Drugs for Alzheimer's Disease: Are They Effective?

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INTRODUCTION

Alzheimer's disease (AD), a devastating neurodegenerative disorder, is the leading cause of dementia in the U.S. and in other developed countries. Patients experience progressive, disabling cognitive impairment and eventually require constant care and supervision. Approximately 96% of AD patients are elderly, but the absolute number of patients younger than 65 years of age has grown with the arrival of the "baby-boomer" generation (those born between 1946 and 1964) to the cusp of old age.[1]

AD is the sixth leading cause of death for all ages and the fifth leading cause of death for those 65 years of age and older in the U.S.[1,2] This disorder affects approximately 5% of people 65 to 74 years of age and almost 50% of people older than 85 years of age, at an annual cost of approximately $148 billion in the U.S. alone.[1] The problem will become much greater as baby-boomers age. An estimated 5.3 million persons in the U.S. have AD. This figure is projected to grow to 13.2 million by 2050.[1]

Given the impact of AD, there is an urgent need for effective therapies. Currently, five drugs have been approved by the FDA for use in AD, including four cholinesterase inhibitors and one N-methyl-D-aspartate (NMDA) receptor antagonist (see Drug Therapy). The five medications are widely utilized, and several respected organizations have endorsed their use.[3] As of this writing, no alternatives to these medications are available. These five drugs are supportive or palliative rather than curative or disease-modifying therapies, and they do not appear to alter the final outcome of the disease.[3] The total dollars expended on these treatments in the U.S. alone exceeds $1 billion annually, and these therapies continue to be heavily promoted by their respective manufacturers.[4] Nevertheless, the ongoing debate over their effectiveness continues, especially in view of the costs incurred.[5]

In this article, we review the evidence supporting the use of these agents and explore the controversies involved. This discussion is timely in view of the national debate on health care reform, because it involves the need to balance costs and benefits on an enormous scale. Similar debates may be expected in many other areas of medicine.

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OVERVIEW

AD is a neurodegenerative process marked by neuronal loss and the deposition of abnormal proteins in the form of amyloid plaques and neurofibrillary tangles. Beta-amyloid deposition culminates in the production of extracellular amyloid plaques in the cerebral cortex and elsewhere in the central nervous system (CNS). Hyperphosphorylation of the intracellular tau protein results in neurofibrillary tangles, which are believed to contribute to neuronal dysfunction and death. The onset of neurodegeneration is believed to precede clinical symptoms by many years.

The underlying cause of these events remains incompletely understood, but the dominant "amyloid hypothesis" in AD research holds that amyloid deposition is the principal etiologic factor.[6] Although much effort has been expended on developing therapies based on these pathological findings, no drugs are yet available that target amyloid or tau and clinical trials of anti-amyloid drugs have been disappointing.[7]

In addition to these findings, AD patients experience declines in various neurotransmitter systems. These changes include a reduction in acetylcholine production, leading to a decreased availability of acetylcholine at the neuronal synapse.[8,9] This reduction is believed to contribute to memory decline. The glutamate system is also affected by the disease process, leading to a relative excess of activity, which is believed to disrupt cellular communication and contribute to neuronal loss.[10] Currently available pharmacological treatments target these two systems.

Clinically, AD is marked by an insidious onset of cognitive loss, which gradually and inexorably progresses from mild, short-term memory impairment to global decline, typically over a course of years. In addition to memory loss, AD typically involves many other symptoms. These include losses in speech and language, activities of daily living (ADL), and the ability to recognize familiar people, places, and objects. Most patients also experience significant changes in personality, sleep, and behavior, all of which may become the major focus of treatment.

