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# Effectiveness of antidementia drugs in delaying Alzheimer's disease progression

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**Abstract**

**Background:** Randomized controlled trials (RCTs) provide safety and efficacy data for regulatory approval of antidementia drugs, but offer limited data regarding real-world effectiveness. Long-term observational controlled studies (LTOCs) extend our understanding by providing longitudinal data across multiple stages of Alzheimer's disease (AD).

**Methods:** Comparisons of strengths, limitations, evidence level, and results for monotherapy (cholinesterase inhibitors) and combination therapy (cholinesterase inhibitors + memantine) in RCTs versus LTOCs were made.

**Results:** Similar to RCTs, LTOCs have shown that both monotherapy and combination therapy are associated with slower cognitive and functional decline. Combination therapy is associated with better cognitive outcomes and greater delays in time to nursing home admission versus monotherapy or no treatment. Persistent antidementia drug treatment is associated with slower decline in cognition, daily function, and global severity, even in patients with advanced disease.

**Conclusions:** LTOCs provide complementary evidence regarding effectiveness of antidementia therapy over many years, a time course relevant to AD management. These findings also provide compelling arguments in favor of using LTOCs to estimate effectiveness, risk–benefit, and costs of AD treatments.



*Keywords:* Alzheimer's disease; Clinical trials; Therapeutics

## 1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia and disability in people aged ≥65 years. AD is increasing in prevalence and impact around the world. There are currently 35.6 million people living with dementia worldwide, and this number is estimated to increase to 65.7 million by 2030. Aging is the number one risk factor for the development of AD, and ever-increasing longevity is the main reason for the rising prevalence rates globally. Eventually, dementia prevalence in low- and middle-income countries will rise above that of high-income countries [1]. After the onset of symptoms, the typical patient lives with the disease for many years; therefore, informed treatment and effective management of the disorder over many years are imperative.

Treatment options for AD include two classes of medication, both of which modulate neurotransmitters. The cholinesterase inhibitors (ChEIs; donepezil, rivastigmine, galantamine) augment levels of acetylcholine in the neuronal synaptic cleft by decreasing hydrolysis of acetylcholine through blocking the enzyme acetylcholinesterase. Memantine, a low-to-moderate affinity uncompetitive *N*-methyl-D-aspartate receptor antagonist, modulates glutamate activity at the postsynaptic membrane and reduces calcium influx into the cell. The tonic activation of the *N*-methyl-D-aspartate receptor in AD is thought to disrupt learning and memory and, hypothetically to, destroy neurons through excitotoxicity.

In the United States, donepezil is approved for treating patients with mild-to-moderate and severe AD, and rivastigmine and galantamine are approved for treating those with

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mild-to-moderate disease. In the United States, galantamine and donepezil are available as generic medications. Recently, high-dose (23 mg/d) versus standard-dose donepezil (10 mg/d) reportedly provided additional cognitive benefit to patients with moderate-to-severe disease [2]. Rivastigmine transdermal once-daily patch (9.5 mg/d) is an alternative to oral treatments; it has been reported to have equivalent efficacy to oral rivastigmine twice-daily capsules (9 mg/d average), but with superior tolerability [3].

Despite intensive research efforts leading to greater understanding of the pathophysiology and risk factors for AD, the last drug approved in the United States was in 2003. Current guidelines for AD treatment do not address long-term disease management, as there have been no long-duration, double-blind, placebo-controlled trials to guide evidence-based practice.

This article is based on an International Congress on Alzheimer's Disease Roundtable with the aim of stimulating thought and discussion in the field to look beyond randomized controlled trials (RCTs) for evaluating the merits of antidementia medications in affecting clinical progression of AD.

## 2. Rationale for long-term observational controlled studies in AD treatment

Efficacy trials (explanatory trials) determine whether an intervention produces the expected result under ideal circumstances. Effectiveness trials (pragmatic trials) measure the degree of beneficial effect in "real-world" clinical settings [4]. Efficacy trials of pharmaceuticals are required for approval purposes, and they are designed to prove an effect and ensure safety in the shortest time possible; however, they may lack external validity [5]. In contrast, observational studies or long-term observational controlled studies (LTOCs) can evaluate drug effectiveness under conditions of usual practice. LTOCs enroll "real" patients with significant comorbidities, taking concurrent medications, and with imperfect treatment adherence [6]; such studies can provide much needed information concerning long-term treatment effects of antidementia drugs. In the United States and Europe, it is increasingly difficult to recruit for studies where placebo is administered as a treatment arm. Further, trials lasting greater than 6 to 12 months may be impractical, due to excessive attrition of subjects, even if the trial is not placebo controlled. Only a few industry-sponsored or publicly sponsored efficacy trials lasting >1 year have been conducted, and most of these involve an open-label extension (OLE) of a shorter-duration trial.

## 3. Undervaluation of current antidementia therapies

Antidementia drug treatment seems to be underrated for many different reasons. There is ongoing controversy about the cost of the medications owing to uncertainty regarding their clinical value [7]. Clinicians, patients, and family members may also hold unrealistic treatment expectations, such as the belief that treatment should produce an obvious improvement [8]. The approved drugs have been proven to induce small improvements over baseline in cognition and function for some patients, but, more commonly, they stabilize abilities or reduce decline. Patients followed in short-term clinical trials seem to remain stable for a year or more, and may subsequently decline at a rate that is slower than untreated patients [9]. However, families or clinicians often discontinue treatment because the patient does not improve, without consideration of the potential impact of the treatment on preservation of abilities or overall rate of decline [10]. Age-based stereotypes may lead to underuse of therapy based on conclusions that an older person's malady is chronic and less susceptible to intervention [11]. Many people still believe that senility or dementia is normal or an expected consequence of aging [12]. Finally, there may be disincentives for third-party payers to cover the cost of treatment, and in many countries, where financial resources are very limited or where there is pressure to reduce the cost of health care expenditures, treatment of dementia may not be considered a health care priority [13].

## 4. Efficacy of ChEIs in RCTs, OLEs, and meta-analyses

In industry-sponsored RCTs of 6-month [14–19] to 1-year duration [20,21], ChEI monotherapy improved cognition, maintained patient function, and reduced the risk of functional decline compared with placebo in mild-to-moderate AD patients. ChEI monotherapy was also associated with reduced behavioral symptoms in mild-to-moderate and moderate-to-severe AD patients [22,23] and slowed decline of activities of daily living in moderate-to-severe AD patients over 6 months [22]. More recent studies have demonstrated efficacy of donepezil in very early AD [24] and in severe AD patients residing in nursing homes and in the community [25,26].

One publicly sponsored RCT conducted in the United Kingdom (AD 2000 trial) [27] failed to show a significant difference between donepezil- and placebo-treated community patients in rates of institutionalism after 1 and 3 years of therapy; however, donepezil treatment was associated with improved function at all time points after 12 weeks (average difference Bristol Activities of Daily Living Scale: 1.0 points; 95% confidence interval [CI]: 0.5 to 1.6; $P = .0004$) and with significant cognitive benefits that were maintained for up to 2 years.

OLEs of the pivotal trials suggest that cognitive benefits continue for patients who continue to take the ChEIs: donepezil for up to 4.9 years [28,29], rivastigmine for up to 5 years [30], and galantamine for up to 3 years [31]. However, attrition and the absence of a control group in these studies may limit confidence in estimates of the duration of benefits from these studies.

Finally, meta-analyses of short-term trials suggest that ChEIs improve or decrease the rate of cognitive decline in