. However, the optimum time to initiate therapy has been debated.

3.1. Treatment initiation: Later

Postmortem data suggest that neocortical cholinergic deficits are minimal in mild AD stages, and that they do not progress until relatively late in the course of the disease [15]. If cholinergic deficits are minimal in the early stages, one might question the urgency for treatment early on. It follows that patients with more advanced AD, that is, with greater cholinergic deficits, would derive greater benefit from cholinesterase inhibitor therapy. There is evidence to support this position: patients with more severe AD tend to exhibit a greater treatment response to cholinesterase inhibitor therapy than those with mild disease [16,17].

3.2. Treatment initiation: Sooner

Pathologic changes in the brains of persons at risk for developing AD can develop as early as 20 to 30 years before clinical dementia symptoms [18]. Diffuse plaques in nondegenerated middle-aged individuals have been associated with an accelerated age-related cortical cholinergic deficit. Lowered glucose metabolism detected by positron emission tomography has been noted in brain regions (frontal, parietal, and temporal) receiving cholinergic projections, also indicative of preclinical AD neurodegenerative changes [19].

By initiating treatment early, that is, during mild stages of AD, higher functional levels may be maintained (see schematic representation; Fig. 1), preserving quality of life and independence. The benefit of early cholinergic treatment is suggested across separate open-label extension studies of donepezil [20], galantamine [21], and rivastigmine (oral and transdermal) [22,23] in patients with AD. In each of these trials, patients who received placebo initially in the core double-blind phase (i.e., a delayed treatment start) did not “catch up” with those who received treatment for the entire study period, suggesting potential benefits of starting therapy early in the disease course.

4. Optimal dosing

Cholinesterase inhibitors exhibit dose–response relationships: a 10-mg dose of donepezil tablets is more effective than a 5-mg dose [24], and similarly, 6 to 12 mg/d rivastigmine given orally has been found to be more efficacious than 1 to 4 mg/d [25]. Higher doses of cholinesterase inhibitors appear to be optimal, assuming they can be attained while maintaining tolerability.

Many patients receive suboptimal doses, as they are unable to reach target therapeutic doses because of associated side effects [26]. Furthermore, the majority of people with AD or their caregivers discontinue treatment after only 4 to 5 months because of perceived lack of effectiveness, side effects, forgetfulness, or the burden of complex drug regimens [27]. Yet reaching and maintaining high doses of cholinesterase inhibitors for as long as possible are recommended, as they appear to confer long-term benefits [28,29].

In the absence of a clear consensus on how and when high-dose cholinesterase inhibition should be targeted for optimal efficacy, it seems that physicians adopt 1 of 2 common strategies: (1) to escalate the dose as quickly as possible and maintain patients on highest recommended target doses; or (2) to stay on lower doses until the patient deteriorates to a point where there are more significant symptoms, effectively keeping something “in reserve” for later. The pros and cons of these 2 approaches were a focus of a debate at the International Conference of Alzheimer’s Disease 2009 in Vienna, Austria.
in reserve until later, when patients exhibit deterioration for as long as deemed adequate, and keeping higher doses on low doses of cholinesterase inhibitors from diagnosis tered on an as-needed basis. This involves keeping patients patient, such that cholinesterase inhibitor therapy is adminis-
edly across individuals[30]. These differences likely reflect that the rate of decline during the course of AD varies mark-
4.1. High-dose cholinesterase inhibition: Later

The first approach favored personalized AD care for every patient, such that cholinesterase inhibitor therapy is adminis-
tered on an as-needed basis. This involves keeping patients on low doses of cholinesterase inhibitors from diagnosis for as long as deemed adequate, and keeping higher doses in reserve until later, when patients exhibit deterioration (Fig. 2A).

Clinical trial outcomes tend to focus on what would be considered an average patient, but it is widely acknowledged that the rate of decline during the course of AD varies mark-
edly across individuals [30]. These differences likely reflect a combination of genetic, pathologic, and environmental fac-
tors. Every patient is unique and this should be reflected in the way they are treated for optimal outcomes. The treatment strategy described in Fig. 2A attempts to provide individual-
ized therapy, adding more efficacy to the patient’s regimen as it becomes necessary or useful.

Patients with more advanced AD (i.e., a greater cholinergic deficit) could conceivably better tolerate high-dose treatment than patients with mild AD. This was found to be the case in a retrospective analysis of data from 3 large random-
ized controlled trials of rivastigmine. Withdrawals as a result of adverse events were greater in the mild cohort receiving rivastigmine than the moderate or the moderately severe cohorts (3.63, 2.95, and 2.49%, respectively) [31]. In terms of cholinergic deficit, tolerability, and treatment response potential, it may be worthwhile keeping high-dose cholinesterase inhibition in reserve.

