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Advances in the pharmacotherapy of Alzheimer's disease

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Abstract The authors reviewed the literature on the agents proposed for the treatment of Alzheimer's disease (AD). Different classes of drugs have been tested for this indication including psychostimulants, anitcoagulants, vasodilators, hyperbaric oxygen, hormones, nootropics, cholinomimetics, monoaminergics and neuropeptides without conclusive evidence of being beneficial for the treatment of this condition. Among the cholinomimetics recent research data seems to indicate that they might produce modest benefits in mild-to-moderate AD patients. Recently, other drugs have also been proposed including neurotrophic factors, phosphatidylserine, argistension converting enzyme (ACE) inhibitors, calcium channel blockers, acetyl-L-carnitine, xanthine derivatives, anti-inflammatory agents, aluminum chelate agents, and D-cycloserine. Of these new strategies few hold promise of more substantial benefits for AD, with the possibility of altering the course of the disease, but these drugs await confirmatory trials.

Key words Alzheimer's disease · Pharmacotherapy Therapeutics · cognitive disorders

Introduction

Alzheimer's disease (AD) is characterized by an acquired intellectual decline manifesting as memory loss together with other cognitive impaiments including dysphasia, visuospatial dysfunction, and disturbances in abstraction, calculation or concentration. The disease is determined pathologically by the presence of senile plaques, which are an accumulations of granular material, including degenerating neurites and glia, with a core formed of amyloid material and neurofibrillary tangles. These pathological changes, despite extensive study, are still poorly understood. Besides the cognitive symptoms AD frequently manifests other behavioral symptoms. These symptoms most commonly include psychomotor agitation, anxiety and depressive symptoms, and psychotic symptoms such as delusions. Such symptoms, together with the cognitive disturbances, are the targets for the treatment of this condition.

A large number of clinical trials with agents aimed at treating this condition have been carried out over the past 30 years (Rosenberg et al. 1991). The main focus of this research has been on finding agents that could improve the cognitive performance in patients suffering from this disease. In the present work we reviewed data on pharmacological agents proposed to improve cognition, with a particular focus on recent research done in this field.

Historical background

Several agents have been tested as potential cognition enhancers. Hyperbaric oxygen, psychostimulants, vasodilators, anticoagulants and hormones (ACTH and vasopressin) are among the initial agents tested, without any conclusive evidence of benficial effects (Goodnick and Gershon 1983, 1984; Vogel-Scibilia and Gershon 1989)

From the drugs investigated for the treatment of AD most are proposed to improve cognition by effects on neurotransmission, promoting enhancement of synaptic transmission. This group includes drugs such as neurotransmitter agonists, neuropeptides, and neurotropics. They are suggested as being potentially useful for palliation. Some agents are proposed to influence the course of the disease, and thus to have the potential to prevent or stop the progression of the disease. This group includes chelation agents, hormone therapy, nerve growth factor, anti-inflammatory agents, phosphatidylserine, and L-deprenyl. Other drugs are proposed to control the behavioral symptoms associated with AD including antipsychotic agents, minor tranquilizers, anticonvulsants, mood stabilizers and antidepressant drugs.

Several compounds have been tested under controlled conditions as potential cognitive enhancers. The strategies

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proposed to alter the course of AD do not have consistent data in their support thus far. Among the possible palliative treatments the cholinergic enhancers have recently gained a lot of attention, because more recent trials with THA (9-amino-1,2,3,4-tetrahydroacridine) have suggested that some benefits have been observed in the higher dosage ranges.

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Nootropics

The nootropics or "metabolic enhancers" are drugs that do not interact directly with any specific neurotransmitter system. Several agents in this class have been investigated including piracetam, oxiracetam, pramiracetam, aniracetam, and BMY 21502.

Piracetam has produced conflicting results in demented patients (Chouinard et al. 1981; Stegnick 1972), but more recent evidence suggests that it could be useful. A controlled trial in a sample of 33 AD patients using higher doses over a peroid of 1 year suggested that this agent might have effects in slowing the cognitive deterioration (Croisile et al. 1993). These results point out the need for further investigation of higher doses of this medication in large controlled trials over longer periods of time. The studies with piracetam in combination with choline or lecithin in AD patients have yielded disappointing results (Friedman et al. 1981; Ferris et al. 1982; Pomara et al. 1984; Smith et al. 1984; Growdon et al. 1986; Davidson et al. 1987).

Oxiracetam was initially found to be more active than piracetam in improving learning and memory in animal models (Banfi and Dorigotti 1986). Some clinical trials in primary degenerative dementia and multi-infarct dementia suggested it could be useful (Dysken et al. 1989; Maina et al. 1989; Bottini et al. 1992; Villardita et al. 1992), but the trials done in AD patients were mostly disappointing (Itil et al. 1982; Itil et al. 1986; Moglia et al. 1986; Villardita et al. 1986; Parnetti et al. 1989; Green et al. 1992)

Pramiracetam and aniracetam have also been tested in the treatment of AD patients, without substantial evidence of efficacy (Branconnier et al. 1983; Mizuki et al. 1984; Sourander et al. 1987; Claus et al. 1991). A recent multicenter controlled trial of aniracetam in AD patients showed indications that it could improve some psychobehavioral measures (Senin et al. 1991).

Hydergine

Hydergine is a vasodilator that also stimulates cerebral metabolism, causing an increase in intracellular cyclic adenosine monophosphate (cAMP). Several trials analyzed its effectiveness as a cognition enhancer, without consistent evidence of benefits for the treatment of these conditions (Gerin et al. 1969; Triboletti and Ferri 1969; Ditch et al. 1971; Jennings 1972; Rao and Norris 1972; McConnachie 1973; Rehman 1973; Banen 1974; Thibault 1974; Hughes et al 1975; McDonald 1979; Thompson et al. 1990).

Phosphatidylserine

Phosphatidylserine (PS) is a natural phospholipid membrane constituent with functions related to membrane fluidity and cellular metabolism. It has been proposed as an agent that would cause structural neuronal modification, instead of just transitory changes in metabolism produced by other agents. The initial clinical trials showed some promise (Delwaide et al. 1986; Allegro et al. 1987; Caffarra and Santamaria 1987; Palmieri et al. 1987; Puca et al. 1987; Granata and Michelle 1987; Sinforiani et al. 1987; Satzger et al. 1988; Villardita et al. 1987; Amaducci et al. 1988), and two recent trials suggested that this agent might be beneficial for AD patients, particularly patients in the early stages of the disease (Crook et al. 1992; Engel et al. 1992). Nevertheless, this agent awaits further confirmation of its effectiveness in large multicenter controlled trials using patients in different stages of the disease.

Cholinomimetics

The findings of a loss of cholinergic neurons in the ventral forebrain and decreased choline acetyltransferase in AD brains initiated extensive investigation of drugs that would increase cholinergic transmission as potential treatments for AD. Choline, lecithin, arecoline, RS-86, 4-AP, bethanecol. oxotremorine, nicotine bitartrate, and pyrodostigmine are among the compounds that have been tested, without consistent evidence of effectiveness (Etienne et al. 1978a; Etienne et al. 1978b; Sitaram et a. 1978; Christie et al. 1981; Etienne et al. 1981; Thal et al. 1981; Brinkman et al. 1982; Dysken et al. 1982; Pomara et al. 1983; Wettstein and Spiegel 1984; Bruno et al. 1985, Bruno et al. 1986; Davis et al. 1987; Harbaugh 1987; Heyman et al. 1987; Hollander et al. 1987; Davidson et al. 1988; Mouradian et al. 1988; Penn et al. 1988; Tariot et al. 1988; Newhouse et al. 1988; Harbaugh et al. 1989; Molloy and Cape, 1989; Vogel-Scibilia and Gershon 1989; Sahakian et al. 1989; Read et al. 1990).

