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Cholinesterase Inhibitors in the Treatment of Dementia

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ÖZET

Demans modern dünyanın en önemli medikal, ekonomik, ve sosyal sorunlarından biridir. Tıp bilimi tarihte ilk defa pekçok insanın ileri yaşlarına kadar yaşamasına imkan tanımakta ve dolayısıyla bu insanların demansa karşı duyarlılaşmalarına yol açmaktadır. Demans krizi şu ana kadar Kuzey Amerika, batı Avrupa ve Japonya'yı etkiledi, ancak uzun yaşam beklentisi yirmibirinci yüzyılın ilk yarısında gelişmekte olan ülkelere doğru önemli bir demografik kayma göstermeye başladığı için, demans global bir sorun haline gelecektir. Aynı zamanda kültürel değişimler de geleneksel toplumların yaşlı ve güçsüzlere bakışını değiştirdiği için, demans prevalansındaki büyük artış bu ülkelerin karşısına ciddi bir sorun olarak çıkacaktır. Krizin üstesinden gelmek için sosyal, politik ve ekonomik düzenlemelere gerek duyulacaktır. Tıp bilimi, demansa yol açan nörolojik hastalıkları hafifletecek, durduracak veya iyileştirecek tedavilerle bu mücadeleye katkıda bulunabilir. Demans özellikle nispeten daha kısa bir yaşam beklentisi olan yaşlı popülasyonu etkilediği için, ilerlemeyi ve semptomların kötüleşmesini sadece kısa bir süreliğine geciktiren tedaviler bile topluma tahmin edilemeyecek yararlar sağlayabilir.

Demansa karşı etkili bir ilaç tedavisinin bulunma ihtimali yakın zamana kadar bir gerçekten daha çok hayaldi. Ancak son on yıl içerisinde ilk defa demans sürecini belirgin ölçüde etkileyecek ajanlara sahibiz. Bununla birlikte, temel araştırma ve ilaç geliştirme aşamaları önümüzdeki yıllarda tedavide ilerlemelerin mümkün olacağını ortaya koymaktadır. Bu makalede demans tedavisi için önerilen ilk ilaç sınıfı olan kolinesteraz inhibitörlerinin geliştirilmesini ele alacağız.

Anahtar Kelimeler: demans, kolinesteraz inhibitörleri

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INTRODUCTION

Dementia is one of the most important medical, economic, and social problems of the modern world. For the first time in history, medical science is allowing many people to live to advanced age, thereby rendering them susceptible to dementia. Up to now, the dementia crisis has primarily affected North America, western Europe, and Japan, but as the fundamental demographic shift of increased life expectancy spreads to the developing world over the first half of the twenty-first century, dementia will become a global problem. Occurring at the same time that cultural changes are altering the ways traditional societies have long cared for the elderly and infirm, the huge increase in the prevalence of dementia will be a tremendous challenge to these countries. Major social, political, and economic adjustments will be needed to meet the crisis. What medical science can contribute are treatments that will ameliorate, arrest, or cure the neurological diseases that causedementia. Because dementia primarily affects an elderly population with a comparatively short life expectancy, even treatments that simply delay progression and worsening of symptoms in the short run may have an inestimable benefit to society.

Until recently, the prospect of an effective drug treatment for dementia was more of a chimera than reality. Yet, in the past decade, for the first time, we now have agents that can significantly impact the course of dementia. Furthermore, the pace of basic research and drug development is such as to suggest that further improvements in therapy will be available in the future. In this paper we will consider the development of the cholinesterase inhibitors, the first class of drugs to be approved for the treatment of dementia. Figure 1 shows major outlines in the pharmacotherapy of dementia.

The pharmacotherapy of dementia was undoubtedly given a big boost by efforts in the 1970's and 1980's to define more precisely the different pathological processes that contribute to dementia. Up until that time, there was a tendency, reinforced by standard nosologies, to group all of these conditions together under the rubric "chronic brain syndrome." Aside from its diagnostic vagueness, the use of this term had a negative impact on the development of therapies[1]. As physicians and scientists became more precise in the identification of different disease processes that result in dementia, the situation changed. Pathological studies showed that the largest number of elderly people with dementia had the histological changes of Alzheimer's disease (AD), hitherto considered to be a rare "presenile" dementia[2]. Although there are clearly many other brain disorders, including cerebrovascular disease and other degenerative conditions such as diffuse Lewy body disease (DLBD) and frontotemporal lobar dementia (FTD), that cause dementia, and the distribution of the different types of dementia may differ from country to country and between different racial groups, studies suggest that AD, either by itself or in combination with other pathologies, is worldwide the most common pathological correlate of dementia in the elderly[3]. This observation was extremely important because it set investigators on the path of trying to understand the pathophysiology of AD, thereby leading to the rational consideration of different forms of treatment. The pathogenesis of AD is complex and likely involves many different mechanisms. This topic cannot be discussed in a comprehensive way here. Rather we will focus on just one of these possible pathophysiologic mechanisms, that of a neurotransmitter deficiency. Figure 2 shows pathophysiology of drug prescription in AD.

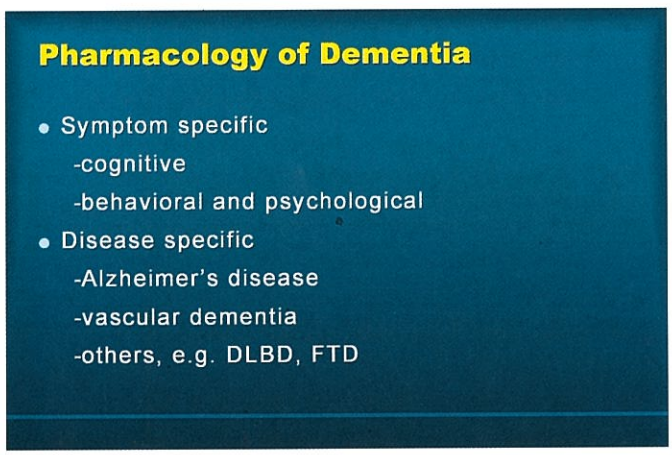


Figure 1.

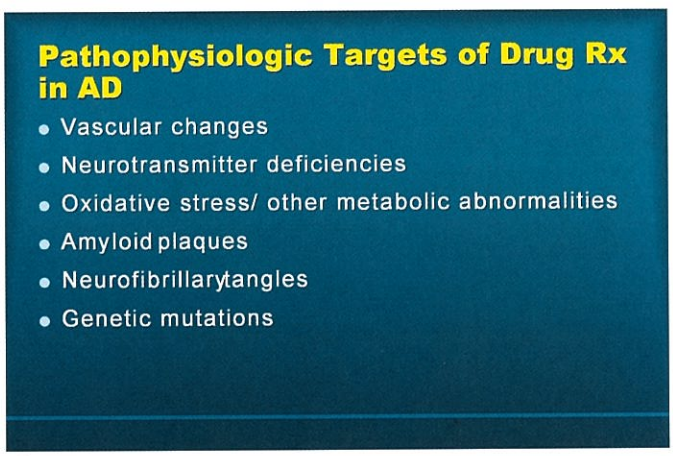


Figure 2.