The diagnosis of AD is made on the basis on these clinical findings, largely through the detection of progressive cognitive loss. Currently available technology does not permit a definitive diagnosis based solely on laboratory findings or neuroimaging.[6]

DRUG THERAPY

Five therapies have been approved for AD. Four of these medications are classified together as cholinesterase inhibitors

(CIs); these are approved for dementia of the Alzheimer's type in the mild-to-moderate stage. These include tacrine (Cognex, First Horizon), donepezil (Aricept, Eisai/Pfizer), rivastigmine (Exelon, Novartis), and galantamine (Razadyne, formerly Reminyl, Ortho-McNeil). Donepezil also carries an approval for severe or late-stage disease. Tacrine is excluded from this discussion, because it is associated with significant liver toxicity and is very rarely prescribed today. The fifth AD drug, memantine (Namenda, Forest), opposes glutamate activity by blocking NMDA receptors.[3]

Cholinesterase Inhibitors

Although there are some differences in putative mechanisms, all of the CIs are believed to function in the same basic manner—to increase the bioavailability of acetylcholine at the synapse. The acetylcholine molecule is released into the synaptic space by the presynaptic neuron and binds to receptors in the postsynaptic neuron, promoting an action potential. The acetylcholine molecule is subject to enzymatic degradation in the synaptic space by one of several cholinesterases. CIs bind to and inactivate these cholinesterases, reducing the normal enzymatic degradation of the acetylcholine molecule into its component parts (acetyl CoA and choline).

CIs also increase acetylcholine activity in the peripheral nervous system. This contributes to side effects, including common ones such as nausea, gastrointestinal (GI) upset, and diarrhea. Less common side effects include muscular weakness, syncope, and significant weight loss on occasion. Despite the adverse effects of the CIs in general, most patients seem to tolerate CIs.[8–10]

Peripheral cholinergic side effects are most notable for rivastigmine; a gradual dose escalation is required for this drug, and only a limited number of patients can tolerate the full dose of 6 mg twice daily. The 24-hour transdermal Exelon patch delivery system is associated with a greatly reduced level of peripheral cholinergic side effects.

A 2004 review of the safety and tolerability of donepezil in AD showed a low incidence of GI and cardiovascular adverse events (including bradycardia), comparable to the rates for placebo.[11] In various studies, donepezil was found to be safe in patients with hepatic impairment as well as in those with moderately to severely impaired renal function. No evidence of significant drug–drug interactions was noted. The incidence of weight loss was similar between donepezil and placebo-treated patients. Some sleep disorders were reported with donepezil, but these can be mitigated by switching to morning dosing or lengthening the time period before increasing the dose from 5 to 10 mg/day.[11]

The clinical effects of CIs may include modest improvement, stabilization, or a slowed rate of clinical decline. Some patients show no clinical effect at all, but a small subset sometimes show dramatic improvement. The greatest effect seems to be appreciated in the first few months of therapy, although some benefits may be sustained for several years.[8,9]

NMDA Antagonists

The sole NMDA medication available for AD, memantine, opposes the effects of the excitatory neurotransmitter glutamate. The role of glutamate in AD is not well understood, but excessive glutamate activity in mid-stage to late-stage disease is believed to interfere with neurotransmission and to contribute to neurodegeneration.[10,12,13] Although memantine differs mechanistically from the CIs, the magnitude and type of clinical effects seem to be similar. The similarity in measured effects may be partly a result of artifact, because the same instruments are used to measure outcomes for both classes, introducing possible measurement bias.

Selection of Therapy

The neurotransmitter effects of the CIs and the NMDA antagonists do not change the underlying brain degeneration characteristic of AD. The drugs do not seem to affect life span or outcomes of the disease.[3] Therefore, they are best viewed as palliative rather than curative or disease-modifying treatments.[3,8,10]

The decision to initiate AD therapy is typically made at the time of diagnosis. The choice of CI is made on the basis of clinical judgment alone. There are no firm criteria suggesting which drug might work best in a particular patient. Most commonly, a CI is started first, whereas memantine is often added when the disease has progressed to a moderate stage.[8,10]

Results of at least one study suggested a synergistic effect between donepezil and memantine for moderate-to-severe AD.[14] Although there is little scientific support for memantine in early AD, some practitioners prescribe both a CI and memantine as soon as the diagnosis is made, citing the relative lack of side effects with memantine. The decision to terminate therapy with a CI or memantine is based on the progress of each individual case, with little scientific evidence to guide the appropriate timing. Many factors influence this decision, including advancing disease, failure to improve or slow the pace of functional decline, family wishes, and costs.