Physostigmine was found to have postitve results in initial infusion studies (Davis et al. 1980; Christie et al. 1981), but the studies done with oral administration were mostly discouraging (Caltagirone et al. 1982; Jotkovitz 1983; Wettstein 1983; Schmechel et al. 1984; Mitchel et al. 1986; Stern et al. 1987; Stern et al. 1988; Jenike et al. 1990a; Jenike et al. 1990b). Nevertheless, two recent trials suggested the possibility that a subgroup of AD patients could benefit from long-term treatment with physostigmine, and that it could decrease the rate of cognitive decline in these patients (Jenike et al. 1990c; Harrel et al. 1990).

Tetrahydroamino acridine (THA) is a potent acetylcholinesterase that also has actions as a partial antagonist of morphine, promoting inhibition of cAMP phosphodi-

esterase, selectively blocking K channels, inhibiting Na channel inactivation, down-regulating type 1 muscarinic receptors, altering phosphorylation, stimulating cholinergic firing, and at high doses blocking pre- and postsynaptic nicotinic and muscarinic receptors. Of 11 double-blind controlled trials with this agent in AD patients, 6 studies failed to show evidence of significant improvements in cognition (Chatellier and Lacomblez 1990; Fitten et al. 1990; Gauthier et al. 1990; Molloy et al. 1991; Weinstein et al. 1991; Minthon et al. 1993), whereas 5 found significant improvement (Eagger et al 1991: Eagger et al. 1992; Davis et al. 1992; Farlow et al. 1992; Knapp et al. 1994). A recent large trial (Knapp et al. 1994) using higher doses of THA (up to 160 mg/day) showed more consistent improvement in cognition, but only one-third of patients using the dose of 160 mg/day could tolerate the medication. Of the patients treated with THA in this trial 54% had increases of at least one alanine aminotransferase (ALT) value during the 30-week trial, and 29% had increases of at least 3 times the upper normal limit. Of all clinically significant elevations of ALT 90% occurred in the first 12 weeks of treatment, and all resolved when the drug was discontinued. Watkins et al. (1994) reviewed the hepatotoxic side effects of THA in six multicenter trials that used doses from 20 to 160 mg/day and reported that in 49% of the patients ALT was found to be increased in at least one occasion, on weekly liver-enzyme monitoring. This increase was at least three times the upper normal limit in 25% of cases. The discontinuation of the medication reversed the ALT elevations in all cases, and no hepatotoxicity-related deaths were reported. Nevertheless, the rates of side effects by the different dose ranges used was not reported. In the higher dose groups, which are the ones shown to produce more clear benefits on cognition, the incidence of side effects is probably higher than the overall 49% for the entire group studied.

The more recent THA data suggests that it might be useful for some mild-to-moderate AD patients, particularly in higher doses of 160 mg/day. For the patients that can tolerate the high incidence of side effects associated with these doses it seems to improve or slow the decline in various tests of cognitive function. However, the studies reported thus far did not show conclusive evidence of substantial functional improvement. The recently reported findings by Knapp et al. (1994) that THA in higher doses would produce more consistently identified benefits still need to be replicated in other trials, and the safety of this drug for large groups of AD patients, particularly patients with systemic disease, is yet to be determined (Winker 1994).

Velnacrine maleate (9-amino-1,2,3,4-tetrahydroacridine-1-ol maleate), a THA derivative, was found to improve memory in animal models (Murphy et al. 1991), to have good oral bioavailability and to be well tolerated in young and elderly volunteers (Puri et al. 1989; Puri et al. 1990). A dose of 225 mg/day was suggested to be safe for administration in AD patients (Cutler et al. 1990), and an initial trial with a single dose of 75 mg/day was shown to significantly improve word-recognition memory in AD patients (Ebmeier et al. 1992). The effectiveness of this drug still awaits further testing in large controlled trials.

Galanthamine is another acetylcholinesterase inhibitor that has been investigated, with contradictory results in preliminary small open trials (Rainer et al. 1989; Dal-Bianco et al. 1991), and E2020 is a new agent in this class that has been reported to be well tolerated in humans (Mihara et al. 1993; Ohnishi et al. 1993).

Monoaminergic drugs

Serotonin (5-HT) reuptake inhibitors have also been tested as possible agents to improve cognition in demented patients, but overall the studies with these drugs have not been promising (Bergmann et al. 1983; Cutler et al. 1985a; Dehlin et al. 1985; Olafsson et al. 1992). Some studies that did not find evidence of significant effects on cogniton, found improvement in behavioral symptoms associated with dementia including mood, anxiety, irritability and restlessness (Nyth and Gottfries 1990; Gottfries et al.1991; Gottfries et al. 1992). The 5-HT agonist meta-chlorophenylpiperazine (m-CPP) has also been tested in AD patients, without evidence of significant effects on cognition (Lawlor et al. 1991).

Initial animal studies suggested that the alpha-2 adrenoreceptor agonists could be useful to treat cognitive deficits (Arnstein et al. 1988) but clinical trials with guanfacine and clonidine in AD have been disappointing (Mohr et al. 1989; Schlegel et al 1989; Crook et al. 1992).

L-Dopa replacement is another strategy that was tried for the treatment of cognitive deficits in AD patients, without evidence of significant effectiveness when tested in double-blind conditions (Jellinger et al. 1980; Ferris et al. 1982).

L-Deprenyl is a selective monoamine oxidase B (MAO-B) inhibitor that has been proposed to be useful for cognitive disorders. It also interferes with the production of free radicals from inactive substrates in the neurons, and has been hypothesized to alter the progression of the disease. Of six trials in AD patients (Tariot 1987; Piccinin 1990; Finali et al 1991; Mangoni et al. 1991; Agnoli et al. 1992; Burke et al. 1993), five found significant effects on cognition, but they involved mainly small samples followed for periods not longer than 6 months. The possibility that this drug might be useful for AD patients, with the potential for retarding the progression of the disease certainly deserves more extensive investigation in larger trials for longer periods of time. Such studies are currently underway.

Milacemide is another MAO-B inhibitor tested as a potential cognition enhancer in AD patients, but reported trials have been disappointing (Dysken et al. 1992; Cutler et al. 1993).

Neuropeptides

The findings of decreased concentrations of different neuropeptides in postmortem brain samples of AD patients

gave rise to several attempts at treating AD cognitive symptoms with replacement of these agents. Clinical trials with several compounds, including gaba agonists (THIP-4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol), lysine vasopressin (LVP), vasopressin-related peptides (DDAVP-1-desamino-8-D-arginine vasopressin, and DGAVP-desglycinamide arginine vasopressin), somatostatin analog (L363, 586) thyroid releasing hormone (TRH), ACTH components 4-9 and 4-10, ACTH analog HOE 427, and a somatostatin analog (octreotide) have been reported, without evidence of significant effects on cognition (Dornbush et al. 1976; Ferris et al. 1976; Branconier et al. 1979; Dornbush et al. 1981; Tamminga et al. 1982; Tinklenberg et al. 1982; Cutler et al. 1985b; Peabody et al. 1985; Soininen et al. 1985; Mohr 1986; Peabody et al. 1986; Mellow et al. 1989; Wolters et al. 1990; Siegfried 1991; Mouradian et al 1991; Heuser et al. 1993; Miller et al. 1993)

Opiate antagonists

Opiate antagonists were reported to increase learning and memory in animal models (Izquierdo 1980) and then were suggested to be potentially useful for the treatment of cognitive dysfunctions. Trials in AD patients have been conducted with naloxone (Panella et al. 1984; Steiger et al. 1985; Henderson et al. 1989) and naltrexone (Hyman et al. 1985; Serby et al. 1986; Pomara et al. 1988), without indications of substantial benefits for cognition.

Neurotrophic factors

Neurotrophic growth factors (NGF) have been proposed to be relevant in the pathogenesis of AD with a hypothesis that a lack of NGF might be involved in the physiopathological process (Hefti 1983; Hefti and Will 1987). There is some evidence supporting this proposition, with NGF being beneficial for degenerating neurons and inducing hypertrophy in AD neurons (Williams et al. 1986; Haggs et al. 1988; Hoffman et al. 1990; Corsi and Coyle 1991; Hefti and Schneider 1991). Thus, the development of strategies for effective administration of these agents might be a promising approach to the treatment of AD (Phelps et al. 1989; Koliatsos et al. 1993; Lapchak 1993; Olson 1993; Seiger et al. 1993).