CHOLINERGIC SYSTEM

In retrospect, it seems inevitable that one of the first ways scientists would look at the pathogenesis and possible treatment of AD was to focus on neurotransmitters. For almost half a century, efforts to treat psychiatric disorders had revolved around the use of drugs that in one way or another alter neurotransmitters. In neurology, there was the precedent of treating Parkinson's disease (PD) by manipulating the dopaminergic system. As is the case in these other neurological conditions, AD is associated with changes in multiple neurotransmitter systems[4], but the most prominent appears to be involvement of the cholinergic system. Figure 3 shows major neurotransmitters in AD. The cortical cholinergic system originates in the basal forebrain nuclei, comprising the medial septal nucleus, vertical and horizontal nuclei of Broca's diagonal band, and, especially, the nucleus basalis of Meynert. From this rather small collection of cells arise fibers that project widely to the cerebral cortex, hippocampus, and amygdala[5]. Figure 4 shows cholinergic pathways from the basal forebrain. Cholinergic input to the cerebral cortex presumably has a modulating effect on cortico-cortical interactions. Whatever the mechanism, it has been established that central cholinergic transmission is important to cognitive function. The cognition impairing effects of anticholinergic drugs have long been known. Experimental studies show that administration of the anticholinergic agent scopolamine can cause temporary cognitive impairment in normal subjects and that this effect can be reversed by the cholinesterase inhibitor drug physostigmine which augments central cholinergic transmission[6,7]. It is not entirely clear how best to characterize the cognitive syndrome produced by anticholinergic agents, whether it is a true memory disorder resembling that which is seen in dementia or is more closely akin to a delirium.

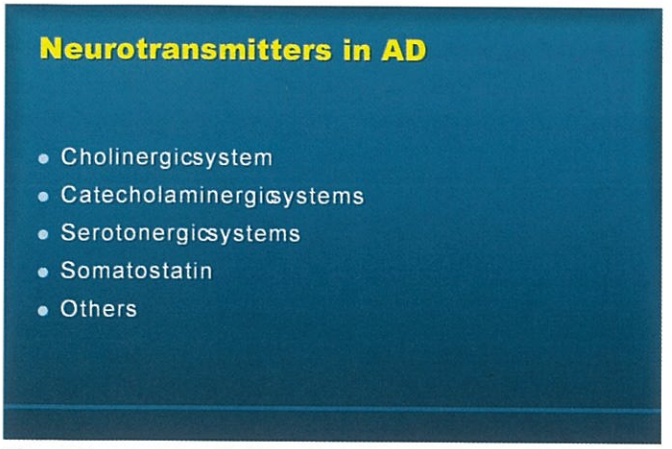


Figure 3.

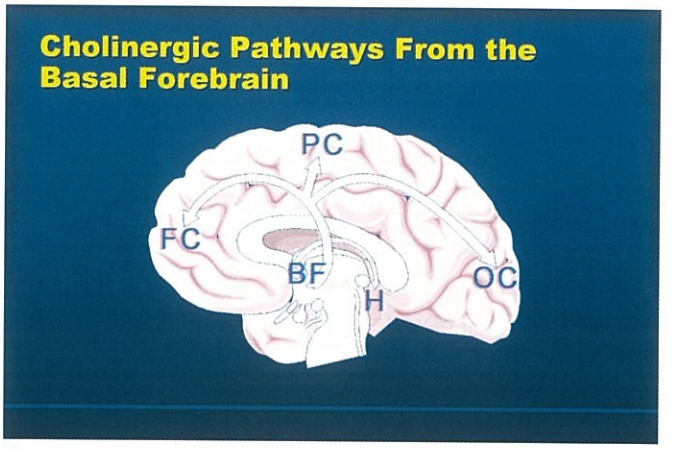


Figure 4.

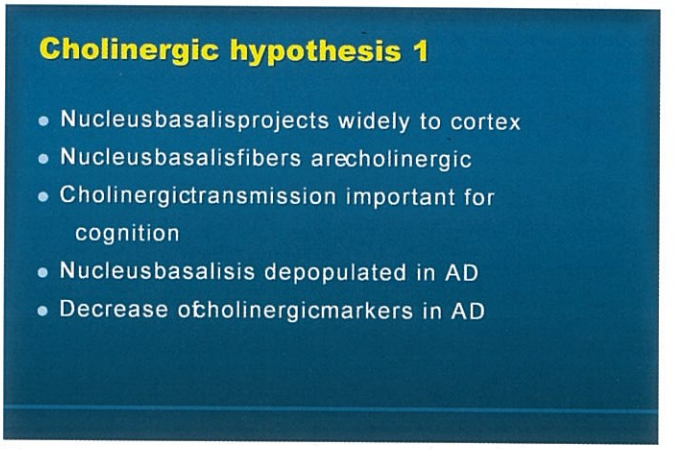


Figure 5.

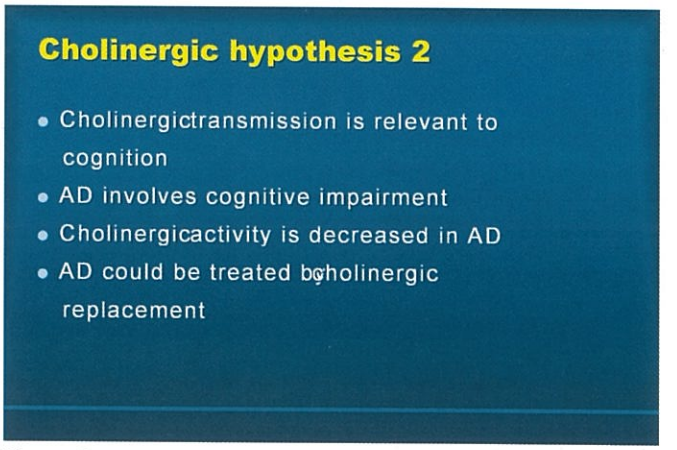


Figure 6.

Nevertheless, experimental work clearly demonstrates the importance of central cholinergic transmission in cognition. Figures 5 and 6 show cholinergic hypothesis.

Although AD is generally thought of as a cortical disease, it also involves a number of subcortical structures, including the nucleus basalis. Pathological studies show a consistent

loss of cells in the nucleus basalis in patients with AD[8]. Furthermore, nearly all markers of cholinergic function, including choline acetyltransferase (ChAT) and acetylcholinesterase (AchE) activity; indicators of choline metabolism, and nicotinic receptor binding, are decreased in the brains of AD patients[9,10]. It has even been shown that there is a correlation between the level of different cholinergic markers in the brains of AD patients and their cognitive function just prior to death[9]. It must be stressed that the cholinergic system is not the only neurotransmitter system affected by AD[4]. Nor is AD the only neurodegenerative condition in which cholinergic function is disrupted. For example, PD is characterized by acetylcholine as well as dopamine loss[11]. It is highly unlikely that any of these disorders are restricted to a single neurotransmitter system. Nevertheless, manipulation of the cholinergic system has been proven to be of benefit in the treatment of AD.

In theory, cholinergic replacement therapy of AD is purely symptomatic in nature since it merely attempts to make up for the loss of acetylcholine engendered by the disease without having any effect on the underlying pathologic process that leads to the development of plaques and tangles and loss of brain cells. Recent studies suggest, however, that the cholinesterase inhibitors, the main cholinergic agents used to treat AD, have a more complex mechanism of action and may, in fact, have a neuroprotective disease modifying, as well as symptomatic, effect on AD[12].