COST

The costs of AD drugs are considerable. Average costs per patient for one of these drugs in the U.S. is about $5.00 per day or about $1,800 per year.[4] Several formulations are available at a similar price. Donepezil (Aricept) is sold as a tablet and as an orally dissolving tablet. Rivastigmine (Exelon) is available as a capsule, a liquid, and a skin patch. Galantamine (Razadyne) comes in standard and extended-release forms as well as a liquid.[8,10]

A generic version of galantamine is available in the U.S., and the FDA recently approved a generic version of donepezil.

MEASUREMENT IN CLINICAL TRIALS

Psychometric instruments, such as rating scales and questionnaires, are used to measure symptomatic effects of the disease and to monitor response to treatments. Several instruments are used in clinical trials to measure the effects of drugs for AD:

- The Alzheimer Disease Assessment Scale–Cognitive (ADAS–Cog) is a battery of tests commonly used in pharmaceutical research, but the test is not widely used in clinical practice.[15]
- The Mini-Mental State Examination (MMSE) is a cognitive test used in both research and clinical practice. It is

a 30-point measure of orientation, short-term memory, attention, naming, speech, visual–spatial skills, and reading and writing.[16]

- The Clinician's Interview-Based Impression of Change (CIBIC) is administered in the form of a semi-structured interview. It identifies four major categories for evaluation: general; mental and cognitive states; behavior; and activities of daily living.[17]
- The Neuropsychiatric Inventory (NPI) is a clinician-rating scale that measures psychiatric symptoms.[18]

The use of such psychometric instruments is necessary, given the lack of any suitable biomarker and given the symptomatic nature of the treatments. However, the choice and design of these instruments do not focus on all important aspects of the disease (e.g., activities of daily living) and, as such, can lead to an underestimate or an overestimate of treatment effects. The fact that AD is a progressive disease, worsening during the course of a clinical trial, also complicates the interpretation of study results. Some critics believe that the use of common statistical techniques, including the last observation carried forward, might exaggerate the benefits of study drugs for AD. Observations carried forward to the endpoint analysis actually reflect an earlier, less severe stage of disease and have the potential to inflate outcome measures.[19]

At least 10 placebo-controlled clinical trials of the CIs for mild-to-moderate AD have been conducted.[8] Although placebo-controlled, head-to-head trials are lacking, the results of these published studies are remarkably consistent, showing a similar magnitude and pattern of effect for all the CIs. These results can be briefly summarized.

The CIs show a pattern of modest initial gain (approximately 1.5 points of gain above baseline on the MMSE), with average MMSE scores falling below the baseline at about six to nine months and continuing to decline. Even after scores fell below the baseline, a modest (but statistically significant) advantage remains for the CIs over placebo for the life of the study, typically a year or less. The initial gain of 1.5 points on the MMSE can be reasonably characterized as quite modest.

An analysis of individual responses paints a somewhat different picture, at least in terms of immediate response—only about half of subjects show evidence of this benefit. A small proportion of subjects show a more dramatic positive response to CIs.[8] Four of the five studies addressing nursing-home placement showed a delay.[20]

Results of clinical trials for CIs in controlling agitation have been inconsistent. One large-scale, placebo-controlled trial of donepezil for agitation in AD patients showed no advantage over placebo.[21] Interpreting the results of trials for rivastigmine and galantamine is complicated by higher dropout rates, reflecting a smaller percentage of patients tolerating the higher doses believed necessary to achieve full therapeutic effects.[8]

Memantine has shown benefits of similar magnitude in clinical trials of mid to late-stage AD, but its effects could not be differentiated from those of placebo in early-stage disease.[10] In one study of combination therapy, a synergistic effect was noted for patients already stabilized with donepezil when memantine was added.[14]

CONTROVERSIES IN DRUG TREATMENT

In 2005, the British National Health Service (NHS), acting on guidance from the British National Institute for Clinical Excellence (NICE), proposed to end the availability of CIs and memantine for most of England's patients with AD. While the agency acknowledged the clinical trial data demonstrating efficacy on psychometric measures, it expressed skepticism that the magnitude of the benefit was worth the cost.