Gangliosides are neurotrophic factors with actions on membrane stability, maturation, and plasticity of neurons. Gottfries et al. (1983) initially reported GM1 decreased in AD brains. It has been tested in some trials with intrathecal and most recently with subcutaneous or intramuscular administration, without evidence of significant improvement in cognition (Svennerholm et al. 1990; Ala et al. 1990; Flicker et al. 1994).

Actetyl-L-carnitine

Actetyl-L-carnitine, the acetylester of carnitine, initially was thought to be a cholinergic agent, but was found later to also have antioxidizing and membrane stabilizing actions and to interfere with mitochondrial energy reserve, thus suggested to have neuroprotective properties (Calvani et al. 1992). The trials with this agent in AD patients have yielded some promising results (Bonnavita 1986; Rai et al. 1990), and two recent studies conducted over longer periods of time (6–12 months) found that it could significantly retard the cognitive deterioration (Spagnoli et al. 1991; Sano et al. 1992). These initial findings await confirmation in other controlled trials over longer periods of time.

ACE inhibitors

Angiotensin converting enzyme (ACE) inhibitors were found to facilitate cholinergic transmission and improve cognitive performance in animal models. Angiotensin II decreased acetylcholine release in the rat and human cortex through angiotensin II receptors (Barnes et al. 1989). Angiotensin was found in animal models to negatively affect cognition (Morgan and Routtenberg 1977), and more recently captopril was reported to have a positive effect on cognitive performance in rats (Mondadori and Etienne 1990). The ACE activity was reported to be increased in brains of AD patients compared to normal contorls (Arregui et al. 1982).

Croog et al. (1987) reported that patients treated for hypertension with captopril had subjective and objective benefits in cognitive functions compared to patients treated with other antihypertensive drugs. Nevertheless, a controlled trial with cenarapril in AD patients failed to yield significant beneficial results (Sudilovsky et al. 1993). Thus, there is no clear indication so far that these agents might be effective as cognitive enhancers.

Calcium channel blockers

Calcium channel blockers were reported to decrease vascular tone in animal brains, and to prevent or restrict cerebrovascular spasms and maintain tissue viability by limiting calcium overload (Harris et al. 1982; LeVere et al. 1989).

Nimodipine, a calcium channel blocker, was found to positively affect learning and memory in animal models (Deyo et al. 1989). Three recent multicenter controlled trials in AD patients suggested that this drug may be beneficial, slowing the cognitive decline (Tollefson 1990) and improving measures of behavior and cognition (Ban et al. 1990; Parnetti et al. 1993). These studies await further confirmation.

Xanthine derivatives

Denbufylline, a new xanthine derivative, was tested in a controlled multicenter trial with 96 mild-to-moderate AD and MID (multiinfarct dementia) patients, and significant effects on psychometric measures in both groups were reported (Saletu et al. 1992). Propentofylline was tested in a

recent controlled trial with mild dementia patients, without significant effects on measures of cogniton (Saletu et al. 1990, 1991). Thus, this class of agent awaits further investigation of its potential as a cognition enhancer.

Glutamatergic approaches

Glutamate is a main neurotransmitter in the cortical pyramidal neurons, which is probably the most important area for corticocortical associative connections. A decrease in these connections secondary to the loss of pyramidal neurons could account for part of the symptoms of AD (Francis et al. 1993). Excitatory amino-acid-mediated excitotoxicity can cause lesions similar to the neurofibrillary tangles of AD, and *N*-Methyl-D-Aspartate (NMDA) receptor blockers were found to protect against ischemic and excitatory amino-acid-mediated cortical lesions (Greenamyre and Young 1989; Palmer and Gershon 1990). Glutamatergic augmentation and receptor blockade have been recently proposed for the treatment of AD cognitive deficits (Lawlor and Davis 1992). The glutamatergic blockade could prevent excitatory amino acid toxicity, and enhancement of glutamatergic transmission could enhance intracortical connections and favor learning and memory (Davidson and Stern 1991).

D-cycloserine (D-4-amino-3-isoxazolidone) has been shown to favor learning in animals (Monahan et al. 1989) and to be a partial agonist at the glycine site (Hood et al. 1989; Henderson et al. 1990; Watson et al. 1990). It has been proposed as a possible approach for the treatment of AD (Breitner et al. 1994), but preliminary data is not promising.

Beta-amyloid manipulations

The beta-amyloid peptide is a self-aggregating protein of 42–43 amino acids that has been found to be deposited in brains of AD patients. This deposit might have an important role in the pathogenesis of AD, and it is possible that the secretion of the amyloid protein can produce membrane damage. The amyloid formation can be related to the proteolytic cleavage of the membrane, and it could be a primary event in the pathogenesis of the disease. Thus, therapies that influence the production of beta-amyloid may have a potential for use in the treatment of AD (Caputo and Salama 1989; Davis 1989; Caputo et al. 1992), but this approach is currently very limited because of our lack of knowledge on the role of the beta-amyloid. Progress in the understanding of this process might bring new possibilities for the development of effective therapeutic interventions.

Anti-inflammatory agents

Anti-inflammatory agents have been recently suggested to affect the course of AD (McGeer and Rogers 1992). Breitner et al. (1994) reported a case-control study of AD twins showing a significant negative association between use of anti-inflammatory agents and occurrence of AD, suggesting that these drugs could interfere with the onset of AD symptoms. A recent controlled trial of indomethacin in mild-to-moderate AD patients over a period of 6 months produced a significant decrease in the cognitive decline rate (Rogers et al. 1993). Thus, recent research with these agents in AD patients produced promising results that await further evaluation in larger controlled studies.

Aluminum chelation therapy

Increased concentration of aluminum has been found in the neurofibrillary tangles of AD brains, originating hypotheses that aluminum may have a role in the pathogenesis of this disease (Shore and Wyatt 1983). These ideas suggested that chelation therapy could be useful as a potential agent for treatment of AD (Kruck and McLahan 1989). A 2-year single-blind trial with intramuscular administration of desferrioxamine to a sample of AD patients was reported to produce a 50% decrease in the rate of cognitive decline (McLachlan et al. 1991). This initial data needs to be further explored in larger double-blind trials. Additionally, this drug is frequently related to significant toxicity and needs intramuscular administration. Other options to aluminum chelation therapy need to be developed with less toxicity and preferably for oral administration.

Conclusions

The variety of compounds tested over the past 25 years as potential treatments for AD cognitive deficits have overall failed to produce consistent benefits when tested in large well-controlled trials. The limited knowledge of the pathogenesis of AD is a major factor in this lack of success. As the abnormalities found in AD involve different brain systems the attempts at replacing a single neurotransmitter are probably limited in producing more considerable advances. Levy (1990) has even suggested that until we have a better understanding of the process involved in the pathological abnormalities present in AD it is not realistic to expect definitive treatments for this condition. Nevertheless, although a single transmitter deficit model for the pathogenesis of AD is not defensible, there is recent evidence that some neurotransmitter replacement strategies might be somewhat beneficial for palliation, mainly in the early stages of the disease, as the recent THA studies seem to suggest (Farlow et al. 1992; Knapp et al. 1994). Combination strategies have also been tested with drugs acting in different neural systems, and several regimens tested thus far failed to produce evidence of meaningful benefits.

The more recent data with THA suggests that it might have a palliative effect in AD when administered in higher

doses. In the context of no availability of treatments that would produce substantial benefits, some chance of temporary improvement for the patients who can tolerate appropriate doses of the medication might be an advance in the treatment of this condition. In these higher doses (160 mg/day) THA seems to produce more noticeable benefits on cognition. Nevertheless, these findings still need to be confirmed in other independent trials. The possibility of development of other cholinergic alternatives with fewer side effects than THA is also an area of current investigation (Beermann 1993).