Given that our aim is to boost and restore CNS cholinergic function, there are several possible ways of going about reaching this goal with medications. The most direct would appear to be the administration of acetylcholine itself to AD patients but this has no effect on central levels of the neurotransmitter. Similarly, the ingestion of lecithin and choline, acetylcholine precursors, is of little or no benefit[13]. This may be due to the fact that lecithin and choline have a negative feedback effect on the central production of acetylcholine.

Cholinergic agonists drugs, including milameline, cevimaline, arecoline, and xanomeline, are attractive candidates for the treatment of AD because they are presumed to act on the M1 muscarinic receptor, located on the post synaptic cortical neuron. These cells are more resistant to the pathology of AD than those arising from the basal forebrain. Cholinergic agonists may also have other beneficial effects on the pathogenesis of AD[14]. Up to this time, however, these drugs have proven difficult to use, either because of intolerable side effects or the need to administer at least some of these agents parenterally or intraventricularly. Clinical trials are under way at the present time for a cholinergic agent called MKC-231, which has a totally different mechanism of action. It is believed to act by increasing the high affinity uptake of choline, which is the rate limiting step in the synthesis of acetylcholine. This is another way of increasing central levels of the neurotransmitter[15]. The results of clinical trials with MKC-231 have not been yet been reported. Figure 7 shows methods of cholinergic replacement.

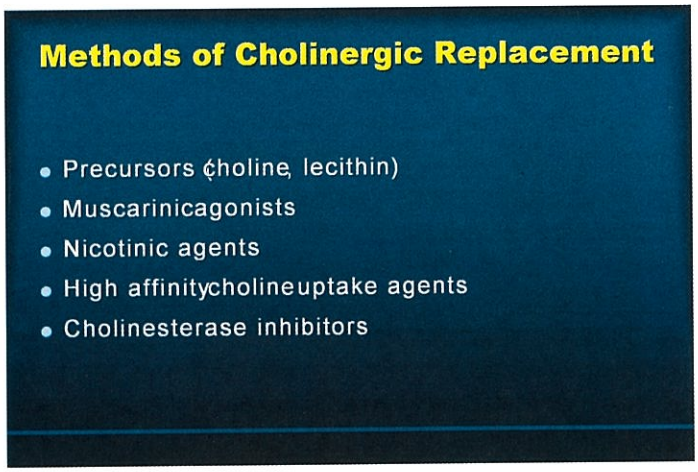


Figure 7.

CHOLINESTERASE INHIBITORS

Thus far, then, the only practical pharmacological way of increasing central cholinergic transmission has been the administration of cholinesterase inhibitors. These agents, of which physostigmine is the prototype, inhibit cholinesterase enzymes which are located in the synapse. The most important cholinesterase is acetylcholinesterase, which degrades acetylcholine into its constituents, choline and acetic acid. But other cholinesterases, especially butyrylcholinesterase, also exist (see below). By blocking the degrading enzyme, the cholinesterase inhibitors indirectly increase the amount of acetylcholine in the synapse, facilitating cholinergic neural transmission which is so important for normal cognitive functioning. As indicated above and discussed below, however, cholinesterase inhibitors may have other beneficial effects on the pathogenesis of AD.

Physostigmine was the first cholinesterase inhibitor to be

tried for AD, and some of the results were positive[16]. Its widespread use was limited, however, by the need to administer physostigmine either parenterally or on a very frequent oral dosing schedule. An extended release, long acting form of physostigmine, while also somewhat effective, produced too many unpleasant muscarinic related gastrointestinal side effects[17,18].

The first novel cholinesterase inhibitor specifically developed for its use in AD was tacrine[19,20]. In doses of 30 or 40 mg, given four times a day, tacrine was found to improve function in AD patients using the standard measures which are described below[17,21]. Because tacrine is an acridine derivative, it produced an elevation of liver enzymes in a substantial proportion of patients in addition to causing muscarinic side effects which are inherent in the use of all cholinesterase inhibitors. The liver enzyme elevations were often only transient in duration, and it was usually possible, after a period of time, to rechallenge patients with tacrine without any adverse hepatic events, but because of these inconveniences, tacrine is rarely used at the present time. It nevertheless occupies a place of historical importance as the first medication ever approved for the treatment of AD.

Over the next ten years a number of other cholinesterase inhibitors were developed to treat AD. Three of these agents, velnacrine[22]. metrifonate[23], and eptastigmine[24], were never in general use, either because of their adverse event profile or for commercial reasons. By contrast, three other agents, donepezil[25,26], rivastigmine[27], and galantamine[28,29], were eventually approved and are in wide use at the present time as the principal pharmacological treatments of AD. Figure 8 shows acetylcholinesterase inhibitor development.

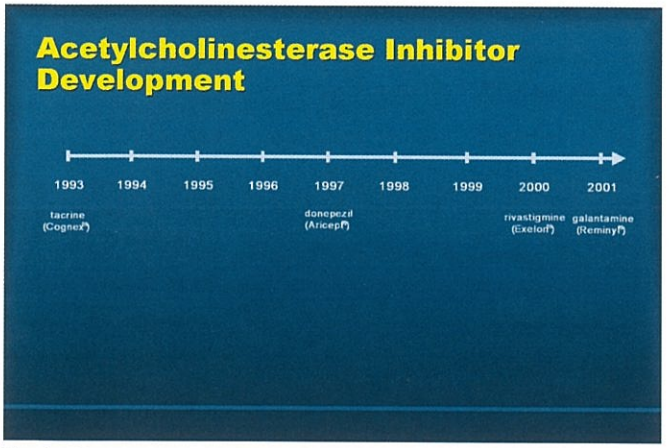


Figure 8.

CHOLINESTERASE INHIBITORS IN AD: CLINICAL TRIALS

Medications are approved for general use on the basis of large- scale clinical trials. In analyzing the results of clinical trials for AD, it is important to keep several facts in mind. One is that AD is a progressive disorder and that patients display different clusters of symptoms at different stages of the disease. Thus, instruments that tap cognitive function in patients with very mild dementia may be inappropriate for those with more severe symptoms. It is also possible, though thus far not demonstrated, that certain drugs will work better than others at different stages of the disease. There is a sequence of pathophysiologic processes that goes on over a long period of time to produce the symptoms and signs of AD. It is not unreasonable to assume that at different stages of the disease certain types of drugs, operating through a particular mechanism of action, might be more effective than others. It is also important to consider at the outset the different treatment outcomes one might expect from an anti-AD drug. Theoretically, there are four possibilities: cure, disease arrest, amelioration of symptoms, and slowing the downward course. In practice, however, it may be difficult to make these distinctions, and the cholinesterase inhibitors may provide both symptomatic benefit as well as some degree of disease modification.