Criticizing the quality and methodology of some studies, the NICE analysis cast doubt on the ability of AD drugs to meaningfully improve quality of life or delay nursing-home placement. This position, reversing a 2001 NHS endorsement of the drugs, caused a firestorm of controversy from the public, patient groups, and the pharmaceutical industry. As a result, its implementation was delayed. In 2006, the NHS announced that it would cover the CIs but only for moderate-to-severe AD.

Access to memantine remains limited in England. These restrictions continue to provoke controversy and have contributed to criticism of the methodology used by NICE to determine cost effectiveness. For example, NICE supports approval of a new drug only if it costs less than 30,000 £ (about $50,000) for each year of good health that it provides.[22] An analysis by the Centers for Medicine in the Public Interest groups in the U.S. have set a figure closer to $175,000, which causes the AD drugs to appear more economically justifiable.[23] In fact, any such valuation, no matter how carefully thought out, involves making subjective value judgments.

Subsequently, many observers have continued the debate, essentially along the same lines.[24] Some have criticized the pharmaceutical industry, which they believe tends to exaggerate the value of the drugs; others lay blame on journal editors for allowing subtle biases in favor of the drugs in papers describing industry-supported trials.[25]

Various medical groups, including the American Psychiatric Association and the American Academy of Neurology, have published treatment guidelines that support providing a trial of these medications to patients with AD.[26,27] The American College of Physicians and the American Academy of Family Physicians have jointly published a practice guideline emphasizing an individualized approach to AD pharmacotherapy for each patient instead of making a blanket endorsement.[27]

EFFICACY VERSUS EFFECTIVENESS

A discussion of the differences between the concepts of efficacy and effectiveness may shed light on the controversies surrounding the use of drugs for AD. Efficacy is essentially a statistical concept; it is measured in placebo-controlled trials by demonstrating a statistically significant superiority of an active treatment over placebo and it uses a predetermined set of validated measures. A finding of statistical significance means that the result is likely to represent a true observation, as opposed to a coincidence. All current AD drugs have met this standard on multiple trials and therefore may be described as being efficacious. However, the concept of efficacy does not embody any value judgment. In the real world of clinical treatments, such values judgments are necessary. A finding of statistical significance does not necessarily imply that the magnitude of the effect, however real, is sufficient to justify the expense or risks involved.

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The concept of effectiveness does embody such value judgments, with the attendant element of subjectivity. Setting the value of a year of life or good health and determining who makes these choices cannot be decided only by statistics.

Questions remain: In treating a devastating and incurable disease such as AD, should we offer expensive but limited therapies? Should we set limits based on cost? While science provides the information needed to help answer these questions, the value judgments involved require a societal debate.

CONCLUSION

Alzheimer's disease is an incurable neurodegenerative disorder that robs its victims of memory, self-care, and quality of life, resulting in major physical, emotional, and economic burdens for caregivers. These burdens must be considered on both societal and personal levels, because AD exacts an enormous financial drain on the medical system. Much of this cost consists of drugs that have some efficacy but limited effectiveness for most patients. Lacking any better alternatives, many clinicians, caregivers, and patients have elected to commit their resources in this way. Most of the cost is borne by third-party payers, who have an interest not only in efficacy but also in cost effectiveness, multiplied by the millions of sufferers for whom they provide medications.

Some critics, especially those concerned with conserving scarce resources, have claimed that these medications are not cost effective enough to justify the expense. Patients and their advocates, looking at the same data but with a different perspective, often come to the opposite conclusion. Other critics have focused on limitations in the methodology of clinical trials and on subtle bias in the way the data are presented, especially in trials sponsored by drug companies, and have concluded that benefits are inflated.

In the American medical system, physicians have a primary responsibility to their patients as individuals. Until better treatments become available, physicians will have to grapple with these dilemmas for each patient and family. Physicians are advised to discuss the pros and cons of therapy, including the possible lack of substantial benefit, and to allow patients and their families to make their own value judgments as to whether to proceed with pharmacotherapy. Because values differ widely in society, it is no surprise that value judgments about these medications also differ. The devastating effects of AD, the fact that it is incurable, the lack of therapeutic alternatives, the relative absence of adverse drug effects, and the fact that some benefits do occur may be persuasive to many physicians, patients, and their families.

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