New research developments in the pathogenesis of AD may bring new possibilities of advances in the pharmacotherapy of this disease. The main areas of research currently focus on the study of amyloid deposition, nerve growth factors, the role of the excitatory amino acids in neuronal degeneration, and the related Ca^{2+} accumulation, as well as the search for biological markers for the disease. Eventual biological markers could be used for early detection of the disease, or to identify subgroups of patients that could respond to different treatment strategies. In this particular area the recent developments on the Apolipoprotein E studies (Saunders et al. 1993; Peacock and Fink 1994; Brousseau et al. 1994) hold the promise of significant progress in this field. Another area of investigation is the use of neural grafts for the treatment of this disease (Fisher et al. 1993).

The treatment strategies proposed as being able to interfere with the progression of the disease, particularly anti-inflammatory agents, calcium channel blockers, NGF, phosphatidylserine, acetyl-L-carnitine, L-deprenyl, and neural transplants, are promising research fields that can lead to more meaningful advances in the treatment of AD. Futher basic research in this field, resulting in a better understanding of its physiopathology, the development of more appropriate animal models, as well as more effective strategies for faster preclinical testing of new compounds are factors that will contribute in the search for better strategies for the treatment of this condition.

References

Agnoli A, Fabbrini G, Fioravanti M et al. (1992) CBF and cognitive evaluation of Alzheimer type patients before and after IMAO-B treatment: a pilot study. Eur Neuropsychopharmacol 2:31–35

Ala T, Romero S, Knight F, Feldt K, Frey WH (1990) GM-1 treatment of Alzheimer's disease. A pilot study of safety and efficacy. Arch Neurol 47:1126–1130

Allegro L, Favaretto V, Zilliotto G (1987) Oral phosphatidylserine in elderly patients with cognitive deterioration: an open study. Clin Trials J 24(1):104–108

Amaducci L (1988) Phosphatidylserine in the treatment of Alzheimer's disease: results of a multicenter study. Psychopharmacol Bull 24:130–134

Arnstein AFT, Cai JX, Goldman-Rakic PS (1988) The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side-effects: evidence for alpha-2 receptor subtypes. J Neurosci 8:4287–4296

Arregui A, Perry EK, Rossor M et al. (1982) Angiotensin converting enzyme in Alzheimer's disease: increased activity in caudate nucleus and cortical areas. J Neurochem 38:1490–1492

Ban TA, Morey L, Aguglia E et al. (1990) Nimodipine in the treatment of old age dementias. Prog Neuro Psychopharmacol Biol Psychiatry 14:525–551

Banen DM (1974) An ergot preparation (hydergine) for relief of symptoms of cerebrovascular insufficiency. J Am Geriatr Soc 20:22–24

Banfi S, Dorigotti L (1986) Experimental behavioral studies with oxiracetam on different type of chronic cerebral impairment. Clin Neuropharmacol 9 (Suppl 3):519–526

Barnes JM, Barnes NM, Costall B et al. (1989) Angiotensin II inhibits the release of (^{3}H) acetylcholine from rat entorhinal cortex in vitro. Brain Res 491:136

Beermann B (1993) Side effects of long acting cholinesterase inhibitors. Acta Neurol Scand (Suppl) 149:53–54

Bergman I, Brane G, Gottfries CG et al. (1983) Alaproclate: a pharmacokinetic and biochemical study in patients with dementia of Alzheimer type. Psychopharmacology 80:279–283

Bonnavita E (1986) Study of the efficacy and the stability of L-acetyl-carnitine therapy in the senile brain. Int J Clin Pharmacol Ther Toxicol 23:511–516

Bottini G, Vallar G, Cappa S et al. (1992) Oxiracetam in dementia: a double-blind, placebo-controlled study. Acta Neurol Scand 86:237–241

Branconnier RJ, Cole JO, Gardos G (1979) ACTH-4-10 in the amelioration of neuropsychological symptomatology associated with senile organic brain syndrome. Psychopharmacology 61:161–165

Branconnier RJ, Cole JO, Dessain EC et al. (1983) The therapeutic efficacy of piracetam in Alzheimer's disease: preliminary observations. Psychopharmacol Bull 19:726–730

Breitner JCS, Gau BA, Welsh KA et al. (1994) Inverse association of antiinflammatory treatments and Alzheimer's disease: initial results of a co-twin control study. Neurology 44:227–232

Brinkman SD, Smith RC, Meyer JS et al. (1982) Lecithin and memory training in suspected Alzheimer's disease. J Gerontol 37:4–9

Brousseau T, Legrain S, Berr C et al. (1994) Confirmation of the E4 allele of the apolipoprotein E gene as a risk factor for late-onset Alzheimer's disease. Neurology 44:342–344

Bruno G, Mohr E, Gillespie M et al. (1985) RS-86 therapy of Alzheimer's disease. Arch Neurol 43:659–661

Bruno G, Mohr E, Gillespie M et al. (1986) Muscarinic agonist therapy of Alzheimer's disease. A clinical trial of RS-86. Arch Neurol 43:659–661

Burke WJ; Roccaforte WH, Wengel SP et al. (1993) L-deprenyl in the treatment of mild dementia of the Alzheimer type: results of a 15-month trial. J Am Geriatr Soc 41:1219–1225

Cafarra P, Santamaria V (1987) The effects of phosphatidylserine in patients with mild cognitive decline: an open trial. Clin Trials J 24(1):109–114

Caltagirone C, Gainotti G, Masullo C (1982) Oral administration of chronic physostigmine does not improve cognitive or mnesic performances in Alzheimer's presenile dementia. Int J Neurosci 16:247–249

Caltagirone C, Albanese A, Gainotti G et al. (1983) Acute administration of individual optimal dose of physostigmine fails to improve mnesic performances in Alzheimer's presenile dementia. Int J Neurosci 18:143–147

Calvani M, Carta A, Caruso G et al. (1992) Action of acetyl-L-carnitine in neurodegeneration and Alzheimer's disease. Ann NY Acad Sci 663:483–486

Caputo CB, Salama AI (1989) The amyloid proteins of Alzheimer's disease as potential targets for drug therapy. Neurobiol Aging 10:451–461

Caputo CB, Scott CW, Sobel IR et al. (1992) Therapeutic approaches targeted at the amyloid proteins in Alzheimer's disease. Clin Neuropharmacol 15 (Suppl 1):414A–415A

Chatellier G, Lacomblez L (1990) Tacrine (tetrahydroaminoacridine; THA) and lecithin in senile dementia of the Alzheimer type: a mulitcentre trial. Groupe Francais d'Etude de la Tetrahydroaminoacridine. BMJ 300:495–499

Chouinard G, Annable L, Ross-Chouinard A et al. (1981) A double-blind, placebo-controlled study of piracetam in elderly psychiatric patients. Psychopharmacol Bull 17(1):129

Christie JE, Shering A, Ferguson J et al. (1981) Physostigmine and arecoline: effects of intravenous infusions in Alzheimer presenile dementia. Br J Psychiatry 138:46–50

Claus JJ, Ludwig C, Mohr E et al. (1991) Nootropic drugs in Alzheimer's disease: symptomatic treatment with pramiracetam. Neurology 41:570–574

Corsi P, Coyle JT (1991) Nerve growth factor corrects developmental impairments of basal forebrain cholinergic neurons in the trisomy 16 mouse. Proc Natl Acad Sci USA 88:1793

Croisile B, Trillet M, Fondarai J et al. (1993) Long-term and high-dose piracetam treatment of Alzheimer's disease. Neurology 43:301–305

Croog SH, Sudilovsky A, Levine S et al. (1987) Work performance, absenteeism and antihypertensive medications. J Hypertens 5(Suppl 1):47–54

Crook T, Petrie W, Wells C et al. (1992) Effects of phosphatidylserine in Alzheimer's disease. Psychopharmacol Bull 28:61–66

Crook T, Wilner E, Rothwell A et al. (1992) Noradrenergic intervention in Alzheimer's disease. Psychopharmacol Bull 28(1):67–70

Cutler NR, Haxby J, Kay AD et al. (1985a) Evaluation of zimeldine in Alzheimer's disease. Cognitive and biochemical measures. Arch Neurol 42:744–748

Cutler NR, Haxby JV, Narang PK et al. (1985b) Evaluation of an analogue of somatostatin (L363, 586) in Alzheimer's disease. N Engl J Med 312:725