Finally, another important issue regarding clinical trials of anti-AD drugs concerns outcome measures. How should we measure whether or not a drug is effective against AD? This is not an easy question to answer since we lack the definite biological markers readily available in testing for drug efficacy in other medical conditions. One way to settle this issue is to conceptualize AD as affecting multiple domains of a person's life. The most obvious domain is cognition so that one clearly wants some measure of cognitive function. Although the Mini-mental State Examination[30] is a well known instrument, used regularly in clinical settings to measure cognitive impairment, it is too short and lacks the psychometric properties needed for an instrument in a large scale-study. Consequently, a longer cognitive instrument, usually the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)[31] is used, at least for subjects with mild to moderate disease. Normative data, gathered during the years when there was no treatment for AD are available for comparison. It might legitimately be argued, however, that these

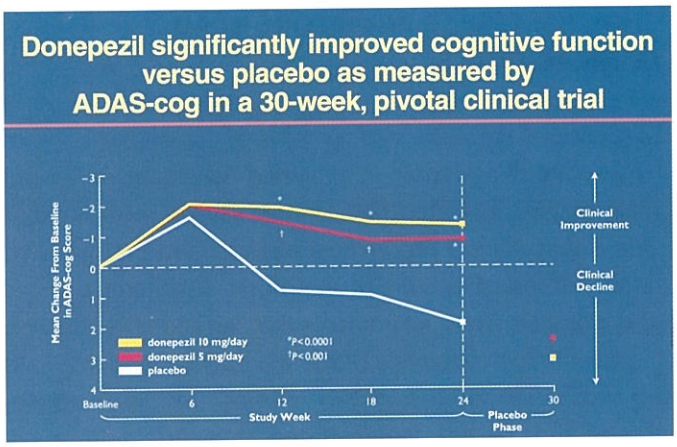
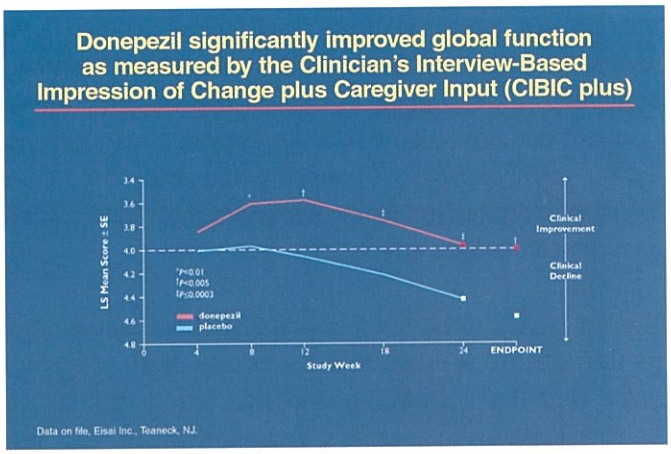


Figure 9.



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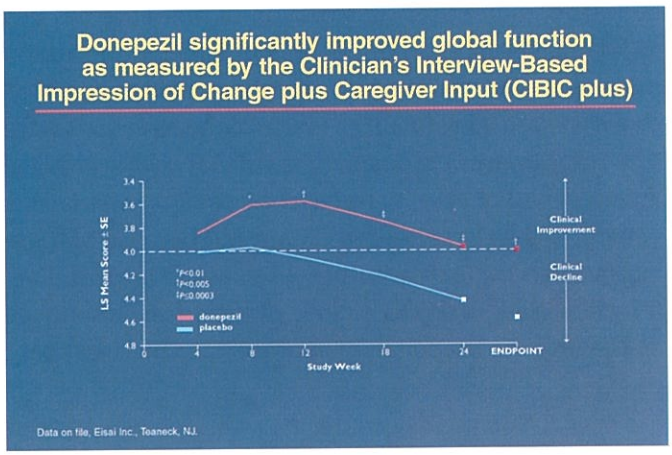

Figure 11.

instruments simply present a statistic that may or may not translate into clinically noticeable changes. To answer this argument, a global measure, such as the Clinician Interview Based Impression (CIBI)[32], Clinicians' Interview-Based Impression of Change-Plus (CIBIC- Plus)[33], or Clinical Global Impression of Change (CGIC)[34] is usually added. With these instruments a blinded clinician interviews the patient and/or family member at different intervals and makes a decision whether the patient is globally the same, slightly better, slightly worse, or much worse compared to his or her baseline evaluation. A measure of activities of daily living (ADL) such as the Interview for Deterioration in Daily Living Activities in Dementia-Complex Task (IDDD-CT)[35], the Disability Assessment in Dementia (DAD)[36] or the Clinical Dementia Rating (CDR) Sum of the Boxes[37] is also added to clinical trials for AD. The concrete functions, e.g. ability to dress oneself or to use the telephone, measured by these scales offer fairly unambiguous evidence for decline or improvement. It is also the custom to investigate the effects of anti-AD drugs on the numerous behavioral disturbances such as agitation, delusions, and hallucinations, so common in the condition. To expect some behavioral benefits from the cholinesterase inhibitor group is not unreasonable given the fact that anti- cholinergic agents are prone to cause confusion, hallucinations, and delusions. An instrument such as the Neuropsychiatric Inventory (NPI)[38] is used to tap this aspect of the disease. In some recent clinical trials instruments that measure the economic consequences of treatment, caregiver distress, and other social indices have also been employed. Very recently, the effects of treatment on objective biological markers, namely, static and dynamic neuroimaging parameters (see for example[39-41], have also been investigated.

The first pivotal trials of all the ChEIs were multicenter, double- blind, placebo-controlled trials lasting approximately six months and directed to relatively healthy patients meeting research criteria for AD[42,43]. These studies focused on patients with mild to moderate (MMSE score ranges typically 10 to 26) dementia and examined safety and dosage as well as efficacy[24-29,44-46]. As shown in Figure 9, which illustrates the results on the cognitive measure, the ADAS-cog, in a trial of donepezil, drug treatment begins to show superiority over placebo at twelve weeks, and by the end of twenty-four weeks, patients on medication remain significantly better than those receiving placebo and above their level at the time they entered the study[26]. (This and subsequent figure illustrate results with donepezil, but it must be emphasized that very similar results have been obtained with rivastigmine and galantamine). Figure 10 shows the results for donepezil on the global measure, the CIBIC-Plus, 26 while Figure 11 gives the findings for the same drug on a measure of ADLs[44]. For both domains (global and ADL), treatment is superior to placebo at the conclusion of the study. There is also evidence from a five month study of galantamine 29 that treatment with a cholinesterase inhibitor maintains or improves behavioral function, as measured by the NPI, compared to placebo

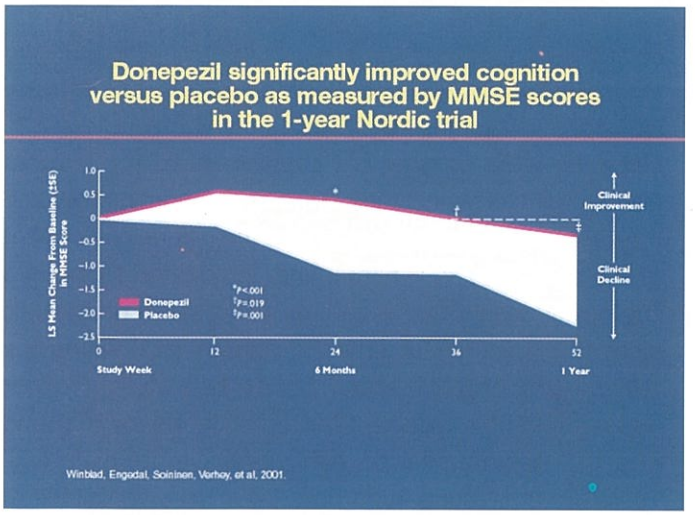

Figure 12.