All cholinesterase inhibitors show symptomatic effects that delay decline [29]. By providing low doses of cholesterylase inhibitors at diagnosis for as long as they are effective, the dose can be increased when the patient shows meaningful decline (Fig. 3). Where further higher doses are available (e.g., oral rivastigmine or galantamine), this “rescue” approach could offer patients and their families further hope and support, even at later stages of AD (Fig. 3).

In clinical practice, many patients do not reach high doses of cholinesterase inhibitors. In a study including more than 5000 patients with mild to moderate AD, 65% of them still received low cholinesterase inhibitor doses (defined as ≤6 mg/d rivastigmine, 5 mg/d donepezil, or ≤16 mg/d galant-
amine) 9 months after treatment initiation [3]. Gastrointesti-
nal side effects (nausea, vomiting, and diarrhea) are the primary reasons that many patients fail to reach high thera-
peutic doses of oral cholinesterase inhibitors [32,33]. These adverse events, however, occur most frequently during titration phases [34] and tend to be transient. They can usually be managed effectively by halting dose titration or decreasing the cholinesterase inhibitor dose. A slow dose escalation strategy is thought to help minimize associated gastrointestinal side effects through 2 mechanisms: slower increases in brain acetylcholine levels [35] and desensitiza-
tion of dopamine receptors in the area postrema of the hypo-
thalamus [36]. A conservative treatment approach, providing a higher dose only when there is meaningful decline, thus might be expected to help minimize associated adverse side effects and potentially improve compliance.

4.2. High-dose cholinesterase inhibition: Sooner

Another option is to use a more vigorous treatment strategy. Abilities and attributes lost during the course of AD cannot be recovered so there is an urgency to treat as quickly and potently as possible. This involves escalating cholinesterase inhibitor doses as fast as can be tolerated—an ambitious treatment approach, in which patients achieve and are main-
tained on highest recommended doses from early on in the disease (i.e., during mild stages following diagnosis). A summary of this treatment strategy is provided in Fig. 2B.

AD currently has no “cure”; the condition of all patients eventually declines, with or without treatment. In mild stages, patients with AD are still relatively independent and can en-
gage with their families. Prolonging the mild stage of the disease for as long as possible and delaying deterioration to more advanced stages might have the greatest positive effect on the quality of life of patients and their families.

Long-term studies indicate that patients started on treat-
ment at an earlier dementia stage do better than those started later [22]. Moreover, in a 5-year, open-label, follow-up study, continued cholinesterase inhibitor treatment was associated with patients being above the projected declines for untreated moderate or severe AD patients [37]. It is possible that the cholinesterase inhibitor dose administered within the first few months of diagnosis could dictate patients’ outcomes in subsequent years (Fig. 4). Offering high-dose efficacy at the earliest opportunity may ensure that patients are main-
tained above the threshold for severe dementia for as long as possible. Reassurance can be provided that everything is being done to preserve their existing quality of life for as long as possible.

Gastrointestinal side-effects associated with oral cholinesterase inhibitor treatment are a common barrier to achieving high doses. Strategies that prolong the time it takes to reach maximal plasma concentrations with rivastigmine capsules (e.g., administration with food, or a tid vs. bid dosing regimen) appear to reduce the incidence of associated gastrointestinal
side-effects [38,39]. Lowering maximal plasma concentrations and reducing fluctuations in plasma levels allow patients to better tolerate rivastigmine, so that they have an increased likelihood of reaching optimal therapeutic doses. This was the pharmacokinetic rationale for developing a patch for the transdermal delivery of rivastigmine. By providing continuous delivery of rivastigmine through the skin into the bloodstream, large fluctuations in plasma levels seen with oral administration can be avoided, allowing plasma levels to be maintained within the desired “therapeutic window” [40].

An open-label, ascending-dose pharmacokinetic study conducted in 51 patients with AD randomized to receive either rivastigmine patch (4.6–17.4 mg/24 h) or capsules (3–12 mg/d) provided proof of concept. As predicted, rivastigmine patch consistently demonstrated significantly lower peak plasma concentrations, which were attained more slowly compared with capsule administration [41]. Yet overall, taking into account adjustments for baseline demographic differences (gender and bodyweight), the target 9.5 mg/24 h rivastigmine patch provided comparable drug exposure (area under the curve) to the highest recommended dose of capsules (12 mg/d) [42]. The efficacy, safety, and tolerability of the rivastigmine patch were investigated in an international 24-week, double-blind, double-dummy, placebo-, and active-controlled study in 1195 patients with mild to moderate AD (the Investigation of transDermal Exelon in ALzheimer’s disease trial) [23,43]. Consistent with comparable drug exposure, the 9.5 mg/24 h rivastigmine patch demonstrated...
similar efficacy to the highest recommended capsule dose (12 mg/d). Additionally, the 9.5 mg/24 h patch was associated with 3-times fewer reports of nausea and vomiting than 12 mg/d capsules [43].