Cutler NR, Murphy MF, Nash RJ et al. (1990) Clinical safety, tolerance, and plasma levels of the oral anticholinesterase 1,2,3,4-tetrahydro-9-aminoacridin-1-oL-maleate (HP 029) in Alzheimer's disease: preliminary findigns. J Clin Pharmacology 30:556–561

Cutler NR, Fakouhi TD, Smith WT et al. (1993) Evaluation of multiple doses of milacemide in the treatment of senile dementia of the Alzheimer's type. J Geriatr Psychiatry Neurol 6:115–119

Dal-Bianco P, Maly J, Wober C et al. (1991) Galanthamine treatment in Alzheimer's disease. J Neural Transm Suppl 33:59–63

Davidson M, Mohs RC, Hollander E et al. (1987) Lecithin and piracetam in patients with Alzheimer's disease. Biol Psychiatry 22:112–114

Davidson M, Stern RG (1991) The treatment of cognitive impairment in Alzheimer's disease: beyond the cholinergic approach. Psychiatr Clin North Am 14(2):461–482

Davidson M, Zemishlany Z, Mohs RC et al. (1988) 4-Aminopyridine in the treatment of Alzheimer's disease. Biol Psychiatry 23:485–490

Davis KL (1989) Toward a therapeutic strategy based on amyloid precursor protein: unanswered questions. Neurobiol Aging 10 : 475–8

Davis KL, Mohs RC, Davis BM et al. (1980) Human memory and the effects of physostigmine and choline chloride. Psychopharmacol Bull 16(4):27–28

Davis KL, Hollander E, Davidson M et al. (1987) Induction of depression with oxotremorine in Alzheimer's disease patients. Am J Psychiatry 144 :468–471

Davis KL, Thal LJ, Gamzu ER et al. (1992) A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. The Tacrine Collaborative Study Group. N Engl J Med 327:1253–1259

Dehlin O, Hedenrub B, Jansson P et al. (1985) A double-blind comparison of alaproclate and placebo in the treatment of patients with senile dementia. Acta Psychiatr Scand 71:190–196

Delwaide PJ, Gyselynck-Mambourg AM, Hurlet A et al. (1986) Double-blind randomized controlled study of phosphatidylserine in senil-demented patients. Acta Neurol Scand 73:136–140

Deyo RA, Straube KT, Disterhoft JF (1989) Nimodipine facilitates associative learning in aging rabbits. Science 243:809–811

Ditch M, Kelly FJ, Resnick O (1971) An ergot preparation (hydergine) in the treatment of cerebrovascular disorders in the geriatric patient; double-blind study. J Am Geriatr Soc 19: 208–217

Dornbush RL, Volavka J (1976) ACTH 4–10: a study of toxicological and behavioral effects in an aging sample. Neuropsychobiolgy 2:350–360

Dornbush RL, Shapiro B, Freedman AM (1981) Effects of an ACTH short chain neuropeptide in man. Am J Psychiatry 138: 962–964

Dysken MW, Fovall P, Harris CM et al. (1982) Lecithin administration in Alzheimer dementia. Neurology 32:1203–1204

Dysken MW, Katz R, Stallone F et al. (1989) Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study. Neuropsychobiology, 21:141

Dysken MW, Mendels J, LeWitt P et al. (1992) Milacemide: a placebo-controlled study in senile dementia of the Alzheimer type. J Am Geriatr Soc 40:503–506

Eagger SA, Levy R, Sahakian BJ (1991) Tacrine in Alzheimer's disease. Lancet 337:989–992

Eagger S, Morant N, Levy R et al. (1992) Tacrine in Alzheimer's disease. Time course of changes in cognitive function and practice effects. Br J Psychiatry 160:36–40

Ebmeier KP, Hunter R, Curran SM et al. (1992) Effects of a single dose of the acetylcholinesterase inhibitor velnacrine on recognition memory and regional cerebral blood flow in Alzheimer's disease. Psychopharmacology 108:103–109

Engel RR, Satzger W, Gunther W et al. (1992) Double-blind cross-over study of phosphatidylserine vs placebo in patients with early dementia of the Alzheimer type. Eur Neuropsychopharmacol 2:149–155

Etienne P, Gauthier S, Dastoor D et al. (1978a) Lecithin in Alzheimer's disease. Lancet 2:1206

Etienne P, Gauthier S, Johnson G et al. (1978b) Clinical effects of choline in Alzheimer's disease. Lancet 1:508–509

Etienne P, Dastoor D, Gauthier S et al. (1981) Alzheimer's disease: lack of effect of lecithin treatment for 3 months. Neurology 31:1552–1554

Farlow M, Gracon SI, Hershey LA et al. (1992) A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. JAMA 268:2523–2529

Ferris H, Sathananthan G, Gershon S et al. (1976) Cognitive effects of ACTH 4-10 in the elderly. Pharmacol Biochem Behav 5(1): 73–78

Ferris SH. Reisberg B, Crook T et al. (1982) Pharmacological treatment of senile dementia: choline, L-DOPA, piracetam and choline plus piracetam, In: Corkin S, Davis KL, Growdon JH et al. (eds) Alzheimer's disease: a report of progress. Raven Press, New York, pp 475–481

Finali G, Piccirilli M, Oliani C et al. (1991) L-deprenyl therapy improves verbal memory in amnesic Alzheimer patients. Clin Neuropharmacol 14:523–536

Fisher LJ, Raymon HK, Gage FH (1993) Cells engineered to produce acetylcholine:therapeutic potential for Alzheimer's disease. Ann NY Acad Sci 695:278–284

Fitten LJ, Perryman KM, Gross PL et al. (1990) Treatment of Alzheimer's disease with short- and long-term oral THA and lecithin: a double-blind study. Am J Psychiatry 147:239–242

Flicker C, Ferris SH, Kalkstein D et al. (1994) A double-blind, placebo-controlled crossover study of ganglioside GM1 treatment for Alzheimer's disease. Am J Psychiatry 151:126–129

Francis PT, Sims NR, Procter AW et al. (1993) Cortical pyramidal neurone loss may cause glutamatergic hypoactivity and cognitive impairment in Alzheimer's disease: investigative and therapeutic perspectives. J Neurochem 60:1589–1604

Friedman E, Sherman KA, Ferris SH et al. (1981) Clinical response to choline plus piracetam in senile dementia: relation to red-cell choline levels. N Engl J Med 304:1490–1491

Gauthier S, Bouchard R, Lamontagne A et al. (1990) Tetrahydroaminoacridine-lecithin combination treatment in patients with intermediate-stage Alzheimer's disease. Results of a Canadian double-blind, crossover, multicenter study. N Engl J Med 322:1272–1276

Gerin J (1969) Symptomatic treatment of cerebrovascular insufficiency with hydergine. Curr Ther Res 11:539–546

Goodnick PJ, Gershon S (1983) Chemotherapy of cognitive disorders. In: Samuel D et al. (eds) Aging of the brain. Raven Press, New York, pp 349–361

Goodnick P, Gershon S (1984) Chemotherapy of cognitive disorders in geriatric subjects. J Clin Psychiatry 45:196–209

Gottfries CG, Adolfsson R, Aquilonius SM et al. (1983) Biochemical changes in dementia disorders of Alzheimer type (AD/SDAT). Neurobiol Aging 4:261

Gottfries CG, Nyth AL (1991) Effect of citalopram, a selective 5-HT reuptake blocker, in emotionally disturbed patients with dementia. Ann NY Acad Sci 640:276–279

Gottfries CG, Karlsson I, Nyth AL (1992) Treatment of depression in elderly patients with and without dementia disorders. Int Clin Psychopharmacol 6(Suppl 5):55–64

Granata Q, Michelle JD (1987) Phosphatidylserine in elderly patients. Clin Trials J 24(1):99–103

Green RC, Goldstein FC, Auchus AP et al. (1992) Treatment trial of oxiracetam Alzheimer's disease. Arch Neurol 49:1135–1136

Greenamyre JT, Young AB (1989) Excitatory amino acids and Alzheimer's disease. Neurobiol Aging 10:593–602

Growdon JH, Corkin S, Huff FJ et al. (1986) Piracetam combined with lecithin in the treatment of Alzheimer's disease. Neurobiol Aging 7:269–276