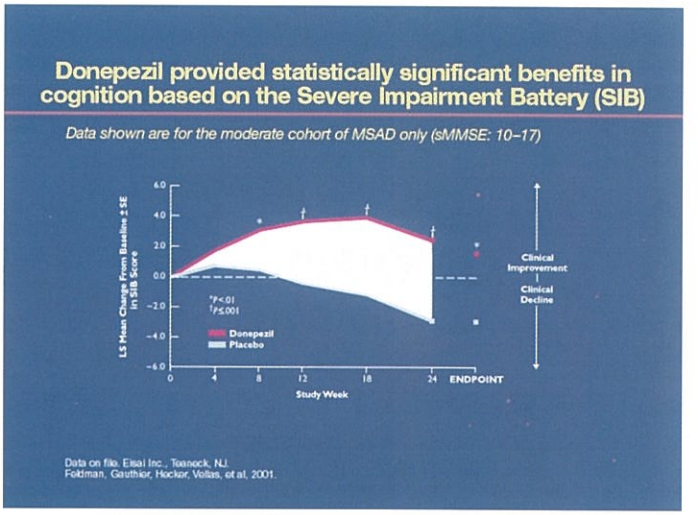

Figure 13.

Undoubtedly, the benefits on all of these measures are modest. Nevertheless, considering the relentless progressive course of untreated AD, it is clear from these and virtually every clinical trial in patients with mild to moderate disease that treatment with a cholinesterase inhibitors provides symptom improvement or stabilization over about a six month period.

What happens after six months? Data from a one-year placebo-controlled study[47] (Figure 12) and the open-label extensions of numerous six months trials (see for example references 28,48,49)[28,48,49] show that subjects eventually fall below baseline between nine months and one year following entry in the study, but the slope of their decline over one to three years is not as steep as the projected slope for matched patients who would have gone untreated for the same length of time. It is also interesting to note that, in virtually all of these studies, when patients originally assigned to placebo are placed on active medication at the end of the double-blind phase and beginning of the open-label extension, they do improve on many of the measures but never "catch up" to the group that received the active medication from the start. This suggests that patients with mild to moderate AD should be treated with cholinesterase inhibitors as soon as possible. There is also evidence that persistent treatment with a cholinesterase inhibitor alters in a favorable direction the natural course of AD[50] and significantly delays the need for patients, in western Europe and North America at least, to enter nursing homes[51,52].

Patients with "mild to moderate" AD represent just one subgroup of the entire AD group so that subsequent clinical trials focussed on patients at the two extremes of the

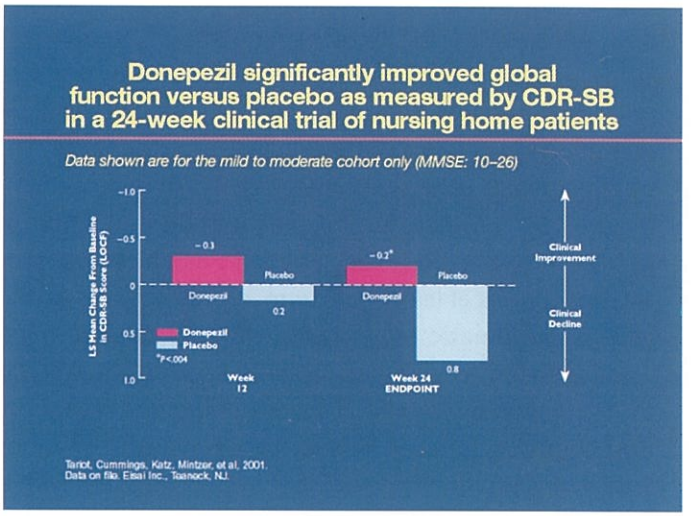

Figure 14.

clinical spectrum: severe/very severe dementia and early/very mild AD. In studying patients with advanced dementia, the Severe Impairment Battery (SIB)[53]. is used instead of the ADAS-cog as the main cognitive outcome measure. Furthermore, since some of these trials have been performed on AD patients in nursing homes, additional measures dealing with nursing care are also sometimes employed Figure 13 shows the results for the drug donepezil on the SIB in outpatients with MMSE scores ranging from 10 to 17[54] while Figure 14 illustrates for the same drug the effects of treatment versus placebo on an ADL measure, the CDR Sum of Boxes, in nursing home patients with a MMSE score range of 10-26. As can be seen, cholinesterase inhibitor therapy continues to be superior to no pharmacotherapy even in later stages of the disease.

At the other end of the spectrum are patients with very mild, early stage AD and those with "mild cognitive

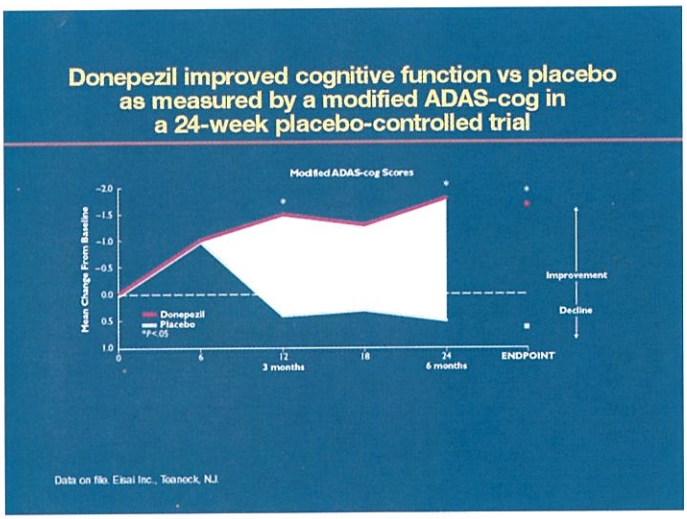

Figure 15.

impairment (MCI)," an intermediate condition that may be a precursor to AD or other dementia[55]. In a recent study, it was shown that in very early stage disease, untreated patients do not change very much over a six month period in terms of their cognitive performance, but treatment with donepezil causes significant improvement (Figure 15)[56]. Studies of the cholinesterase inhibitors in MCI have two main goals. One is to establish whether treatment gives at least short term, e.g. six months to one year, symptomatic benefit; the other is to determine whether treatment delays or prevents a person's conversion to AD. Preliminary results of studies of the first type show that cognitive function in subjects on placebo changes little over a six month period, but subjects treated with a cholinesterase inhibitor improve[57]. Studies of the second type are still in progress.