Almost all patients (95.9%) who received the 9.5 mg/24 h patch reached their target dose as compared with 64.4% of those who received the comparable oral dose (12 mg/d) [26]. By eliminating gastrointestinal side-effects as a confounding factor, a transdermal patch may offer easier access to high-dose efficacy.

4.3. Factors for consideration

Considering therapy on an individual patient basis is an accepted standard of good clinical practice. For example, inter-patient variability in body weight might be expected to affect the pharmacokinetic profile of cholinesterase inhibitors, and subsequently associated gastrointestinal tolerability [32,42]. Adverse events in the rivastigmine patch trial have been re-analyzed, stratified by baseline body weight [44]. This showed that although low-weight patients (<50 kg) tended to report more nausea than high-weight patients (>80 kg), those remaining in the study at week 24 were all able to reach the target dose 9.5 mg/24 h patch. By contrast, 58.6% of the low-weight patients achieved the target capsule dose (12 mg/d). Therefore, while additional care may be required to manage events such as nausea in low-weight patients, there is no reason why this patient subpopulation should not also access the clinical benefits associated with high-dose efficacy [44].

A 2-year comparison of oral rivastigmine and donepezil was conducted in almost 1000 patients with moderate to moderately severe AD [45]. Rivastigmine and donepezil displayed similar efficacy in terms of cognition and behavior, whereas a statistically significant advantage was seen for rivastigmine in terms of activities of daily living and global functioning. These findings were achieved despite the mean end-of-study rivastigmine capsule dose being 9.4 mg/d [45], which is lower than the recommended target dose of 12 mg/d. It is interesting to consider how this comparison may have looked had all patients been receiving the target 9.5 mg/24 h patch (which has comparable pharmacokinetic exposure to 12 mg/d capsules). With time, transdermal delivery may enable access to even higher than currently recommended rivastigmine doses (9.5 mg/24 h [10 cm2] patch or 12 mg/d capsules). A clinical trial evaluating the efficacy of a 13.3 mg/24 h (15 cm2) rivastigmine patch is currently ongoing (ClinicalTrials.gov Identifier: NCT00506415).

5. Optimal treatment duration

Treatment initiation is only part of the challenge in AD management. After a cholinesterase inhibitor therapy is prescribed, treatment compliance is notoriously low. AD is a chronic disease, yet the average treatment duration is estimated to be a mere 4 to 5 months [27]. It is difficult to ensure that patients remain on any medication long-term, but the AD population (including caregivers) is particularly susceptible to poor compliance. They have a tendency to be plagued by risk factors such as advanced age, co-morbidities, high-medication burden, and memory deficits. Consequently, non-compliance because of forgetfulness and difficulties coping with multiple medication regimens is common [46]. Considering the established importance of compliance to AD therapies over the long-term [28,29,37], a clear need exists to improve compliance in this setting. The once-daily rivastigmine patch offers a user-friendly alternative approach to treatment that could help address some of the common problems [37]. In a sub-study of the Investigation of transDermal Exelon in Alzheimer’s disease trial, caregivers of patients with AD expressed a preference for patches over capsules. Their feedback suggested that a patch helps to relieve some of the pressure associated with medication management [47]. Approaches that optimize tolerability would be expected to minimize treatment discontinuations because of gastrointestinal issues. Perceived lack of effectiveness is another barrier to achieving long-term compliance. Ongoing emotional support and encouragement for patients and caregivers at each follow-up visit is crucial to combat negative attitudes toward treatment. However, equally important is to communicate realistic expectations (stabilization vs.
improvement) so they understand the potential benefits of long-term treatment in view of the limitations of cholinesterase inhibitor therapy [29].