Hagg T, Hanthorpe M, Vahlsing HC et al. (1988) Delayed treatment with nerve growth factor reverses the apparent loss of cholinergic neurons after acute brain damage. Exp Neurol 101:303

Harbaugh RE (1987) Intracerebroventricular cholinergic drug administration in Alzheimer's disease: preliminary results of a double-blind study. J Neural Transm Suppl 24:271–277

Harbaugh RE, Reeder TM, Senter HJ et al. (1989) Intracerebroventricular bethanechol chloride infusion in Alzheimer's disease. Results of a collaborative double-blind study. J Neurosurg 71:481–486

Harell LE, Callaway Rl, Morere D et al. (1990) The effect of long-term physostigmine administration in Alzheimer's disease. Neurology 40:1350–1354

Harris RJ, Branston WM, Symon L et al. (1982) Cerebral ischemia and calcium. Stroke 13:759–766

Hefti F (1983) Alzheimer's disease caused by a lack of nerve growth factor? Ann Neurol 13:109–110

Hefti F, Schneider LS (1991) Nerve growth factor and Alzheimer's disease. Clin Neuropharmacol 14 (Suppl 1):S62–S76

Hefti F, Will B (1987) Nerve growth factor is a neurotrophic factor for forebrain cholinergic neurons; implications for Alzheimer's disease. J Neural Transm Suppl 24:309–315

Henderson VW, Roberts E, Wimer C et al. (1989) Multicenter trial of naloxone in Alzheimer's disease. Ann Neurol 25:404–406

Henderson G, Johnson JW, Ascher P (1990) Competitive antagonists and partial agonist at the glycine modulatory site of the mouse *N*-methyl-D-aspartate receptor. J Physiol 430:189–212

Heuser I, Heuser-Link M, Gotthardt U et al. (1993) Behavioral effects of a synthetic corticotropin 4–9 analog in patients with depression and patients with Alzheimer's disease. J Clin Psychopharmacol 13:171–174

Heyman A., Schmechel D, Wilkinson W et al. (1987) Failure of long term high-dose lecithin to retard progression of early-onset Alzheimer's disease. J Neural Transm Suppl 24:279–286

Hoffman D, Wahlber L, Aebischer P (1990) NGF released from a polymer matrix prevents loss of ChAT expression in basal forebrain neurons following a fimbria-fornix lesion. Soc Neurosci (Abstr) 16:477

Hollander E, Davidson M, Mohs RC et al. (1987) RS 86 in the treatment of Alzheimer's disease: cognitive and biological effects. Biol Psychiatry 22:1067–1078

Hood WF, Compton RP, Monahan JB et al. (1989) D-Cycloserine: a ligand for the *N*-methyl-D-aspartate coupled glycine receptor has partial agonist characteristics. Neurosci Lett 98:91–95

Hughes J, Williams J, Currier A (1975) An ergot alkaloid preparation (hydergine) in the treatment of dementia: critical review of literature. J Am Geriat Soc 24:490–497

Hyman BT, Eslinger PJ, Damasio AR (1985) Effect of naltrexone on senile dementia of the Alzheimer type. J Neurol Neurosurg Psychiatry 48:1169–1171

Itil TM, Gopi N, Menon GN (1982) The effects of oxiracetam (ISF 2522) in patients with organic brain syndrome (a double-blind controlled study with piracetam). Drug Dev Res 2:447–461

Itil TM, Menon GN, Songar A et al. (1986) CNS pharmacology and clinical therapeutical effects of oxiracetam. Clin Neuropharmacol 9 (Suppl 3):670–672

Izquierdo I (1980) Effect of beta-endorphin and naloxone on acquisition, memory and retrieval of shuttle avoidance and habituation learning in rats. Psychopharmacology 69:111

Jellinger K, Flament H, Reiderer P et al. (1980) Levodopa in the treatment of (pre)senile dementia. Ageing Dev 14:253–264

Jenike MA, Albert M, Baer L et al. (1990a) Oral physostigmine as treatment for primary degenerative dementia: a double-blind placebo-controlled inpatient trial. J Geriat Psychiat Neurol 3:13–16

Jenike MA, Albert MS, Heller H et al. (1990b) Oral physostigmine treatment for patients with presenile and senile dementia of the Alzheimer's type: a double-blind placebo-controlled trial. J Clin Psychiatry 51:3–7

Jenike MA, Albert MS, Baer L (1990c) Oral physostigmine as treatment for dementia ot the Alzheimer's type: a long-term outpatient trial. Alzheimer Dis Assoc Disord 4:226–231

Jennings WG (1972) An ergot alkaliod preparation (hydergine) versus placebo for the treatment of symptoms of cerebrovascular insufficiency: double-blind study. J Am Geriat Soc 20:407–412

Jotkowitz S (1983) Lack of clinical efficacy of chronic oral physostigmine in Alzheimer's disease. Ann Neurol 14:690–691

Knapp MJ, Knopman DS, Solomon PR et al. (1994) A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. JAMA 271:985–991

Koliatsos VE, Price DL, Clatterbuck RE et al. (1993) Neurotrophic strategies for treating Alzheimer's disease: lessons from basic neurobiology and animal models. Ann NY Acad Sci 695:292–299

Kruck TP, McLachlan DR (1989) Aluminum as a pathogenic factor in senile dementia of the Alzheimer type: ion-specific chelation. Prog Clin Biol Res 317:1155–1167

Lapchak PA (1993) Nerve growth factor pharmacology: application to the treatment of cholinergic neurodegeneration in Alzheimer's disease. Exp Neurol 124:16–20

Lawlor BA, Davis KL (1992) Does modulation of glutamatergic function represent a viable therapeutic strategy in Alzheimer's disease? Biol Psychiatry 31:337–350

Lawlor BA, Sunderland T, Mellow AM et al. (1991) A pilot placebo-controlled study of chronic m-CPP administration in Alzheimer's disease. Biol Psychiatry 30:140–144

LeVere TE, Brugler T, Sandin M et al. (1989) Recovery of function after brain damage: facilitation by the calcium entry blocker nimodipine. Behav Neurosci 103(3):561–565

Levy R (1990) Are drugs targeted at Alzheimer's disease useful? 1. Useful for what? BMJ 300:1131–1132

Maina G, Fiori L, Torta R et al. (1989) Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study. Neuropsychobiology 21:141–145

Mangoni A, Grassi MP, Frattola L et al. (1991) Effects of a MAO-B inhibitor in the treatment of Alzheimer disease. Eur Neurol 31:100–107

McConnachie RW (1973) A clinical trial comparing "hydergine" with placebo in the treatment of cerebrovascular insufficiency in elderly patients. Curr Med Res Opin 1:463–468

McDonald R (1979) Hydergine: a review of 26 clinical studies. Neuropsychopharmacology 12:407–422

McGeer PL, Rogers J (1992) Anti-inflammatory agents as a therapeutic approach to Alzheimer's disease. Neurology 42:447–449

McLachlan DRC, Dalton AJ, Kruck TPA et al. (1991) Intramuscular desferrioxamine in patients with Alzheimer's disease. Lancet 337:1304–1308

Mellow AM, Sunderland T, Cohen RM et al. (1989) Acute effects of high-dose thyrotropin releasing hormone infusions in Alzheimer's disease. Psychopharmacology 98:403–407

Mihara M, Ohnishi A, Tomono Y et al. (1993) Pharmacokinetics of E2020, a new compound for Alzheimer's disease, in healthy male volunteers. Int J Clin Pharmacol Ther Toxicol 31:223–229

Miller TP, Fong K, Tinklenberg JR (1993) An ACTH-4-9 analog (Org 2766) and cognitive performance: high-dose efficacy and safety in dementia of the Alzheimer's type. Biol Psychiatry 33:307–309

Minthon L, Gustafson L, Dalfelt G et al. (1993) Oral tetrahydroaminoacridine treatment of Alzheimer's disease evaluated clinically and by regional cerebral blood flow and EEG. Dementia 4:32–42