Since there are three different cholinesterase inhibitors in wide use at the present time, the question inevitably arises

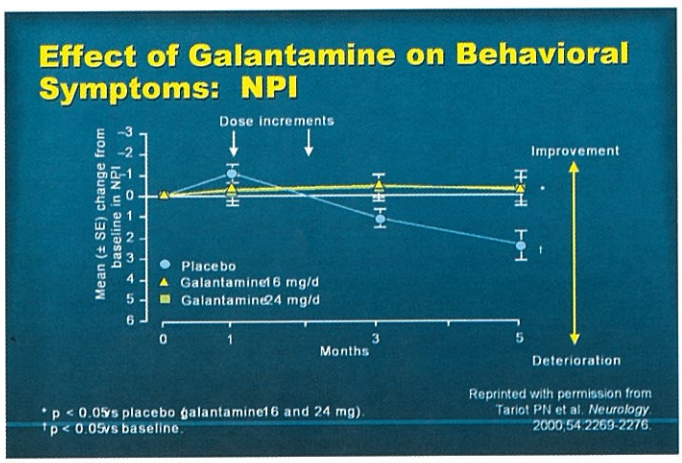

Figure 16.

as to which one is "best" and whether or not there are any significant differences in mechanism of action among them. While donepezil is a relatively pure acetylcholinesterase inhibitor, rivastigmine also inhibits butyrylcholinesterase[58]. Since the latter enzyme is a component of the amyloid plaque[59], it has been suggested that rivastigmine may act, at least in part, by directly attacking the plaque component of AD pathology[60]. Galantamine, in addition to being a cholinesterase inhibitor, is thought to act at the presynaptic nicotinic cholinergic receptor[61], thereby modulating the release not only of acetylcholine but also of other neurotransmitters important for cognition. Figure 16 shows effect of galantamine on behavioral symptoms in NPI. These are interesting hypotheses, but the significance of these different putative therapeutic mechanisms will only be resolved by the development and testing of drugs that are relatively pure butyrylcholinesterease inhibitors or nicotinic modulators. Whatever the different mechanisms of actions, the clinical efficacies of the three cholinesterase inhibitors in common usage at the present time are very similar. A few "head-to-head" trials pitting one drug against another give contradictory results[62,63]. It is, of course, true that individual patients may respond better to one agent than another, and it is possible that a particular cholinesterase inhibitor may be more appropriate for a certain subgroup of AD patients compared to another, but we have no basis at the present time of predicting which of the three agents is best for a particular patient. When patients who have been receiving cholinesterase for a year or more begin to show deterioration, some physicians choose to switch the patient to another drug in the same category. There is, however, no scientific basis for this practice. A more logical step at the present time would be to add the NMDA-receptor drug memantine[64]. to the cholinergic therapy. Another therapeutic ploy used by some physicians, namely, raising the cholinesterase inhibitor dose above the recommended daily ceiling (for donepezil, 10 mg, galantamine, 24 mg, and rivastigmine, 12 mg) invites too many potential side effects.

Fortunately, when used in recommended doses, the cholinesterase inhibitors are well tolerated by the majority of patients. As might be predicted, the primary side effects are gastrointestinal, e.g. anorexia, nausea, vomiting, diarrhea, and secondary to the inherent muscarinic properties of this class of drugs. If the amount of drug is slowly titrated up over several weeks, most patients will be able to reach therapeutic daily doses (donepezil, 5-10 mg; galantamine, 16-24 mg; rivastigmine, 6-12 mg). Taking

the medication with meals or an antiemetic can also help the individual adjust to the therapeutic dose. Other side effects of cholinesterase inhibitors are distinctly uncommon. The very mild bradycardiac effect is clinically insignificant in nearly all patients. AD patients are elderly and often have other medical illnesses that require taking numerous other medications, but significant drug-drug interactions involving the cholinesterase inhibitors are rare. Because of the mechanism of action, the concomitant use of drugs with anticholinergic properties, might reduce their clinical efficacy. Occasionally, caregivers report an increase in confusion or behavioral problems in patients receiving cholinesterase inhibitor therapy. The relationship of these symptoms to the drug is often difficult to determine since AD itself is a prominent cause of such symptoms. It is possible that, in an occasional individual, increased attention and awareness induced by the medication might cause confusion or agitation, but the preponderance of the evidence, summarized above, suggests the opposite, namely, that cholinesterase inhibitors improve such symptoms.

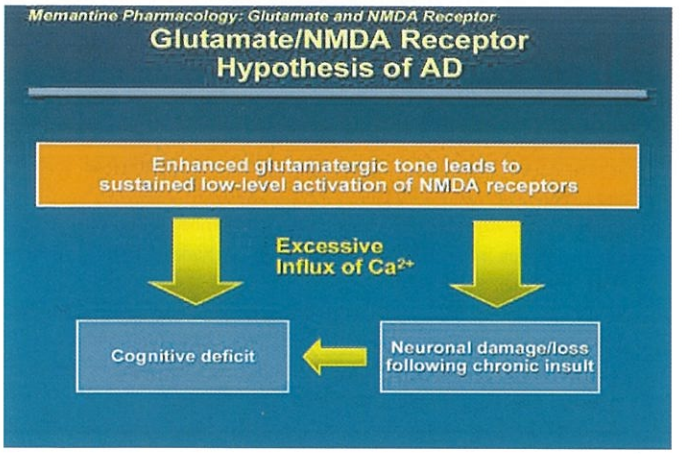

Figure 17.

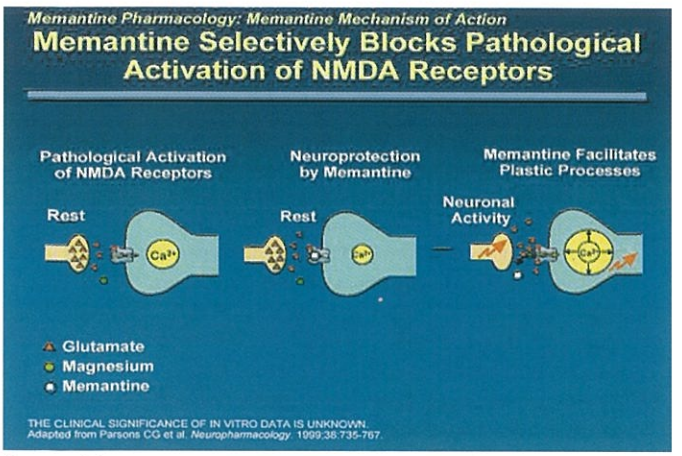

Figure 18.

The future course of cholinesterase inhibitors in the therapy of dementia is difficult to predict. Combinations with anti-AD drugs working through different mechanisms of action are a possibility. Recently, the combination of donepezil and memantine, an anti-excitotoxic NMDA receptor antagonist, has been shown to be superior to treatment with donepezil alone in patients with moderate to severe (MMSE score range, 3-14) AD[64]. Figure 17 shows glutamate/NMDA receptor hypothesis of AD and figure 18 shows the possible effect of memantine. Current studies are also evaluating the concomitant use of donepezil and statin drugs, since the latter, through a complicated mechanism of action, may have disease modifying effects on AD. Although cholinesterase inhibitors, as mentioned above, may be of some benefit in treating behavioral symptoms in AD patients, they are not first line drugs for individuals with severe symptoms, in which case they must be combined with another class of drug, most often an atypical antipsychotic.