Although rivastigmine, donepezil, and galantamine are all cholinesterase inhibitors, their pharmacologic profiles vary. Rivastigmine inhibits 2 distinct cholinesterase enzymes (acetylcholinesterase [AChE] and butyrylcholinesterase [BuChE]), whereas donepezil and galantamine are more selective AChE inhibitors [48]. Logically one would expect that all cholinesterase inhibitors should reduce the activities of their target enzymes. Numerous studies, however, suggested that over the long-term, AChE-selective cholinesterase inhibitors might actually upregulate AChE activity [49–53]. A recent 13-week, open-label comparative study has provided the first comparison of cholinesterase inhibitor effects on activities and protein levels of target enzymes in the CSF of patients with AD [54]. Overall, only rivastigmine effectively inhibited AChE and BuChE activities, with no change in protein levels. Donepezil and galantamine had no effect on BuChE; however, both increased AChE activity and protein levels (donepezil to a greater extent than galantamine) [54].

Current evidence highlights the importance of continued vigilant follow-up to monitor the status of patients on long-term therapy, taking into account the differential underlying effects of approved cholinesterase inhibitors.

6. Discussion

Regardless of differences in opinion that exist in the practical implementation of cholinesterase inhibitor therapy, there is apparent consensus on some aspects of AD management. First, symptoms of dementia are not “normal” at any age, so timely detection and diagnosis is essential. Second, in a setting where treatments are available, a nihilistic approach to care is not acceptable. Individuals with AD, their families, and caregivers have a right to the best available treatment at diagnosis. It follows that the earlier the treatment is initiated (in mild stages), the better the long-term outlook. Although no recommendations exist for the formal screening of mild to moderate AD, there are several simple assessment tools available [55,56], which can help to proactively identify individuals who might benefit from further diagnostic testing. The ultimate goal is to take control of AD in its mildest stages, so that patients’ abilities can be preserved as close to normal for as long as possible.

Whether the clinician chooses to target high-dose cholinesterase inhibition in an AD patient immediately or later, there are advantages associated with either strategy (Table 1). Regardless of specific strategy, patients should be encouraged to reach what is considered to be an optimal therapeutic dose at a given stage, and to stay on treatment long term. Ongoing emotional support and monitoring are important aspects of regular follow-up visits.

The development of the transdermal patch for AD may warrant reconsideration of physicians’ existing treatment strategies. Rivastigmine patch provides smooth, continuous drug delivery versus oral administration, with comparable exposure. Therefore, gastrointestinal side-effects may no longer limit access to high-dose efficacy [26]. Practical advantages associated with patch delivery may also help to improve long-term treatment compliance in AD [46].

Acknowledgments

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Dr. Small reports having served as a consultant and/or having received lecture fees from Abbott, Brainstorming Co., Dakim, Eisai, Forest, Myriad Genetics, Medivation, Novartis, Ortho-McNeil, Pfizer, Radica, Siemens, and Wyeth. Dr. Bullock reports of having received stock options from Dakim and of having served as a consultant, received lecture fees for local, national, and international meetings, and

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### Table 1

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<tr>
<th>Arguments favoring common “optimal treatment” strategies</th>
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<tr>
<td><strong>A. Treatment initiation</strong></td>
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<tr>
<td><strong>Now</strong></td>
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<tr>
<td>- Preclinical AD neurodegenerative changes can emerge as early as 20–30 years prior to formal diagnosis</td>
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<td>- Ensure best possible long-term clinical outcomes—in open-label studies, patients who receive placebo initially never “catch up” with those who receive treatment throughout</td>
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<td><strong>Later</strong></td>
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<td>- Cholinergic deficits only become significant relatively late in the disease course</td>
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<td>- Greatest treatment benefits seen in patients with more advanced AD (i.e., with greater cholinergic deficits)</td>
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<td><strong>B. High-dose cholinesterase inhibition</strong></td>
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<tr>
<td><strong>Forward-loading efficacy, high-dose efficacy early</strong></td>
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<tr>
<td>- Provides high-dose efficacy when it can have greatest effect</td>
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<td>- Maintains function at the highest level, for as long as possible</td>
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<td>- Transdermal delivery permits access to high-dose efficacy without sacrificing tolerability</td>
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<td>- Reassurance for patients and their families that everything is being done to preserve existing quality of life for as long as possible</td>
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<td><strong>Rescue approach, holding high-dose efficacy “in reserve”</strong></td>
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<tr>
<td>- Offers personalized therapy for every individual patient</td>
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<td>- Minimizes cholinergic adverse events (associated with oral therapies) with very slow dose titration</td>
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<td>- Allows patients to reach high doses eventually, and may increase compliance</td>
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<td>- Healthcare professionals able to offer practical support later in the disease course with “rescue” treatment</td>
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performed commercial research for Novartis, as well as other pharmaceutical companies including Pfizer, Eisai, J&J, Lundbeck, Sanofi, Lilly, and Servier.

References