Mitchel A, Drachman DA, O'Donnel B et al. (1986) Oral physostigmine in Alzheimer's disease. Neurology 36 (Suppl 1):295

Mizuke Y, Yamada M, Kato I et al. (1984) Effects of aniracetam, a nootropic drug, in senile dementia – a preliminary report. Kurume Med J 31:135–143

Moglia A, Sinforiani E, Zandrini C et al. (1986) Activity of oxiracetam in patients with organic brain syndrome: a neuropsychological study. Clin Neuropharmacol 9(Suppl 3):573–578

Mohr E, Bruno G, Foster N et al. (1986) GABA-agonist therapy for Alzheimer's disease. Clin Neuropharmacol 9(3):257–263

Mohr E, Schlegel J, Fabbrine G et al. (1989) Clonidine treatment of Alzheimer's disease. Arch Neurol 46:376–378

Molloy DW, Cape RD (1989) Acute effects of oral pyridostigmine on memory and cognitive function in SDAT. Neurobiol Aging 10:199–204

Molloy DW, Guyatt GH, Wilson DB et al. (1991) Effect of tetrahydroaminoacridine on cognition, function and bahviour in Alzheimer's disease. Can Med Assoc J 144:29–34

Monahan JB, Handelmann GE, Hood WF et al. (1989) D-Cycloserine, a positive modulator of the *N*-methyl-D-aspartate receptor, enhances performance of learning task in rats. Pharmacol Biochem Behav 34:649–653

Mondadori C, Etienne P (1990) Nootropic effects of ACE inhibitors in mice. Psychopharmacology 100:301–307

Morgan JM, Routtenberg A (1977) Angiotensin injected into the neostriatum after learning disrupts retention performance. Science 196:87–89

Mouradian MM, Mohr E, Williams AJ et al. (1988) No response to high-dose muscarinic agonist therapy in Alzheimer's disease. Neurology 38:606–608

Mouradian MM, Blin J, Giuffra M et al. (1991) Somatostatin replacement therapy for Alzheimer's dementia. Ann Neurol 30:610–613

Murphy MF, Hardiman ST, Nash RJ et al. (1991) Evaluation of HP 029 (velnacrine maleate) in Alzheimer's disease. Ann NY Acad Sci 640:253–262

Newhouse PA, Sunderland T, Tariot PN et al. (1988) Intravenous nicotine in Alzheimer's disease: a pilot study. Psychopharmacology 95:171–175

Nyth AL, Gottfries CG (1990) The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study. Br J Psychiatry 157:894–901

Ohnishi A, Mihara M, Kamakura H et al. (1993) Comparison of the pharmacokinetics of E2020, a new compound for Alzheimer's disease, in healthy young and elderly subjects. J Clin Pharmacology 33:1086–1091

Olafsson K, Jorgensen S, Jensen HV et al. (1992) Fluvoxamine in the treatment of demented elderly patients: a double-blind, placebo-controlled study. Acta Psychiatr Scand 85:453–456

Olson L (1993) NGF and the treatment of Alzheimer's disease. Exp Neurol 124:5–15

Palmer AM, Gershon S (1990) Is the neuronal basis of Alzheimer's disease cholinergic or glutamatergic? FASEB J 4:2745–2752

Palmieri G, Palmieri R, Inzoli MR et al. (1987) Double-blind controlled trial of phosphatidylserine in patients with senile mental deterioration. Clin Trials J 24(1):73–83

Panella JJ Jr, Blass JP (1984) Lack of clinical benefit from naloxone in a dementia day hospital. Ann Neurol 15:308

Parnetti L, Mecocci P, Petrini A et al. (1989) Neuropsychological results of long-term therapy with oxiracetam in patients with dementia of Alzheimer type and multi-infarct dementia in comparison with a control group. Neuropsychobiology 22:97–100

Parnetti L, Senin U, Carosi M et al. (1993) Mental deterioration in old age: results of two multicenter, clinical trials with nimodipine. Clin Ther 15(2):394–406

Peabody CA, Thiemann S, Pigache R et al. (1985) Desglycinamide-9-arginine-8-vasopressin (DGAVP, Organon 5667) in patients with dementia. Neurobiol Aging 6:95–100

Peabody CA, Davies H, Berger PA et al. (1986) Desamino-D-arginine-vasopressin (DDAVP) in Alzheimer's disease. Neurobiol Aging 7:301–303

Peabody CA, Deblois TE, Tinklenberg JR (1986) Thyrotropin-releasing hormone (TRH) and Alzheimer's disease. Am J Psychiatry 143:262–263

Peacock ML, Fink JK (1994) ApoE E4 allelic association with Alzheimer's disease: independent confirmation using denaturing gradient gel electrophoresis. Neurology 44:339–341

Penn RD, Martin EM, Wilson RS et al. (1988) Intraventricular bethanechol infusion for Alzheimer's disease: results of double-blind and escalating-dose trials. Neurology 38:219–222

Phelps CH, Gage FH, Growdon JH et al. (1989) Potential use of nerve growth factor to treat Alzheimer's disease. Neurobiol Aging 10:205–207

Piccinin GL, Finali G, Piccirilli M (1990) Neuropsychological effects of L-deprenyl in Alzheimer's type dementia. Clin Neuropharmacol 13:147–163

Pomara N, Domino EF, Yoon H et al. (1983) Failure of single-dose lecithin to alter aspects of central cholinergic acitivity in Alzheimer's disease. J Clin Psychiatry 44:293–295

Pomara N, Block R, Moore N et al. (1984) Combined piracetam and cholinergic precursor treatment of primary degenerative dementia. IRCS Med Sci 12:388–389

Pomara N, Stanley M, Rhiew HB et al. (1988) Loss of the cortisol response to naltrexone in Alzheimer's disease. Biol Psychiatry 23:726

Puca FM, Savarese MA, Mirervine MG (1987) Exploratory trial of phosphatidylserine efficacy in mildly demented patients. Clin Trials J 24(1):94–98

Puri SK, Hsu RS, Ho I et al. (1989) Single dose safety, tolerance, and pharmacokinetics of HP 029 in healthy young men: a potential Alzheimer agent. J Clin Pharmacol 29:278–284

Puri Sk, Ho I, Hsu R et al. (1990) Multiple dose pharmacokinetics, safety, and tolerance of velnacrine (HP 029) in healthy elderly subjects: a potential therapeutic agent for Alzheimer's disease. J Clin Pharmacol 30:948–955

Rai G, Wright G, Scott L et al. (1990) Double-blind, placebo cotrolled study of acetyl-L-carnitine in patients with Alzheimer's dementia. Curr Med Res Opin 11:638–647

Rainer M, Mark TH, Haushofer A (1989) Galanthaminun hydrobromicum in treatment of senile dementia (Alzheimer's disease). Presented at the Fourth World Conference on Clinical Pharmacology and Therapeutics. Berlin (West), July 28–30

Rao DB, Norris JR (1972) A double-blind investigation of hydergine in the treatment of cerebrovascular insufficiency in the elderly. Johns Hopkins Med J 130:317–324

Read SL, Frazee J, Shapira J et al. (1990) Intracerebroventricular bethanechol for Alzheimer's disease. Variable dose-related responses. Arch Neurol 47:1025–1030

Rehman SA (1973) Two trials comparing "hydergine" with placebo in the treatment of patients suffering from cerebrovascular insufficieny. Curr Med Res Opin 1:456–462

Rogers J, Kirby LC, Hempelman SR et al. (1993) Clinical trial of indomethacin in Alzheimer's disease. Neurology 43:1609–1611

Rosenberg DR, Wright BA, Gershon S (1991) Cognitive enhancing agents for the treatment of senile dementia of the Alzheimer type. Drugs Today 26(7):449–471

Sahakian B, Jones G, Levy R et al. (1989) The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type. Br J Psychiatry 154:797–800

Saletu B, Moller HJ, Grunberger J et al. (1990–91) Propentofylline in adult-onset cognitive disorders: double-blind, placebo-controlled, clinical, psychometric and brain mapping studies. Neuropsychobiology 24:173–184

Saletu B, Anderer P, Fischhof PK et al. (1992) EEG mapping and psychopharmacological studies with denbufylline in SDAT and MID. Biol Psychiatry 32:668–681