CHOLINESTERASE INHIBITORS FOR CONDITIONS OTHER THAN AD

Early studies on the therapeutic use of cholinesterase inhibitors focused on AD because it is the most common cause of dementia and there is a clear rationale for treating AD by cholinergic replacement. Once the benefits against AD were clearly established, investigators inevitably began to examine the use of these drugs in other conditions. Vascular dementia (VaD) is the second most common form of dementia in the elderly and may be even more prevalent than AD in certain countries. Although not traditionally conceptualized as a cholinergic deficiency syndrome, VaD is indeed associated with a decrease in various cortical cholinergic markers, presumably due to infarction of cholinergic fibers in the cortical white matter. It is also a fact that, in any given patient, VaD is often combined with AD so that treatment with cholinergic drugs including the cholinesterase inhibitors might reasonably be predicted to play a role in the therapy of VaD[65]. Several recent studies have demonstrated significant benefits of treatment over placebo in patients with VaD strictly diagnosed according to NINDS-AIREN[66] criteria[67,68] or in patients with mixed vascular and degenerative disease[69,70]. Diffuse Lewy Body Disease (DLBD)[71], part of the spectrum of synucleinopathies that include PD, is characterized by a significant loss of cholinergic neurotransmission and so might be expected

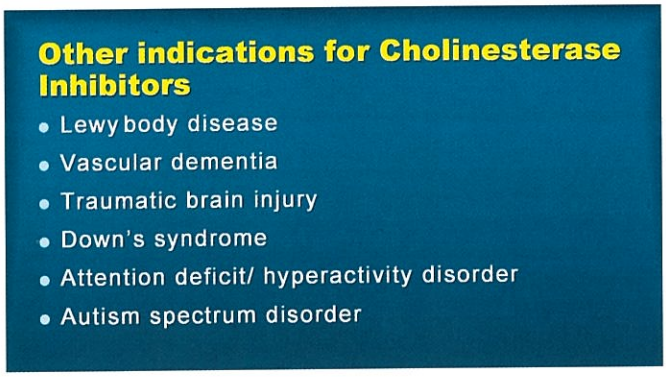

Figure 19.

to respond to cholinesterase inhibitor therapy. Although benefit was shown in one placebo controlled study with rivastigmine[72], problems with the diagnostic criteria for DLBD have hampered other trials for this indication. Easier to identify is dementia associated with PD. Since anticholinergic drugs have been used to treat PD, there was concern that the use of a cholinergic agent might worsen the motor signs of PD. This turns out not to be the case. In fact, as mentioned above, PD is characterized by a consistent cholinergic, and the recent preliminary report of a multi-center study revealed positive benefits with the use of rivastigmine in patients with PD dementia[73] Other conditions for which there are reports of open label studies of a cholinesterase inhibitor include cognitive impairment after traumatic brain injury[74], multiple sclerosis[75], and Down syndrome[76]. Finally, there is the group of disorders now designated as the "frontotemporal lobar dementias." Pathologically, these conditions have been characterized as "tauopathies,", which is fundamentally different from the pathology of AD, so that one would not expect any therapeutic benefit from a cholinesterase inhibitor. There may, however, be some overlap between the two conditions, but there are no reports at the present time of the effects of a cholinesterase inhibitor on the symptoms of frontotemporal dementia. Figure 19 shows other indications for cholinesterase inhibitors.

SUMMARY

The cholinesterase inhibitors are the first group of drugs to have been rigorously studied and then approved by governmental agencies for the treatment of AD. The development of these drugs was made possible by advances in understanding the pathophysiology of the disorder. While the cholinergic hypothesis was the basis for choosing these drugs for study, they may turn out to have additional mechanisms of action. Indeed, basic science studies of the cholinesterase inhibitors may provide fresh insights into the fundamental pathophysiology of AD. Numerous clinical trials as well as general clinical experience clearly indicate that these medications do benefit patients with dementia. The original studies focused on individuals with mild to moderate AD, but subsequent trials, some of which are still ongoing, have extended the indication to patients in early and late AD as well as other cognitive disorders. Despite the remarkable advances of the past decade, however, it is unquestionable that we are far from having treatments that halt or reverse the course of the illness. In using cholinesterase inhibitors, it is important for both the clinician and the patient and his or her family to have realistic expectations. It must be understood that these medications cause only mild, temporary visible improvement and simply attenuate the downhill course. Furthermore, for maximum benefit, treatment should be instituted as early as possible and continue through most of the course of the illness. In the future, we may combine cholinesterase inhibitors with other classes of drugs, use other types of cholinergic drugs, or rely on medications that are based on a totally different approach to the pathophysiology of AD. But the cholinesterase inhibitors will always retain their historical place in the treatment of dementia.

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Gerontological Society of America

International Neuropsychological Society

Boston Society of Neurology and Psychiatry

Behavioral Neurology Society

American Neuropsychiatric Association

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Member, Advisory Committee on Organic Mental Disorders, Task Force on Nomenclature, American Psychiatric Association

Editor, Section on Organic Mental Disorders, Diagnostic and Statistical Manual of Mental Disorders, Third edition. Washington: American Psychiatric Association, 1980.

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Principal Investigator, V.A. Medical Research Service, Merit Review Approved Program, "Cortical Connections in the Monkey," 1981-93

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Senior Affiliate Investigator, Mid-South Mental Illness Research, Education, and Clinical Center (MIRECC), Department of Veterans Affairs VISN 16, 1999-

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Participating Investigator, A Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study of Tacrine (CI-970) in Alzheimer's Disease Patients (Parke-Davis Pharmaceutical Research), 1990-92

Participating Investigator, A Long-term Tolerance and Safety Study of HP 029 (2 ,3, 4, -Tetrahydro-9-Aminoacridin-1-OL-Maleate) in Patients with Alzheimer's Disease (Hoechst-Roussel), 1990-1992

Participating Investigator, An Open Label Study of DuP 996 30 mg T.I.D. (90 mg. Daily) in Patients with Mild to Moderate Dementia of the Alzheimer Type (DuPont Merck), 1991-1993

Participating Investigator, Cognex Access Program, (Parke-Davis Pharmaceutical Research), 1992-1993

Participating Investigator, A Controlled Study of Ondansetron in the Treatment of Alzheimer-type Dementia (Glaxo Pharmaceuticals), 1993-1994

Participating Investigator, Multi-center, 30-Week, Double-blind, Parallel Group Safety, Tolerance and Efficacy Comparison of Placebo and Mentane (150mg/d,225mg/d and 300 mg/d) in Outpatients with Alzheimer's Disease (Hoechst-Roussel), 1993-1994

Participating Investigator, A 30-week, Multi-center, Double blind, Placebo-controlled, Evaluation of the Safety and Efficacy of E2020 in Patients with Alzheimer's Disease (Eisai America), 1994-1997

Participating Investigator, Clinical Evaluation of Extended-release Oral Physostigmine in the Treatment of Patients with Dementia of the Alzheimer's Type (Forest Laboratories), 1994-99

Participating Investigator, A Controlled Study of Ondansetron in the Treatment of Primary Degenerative Dementia of the Alzheimer Type (Glaxo Pharmaceuticals), 1994

Participating Investigator, A Prospective, Randomized, Multi-center, Double blind, Placebo-controlled, Parallel Group Comparison of the Efficacy and Safety of SDZ-ENA 713, 1-4 mg./day, and SDZ-ENA 713, 6-12 mg./day, in Patients with probable Mild to Moderate Alzheimer's disease (Sandoz), 1995-2000

Participating Investigator, Study of Midodrine in Patients with Neurogenic Orthostatic Hypotension (Roberts Pharmaceuticals), 1995-1996

Participating Investigator, Cognex: Neuropsychiatric Testing and Assessment of Caregiver Time (CONTACT) Study (Parke-Davis), 1996-1997

Participating Investigator, A 48 Week Study to Compare the Efficacy and Safety of Propentophylline (HWA-285) with Placebo in Patients with Alzheimer's Disease (Hoechst-Marion-Roussel), 1996-

Participating Investigator, A 24 Week Study to Compare the Efficacy and Safety of Propentophylline (HWA-285) with Placebo in Outpatients with Vascular Dementias (Hoechst-Marion-Roussel), 1996-

Participating Investigator, An Open-label, Multi-center Clinical Trial Investigating the Safety and Efficacy of Donepezil Hydrochloride (E2020) in Patients with Alzheimer's Disease (Eisai America/Pfizer), 1996-1997

Participating Investigator, The Efficacy, Safety, and Tolerability of Lazabemide (Ro 19-6327) Versus Placebo, Administered for One Year, in Patients with Probable Alzheimer's Disease (Protodigm; Hoffman-Laroche), 1997-1999

Participating Investigator, Metrifonate Investigational Nationwide Trial (MINT) (Bayer), 1997-1998

Participating Investigator, A 24 Week, Multicenter, Randomized, Double-blind, Placebo-controlled, Evaluation of the Efficacy and Safety of Donepezil Hydrochloride (E2020) in Patients with Dementia Associated with Cerebrovascular Disease (Eisai), 1998-

Participating Investigator, A Randomized, Double- blind, Placebo-controlled, 12 Month Safety and Efficacy Study of Idebenone (CV2619) 240 mg. t.i.d. and 360 mg. t.i.d. in Patients with Probable Alzheimer's Disease (Takeda), 1998-1999

Participating Investigator, A Randomized, Double- blind, 12 Month Safety and Efficacy Study of Idebenone (CV2619) 360 mg. t.i.d. or Placebo Added to Donepezil 10 mg. q.d. in Patients with Probable Alzheimer's Disease (Takeda), 1998-1999

Participating Investigator, Randomized, Double-blind, Placebo-controlled Multicenter Trial to Demonstrate the Efficacy and Safety of Two Different Doses of Ginkgo biloba Special Extract EGb 761 in Patients suffering from Dementia of the Alzheimer's type according to DSM-IV and NINCDS/ADRDA criteria (Schwabe GmbH), 1999-2000

Participating Investigator, A 24- Week Multicenter, Randomized, Double-blind, Placebo-controlled Evaluation of the Efficacy and Safety of Donepezil HCl (E2020) in Patients with Early Alzheimer's Disease (Eisai), 1999-2001

Participating Investigator, "Delay to Nursing Home Placement in Patients Treated in the Aricept Clinical Program (Battelle), 1999-

Participating Investigator, "A Multicenter, Randomized, Double-blind, Placebo controlled Study of Three Fixed Doses of Aripiprazole in the Treatment of Institutionalized Patients with Psychoses associated with Dementia of the Alzheimer's Type" (Bristol-Myers Squibb), 2000-

Participating Investigator, "Placebo Controlled Evaluation of Galantamine in the Treatment of Alzheimer's Disease: Safety and Efficacy of a Controlled Release Formulation (Janssen Pharmaceutica)," 2001-

Participating Investigator, "A Twelve Week, Multicenter, Randomized, Double-blind, Placebo-controlled Evaluation of the Efficacy, Tolerability, and Safety of Donepezil HCl (E2020) in the Treatment of Young Adults with Down Syndrome (Eisai-Pfizer)," 2001-2004

Participating Investigator, "A Randomized Double Blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Galantamine in Subjects with Mild Cognitive Impairment (MCI) Clinically at Risk for the Development of Clinically Probable Alzheimer's Disease" (Janssen Pharmaceutica), 2001-

Participating Investigator, "A Randomized, Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type" (Forest Labs), 2001-

Participating Investigator, "A 24-week, Multi-center, Randomized Placebo-controlled Evaluation of Donepezil HCl (E2020) in Patients with

Severe Alzheimer's Disease, Followed by a 12 Week Open Label Extension Period" (Eisai-Pfizer), 2001-

Participating Investigator, "A Double-Blind, Placebo-Controlled, Dose-Finding Study Evaluating the Safety and Efficacy of MKC-231, 80 mg. b.i.d., and 20 and 80 mg. qd, in the Treatment of Alzheimer's Disease" (Mitsubishi Pharma America), 2003-

Participating Investigator, "An 80-Week, Randomized, Multicenter, Parallel group, Double blind, Study of the Efficacy and Safety of Atorvastatin 80 mg. and an Acetylcholinesterase Inhibitor vs. an Acetylcholinesterase Inhibitor alone, in the Treatment of Mild to Moderate Alzheimer's Disease" [Pfizer], 2003-

Participating Investigator, "A One Year, Multicenter, Randomized, Double-blind, Placebo Controlled, Evaluation of the Efficacy and Safety of Donepezil HCl (E2020) in Subjects with Mild Cognitive Impairment" (Eisai-Pfizer), 2004-

Participating Investigator, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase II Study of-Efficacy and Safety of SGS 742 in Subjects with mild to moderate Alzheimer's Disease" (Saegis Pharmaceuticals), 2004-

Discipline Coordinator for Neurology and Psychiatry, Louisiana Geriatric Education Center (P.H.S. Bureau of Health Professions)

Charter Fellow, Louisiana Geriatric Education Center

Member, Education Subcommittee, Section on Aging, American Academy of Neurology

Member, Scientific Advisory Board, Alzheimer's Disease and Related Disorders Association (Eastern Mass. Chapter)

Member, Board of Directors, Alzheimer's Disease and Related Disorders Association (Greater New Orleans Chapter), 1992-2000

Member, Medical A dvisory Board, Alzheimer's Disease and Related Disorders Association (Greater New Orleans Chapter), 2000-2002

Founding Member, Board of Directors, Louisiana State Chapter of the Alzheimer's Association, 2002-

Member, Scientific Review Committee, Research Service, Bedford V.A. Hospital

Member, Education Committee, Department of Psychiatry and Neurology, Tulane University School of Medicine, 1989-

Member, Executive and Finance Committee, Department of Psychiatry and Neurology, Tulane University School of Medicine, 1995-1998

Member, Neuroscience Faculty Committee, Tulane University School of Medicine, 1990-

Member, Tulane Committee on Aging Research, Education, and Service, 1988-

Member, Geriatrics Planning Committee, Tulane University School of Medicine, 1991-

Member, Committee on Use of Human Subjects, Tulane University Medical Center, 1994-

Chairman, Ad Hoc Committee on Geriatrics, New Orleans VA Medical Center, 1991

Member, Geropsychiatry Planning Steering Committee, Tulane University School of Medicine, 1998-

Member, Search Committee, Robert Heath Profes-shorship of Biological Psychiatry, Tulane University

External Grant Reviewer, National Science Foundation

External Grant Reviewer, Arizona Disease Control Commission

Ad Hoc Reviewer, Alcohol, Drug Abuse, and Mental Health Administratic

Ad Hoc Reviewer, V.A. Research Service Merit Review Program

Ad Hoc Grant Reviewer, Alzheimer's Association

Member, Scientific Study Section, National Institute on Aging, Program f Alzheimer's Disease Research Centers

Grant Reviewer, Alzheimer's Association

Consultant, China Medical Board of New York

Member, International Scientific Advisory Committee, Turkish Journal of Neurology, 2003-

Reviewer,

American Journal of Psychiatry
Annals of Neurology
Archives of Internal Medicine
International Journal of Geriatric Psychiatry
Journal of the American Medical Association
Journal of the American Medical Directors Association
The Brain and Behavioral Sciences
Journal of Applied Gerontology
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