Sano M, Bell K, Cote L et al. (1992) Double-blind parallel design pilot study of acetyllevocarnitine in patients with Alzheimer's disease. Arch Neurol 49:1137–1141

Satzger W, Bove D, Gerko S et al. (1988) Preliminary results of a six-month double-blind crossover study of phosphatidylserine vs placebo in patients with early senile dementia of Alzheimer's type. Psychopharmacology 96:301

Saunders AM, Strittmatter WJ, Schmechel D et al. (1993) Association of apolipoprotein E allele E4 with late-onset familial and sporadic Alzheimer's disease. Neurology 43:1467–1472

Schlegel J, Mohr E, Williams J et al. (1989) Guanfacine treatment of Alzheimer's disease. Clin Neuropharmacol 12:124–128

Schmechel D, Schmitt F, Horner J et al. (1984) Lack of effect of oral physostigmine and lecithin in patients with probable Alzheimer's disease. Neurology 34 (Suppl 1):280

Seiger a, Nordberg A, von Holst H et al. (1993) Intracranial infusion of purified nerve growth factor to an Alzheimer patient: the first attempt of a possible future treatment strategy. Behav Brain Res 57:255–261

Senin U, Abate G, Fieschi C et al. (1991) Aniracetam (Ro 13-5057) in the treatment of senile dementia of Alzheimer type (SDAT): results of a placebo controlled multicentre clinical study. Eur Neuropsychopharmacol 1:511–517

Serby M, Resnick R, Jordan B et al. (1986) Naltrexone and Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiat 10:587

Shore D, Wyatt RJ (1983) Aluminum and Alzheimer's disease. J Nerv Ment Disord 171:553–558

Siegfried KR (1991) First clinical impressions with an ACTH analog (HOE 427) in the treatment of Alzheimer's disease. Ann NY Acad Sci 640:280–283

Sinforiani E, Agostinis C, Merlo P et al. (1987) Cognitive decline in aging brain: therapeutic approach with phosphatidylserine. Clin Trials J 24(1):115–124

Sitaram N, Weingartner H, Gillin JC (1978) Human serial learning: enhancement with arecoline and impairment with scopolamine correlated with performance on placebo. Science 201: 274–276

Smith RC, Vroulis G, Johnson R et al. (1984) Comparison of therapeutic response to long-term treatment with lecithin versus piracetam plus lecithin in patients with Alzheimer's disease. Psychopharmacol Bull 20:542–545

Soininen H, Koskinen T, Helkala EL et al. (1985) Treatment of Alzheimer's disease with a synthetic ACTH 4–9 analog. Neurology 35:1348–1351

Sourander LB, Portin R, Molsa P et al. (1987) Senile dementia of the Alzheimer type treated with aniracetam: a new nootropic agent. Psychopharmacology 91:90–95

Spagnoli A, Lucca U, Menasce G et al. (1991) Long-term acetyl-L-carnitine treatment in Alzheimer's disease. Neurology 41: 1726–1732

Stegnick A (1972) The clinical use of piracetam, a new nootropic drug, Arzneimforsch (Drug Res) 22:975–977

Steiger WA, Mendelson M, Jenkins T et al. (1985) Effects of naloxone in treatment of senile dementia. J Am Geriat Soc 33(2): 155

Stern Y, Sano M, Mayeux R (1987) Effects of oral physostigmine in Alzheimer's disease. Ann Neurol 22:306–310

Stern Y, Sano M, Mayeux R (1988) Long-term administration of oral physostigmine in Alzheimer's disease. Neurology 38: 1837–1841

Sudilovsky A, Cutler NR, Sramek JJ et al. (1993) A pilot clinical trial of the angiotensin-converting enzyme inhibitor ceranapril in Alzheimer disease. Alzheimer Dis Assoc Disord 7:105–111

Svennerholm L, Gottfries CG, Blennow K et al. (1990) Parenteral administration of GM1 ganglioside to presenile Alzheimer patients. Acta Neurol Scand 81:48–53

Taminga CA, Durso R, Fedio P et al. (1982) Vasopressin studies in Alzheimer's disease. Psychopharmacol Bull 18:48

Tariot PN, Cohen RM, Sunderland T et al. (1987) L-deprenyl in Alzheimer's disease. Preliminary evidence for behavioral change with monoamine oxidase B inhibition. Arch Gen Psychiatry 44:427–433

Tariot PN, Sunderland T, Weingartner H et al. (1987) Cognitive effects of L-deprenyl in Alzheimer's disease. Psychopharmacology 91:489–495

Tariot PN, Cohen RM, Welkowitz JA et al. (1988) Multiple-dose arecoline infusions in Alzheimer's disease. Arch Gen Psychiatry 45:901–905

Thal LJ, Rosen W, Sharpless NS et al. (1981) Choline chloride fails to improve cognition of Alzheimer's disease. Neurobiol Aging 2:205–208

Thibault A (1974) A double-blind evaluation of "hydergine" and placebo in the treatment of patients with organic brain syndrome and cerebral arteriosclerosis in a nursing home. Curr Med Res Opin 2:482–487

Thompson TL, Filley CM , Mitchell WD et al. (1990) Lack of efficacy of hydergine in patients with Alzheimer's disease.N Engl J Med 323:445–448

Tinklenberg JR, Pigache R, Berger PA et al. (1982) Desglycinamide-9-arginine-8-vasopressin (DGAVP, Organon 5667) in cognitively impaired patients. Psychopharmacol Bull 18:202

Tollefson GD (1990) Short-term effects of the calcium channel blocker nimodipine (Bay-e-9736) in the management of primary degenerative dementia. Biol Psychiatry 27:1133–1142

Triboletti F, Ferri H (1969) Hydergine for treatment of symptoms of cerebrovascular insufficiency. Curr Ther Res 11:609–620

Villardita C, Parini J, Grioli S et al. (1986) Clinical and neuropsychological investigations on oxiracetam in patients with mild to moderate dementia. Clin Neuropharmacol 9(Suppl 14):301–303

Villardita C, Grioli S, Salmeri G et al. (1987) Multicenter clinical trial of brain phosphatidylserine in elderly patients with intellectual deterioration. Clin Trials J 24(1):84–93

Villardita C, Grioli S, Lomeo C et al. (1992) Clinical studies with oxiracetam in patients with dementia of Alzheimer type and multi-infarct dementia of mild to moderate degree. Neuropsychobiology 25:24–28

Vogel-Scibilia S, Gershon S (1989) An update on cognitive enhancers for the elderly. New Trends in Clin Neuropharmacol 3(4):207–216

Watkins PB, Zimmerman HJ, Knapp MJ et al. (1994) Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA 271:992–998

Watson GB, Bolanowski MA, Baganoff MP et al. (1990) D-Cycloserine acts as partial agonist in the glycine modulatory site of the NMDA receptor expressed in *Xenopus oocytes*. Brain Res 510:158–160

Weinstein HC, Teunisse S, van Gool WA (1991) Terahydroaminoacridine and lecithin in the treatment of Alzheimer's disease. Effect on cognition, functioning in daily life, behavioural disturbances and burden experienced by the carriers. J Neurol 238: 34–38

Wettstein A (1983) No effect from double-blind trial of physostigmine and lecithin in Alzheimer disease. Ann Neurol 13:210–212

Wettstein A, Spiegel R (1984) Clinical trials with the cholinergic drug RS 86 in Alzheimer's disease (AD) and senile dementia of the Alzheimer type (SDAT). Psychopharmacology 84:572–573

Williams LR, Varon S, Peterson GM et al. (1986) Continuous infusion of nerve growth factor prevents vasal forebrain neuronal death after fimbria fornix transection. Proc Natl Acad Sci USA 83:9231–9235

Winker MA (1994) Tacrine for Alzheimer's disease. Which patient, what dose? JAMA 271:1023–1024

Wolters EC, Riekkinen P, Lowenthal A et al. (1990) DGAVP (Org 5667) in early Alzheimer's disease patients: an international double-blind, placebo-controlled, multicenter trial. Neurology 40:1099–1101