Alzheimer disease (AD) involves neuronal degeneration with impaired cholinergic transmission in the cerebral cortex and hippocampus in areas of the brain particularly associated with memory and higher intellectual functioning. Other neurotransmitter deficits also occur, but the mechanisms underlying the widespread impairment of synaptic functions remain uncertain. Research on the molecular basis of AD has elucidated a pathogenic pathway from which a range of rational pharmacological interventions has emerged. Although at least 3 cholinesterase inhibitors (tacrine hydrochloride, donepezil, and rivastigmine tartrate) are now available and provide patients with modest relief, the most promising strategy involves approaches to retarding, halting, or preventing the formation or accumulation of β-amyloid (Aβ) plaques. Estrogen is believed to have antioxidant or other anti-Aβ effects, as hormonal replacement therapy in women with menopause is associated with a reduced risk or delayed onset of AD. The association between nonsteroidal anti-inflammatory drugs and a reduced risk of AD has not yet been confirmed, but these agents may protect the brain from the reactive glial and microglial responses associated with Aβ deposition. Also, recent studies suggested that antioxidants, such as vitamin E taken alone or in combination with selegiline hydrochloride, can delay the progression of AD. Despite these encouraging results, no current therapy has been shown to halt or reverse the underlying disease process. The proof of the principle that anti-Aβ drugs will work in the transgenic models of AD is eagerly awaited with the expectation that they will eventually prove successful in humans.

The accumulation of β-amyloid (Aβ) plaques is the pathognomonic feature of Alzheimer disease (AD). How does this accumulation relate to the neuronal degeneration that manifests as a progressive cognitive impairment with widespread neurological and neuropsychiatric disturbances? The slowly emerging answer is that Aβ induces a variety of neurotoxic phenomena, including reactive oxygen species. However, to date only the secondary degenerative effects have been amenable to therapy, as seen in the beneficial effects of cholinergic-boosting strategies. In addition to the 3 licensed compounds (tacrine hydrochloride, donepezil, and rivastigmine tartrate), there are many drugs awaiting approval or undergoing phase 3 trials (Table 1). While drugs specifically targeting the β-amylloidogenic pathway only now are beginning to emerge in a preclinical setting, most other drugs are directed at the cholinergic system. There are many psychotropic agents available to treat the behavioral manifestations of AD, including antipsychotic, agitation-reducing, antidepressant, anxiolytic, and sedative-hypnotic drugs. Interventions in AD include treatment of the underlying disease process and amelioration of neurochemical deficits produced by the cellular changes. This review discusses current perspectives in the pharmacotherapy of AD.
of AD and examines how the different disciplinary approaches are being incorporated into clinical research for effective drug treatments. Attention is drawn to new compounds with novel mechanisms of action that could have a tremendous impact in the future treatment of AD.

MODULATION OF THE CHOLINERGIC SYSTEM

Different strategies have been developed to boost the cholinergic system, including increased acetylcholine production with cholinergic precursors (choline and lecithin), prevention of synaptic acetylcholine destruction with acetylcholinesterase (AChE) inhibitors, such as tacrine (9-amino-1,2,3,4-tetrahydroacridine, Cognex; Parke-Davis, Morris Plains, NJ), donepezil (developed under the code E2020, Arixcept; Pfizer Inc, New York, NY), rivastigmine (developed under the code SDZ ENA 713, Exelon; Novartis Pharmaceuticals, East Hanover, NJ), physostigmine salicylate, and galantamine, or direct stimulation of postsynaptic muscarinic receptors with receptor agonists. However, tacrine and donepezil are the only drugs that have been approved by the Food and Drug Administration (FDA).

Evidence now indicates that some AChE inhibitors also may provide neuroprotective effects, perhaps through the activation of nicotinic receptors, and may even enhance neurotrophic regeneration. Other possible actions include the effect of cholinergic agonists on the processing and secretion of the amyloid precursor protein and Aβ.1,2

Tacrine

After the initial positive and overly optimistic reports in 1986 on the efficacy of tacrine, it was subsequently noted to be an even stronger inhibitor of the butyrylcholinesterase family of enzymes. More recently, apart from AChE inhibition, tacrine has been shown to possess a much broader pharmacological profile, such as blockage of potassium channels, inhibition of the neuronal monoamine uptake processes, and inhibition of monoamine oxidase.3 The heightened efficacy of tacrine in alleviating some of the behavioral symptoms of AD compared with other AChE inhibitors might be related to these other pharmacological actions. The purported cognitive-enhancing effects of tacrine and the AChE inhibitors are often difficult to disentangle from their nonspecific arousal and behavioral effects, which can be expected from all classes of cholinergic stimulants. Serious adverse effects of tacrine, including hepatotoxic effects,4 have weakened its position as a drug of choice.

Tacrine has a mean bioavailability of 17%, with interindividual variability from 2% to 36% (Table 2).10 This low bioavailability is thought to be secondary to large presystemic clearance. Food appears to decrease the rate but not the extent of absorption. Tacrine hydrochloride is rapidly metabolized, with mean half-lives of 1.6 and 2.1 hours after single doses of 25 mg and 50 mg, respectively, which must be taken 4 times a day. Tacrine metabolism appears to be mediated through cytochrome P-450 1A2 isoenzyme. Clinical dosages of 80 to 160 mg/d usually achieve approximately 30% AChE inhibition.

Donepezil

In November 1996, donepezil (a piperidine-based AChE inhibitor with specificity for AChE) was approved by the FDA as a symptomatic therapy for mild to moderate AD. The bioavailability of donepezil is approximately 100%, with peak plasma concentrations occurring between 2 and 4 hours after an oral dose. Food appears to have no significant effect on the drug absorption. Donepezil has a mean elimination half-life of 70 hours, with significant interindividual variation; a daily dose is recommended. Donepezil is bound highly (93%-96%) to the proteins albumin and α1-acid glycoprotein. The drug is metabolized in the liver by CYP2D6 and CYP3A4/5 and by glucuronidation. A dosage of 5 mg/d yields steady-state AChE inhibition of approximately 64% as determined by cholinesterase inhibition in human red blood cell samples.10 In a 30-week phase 3 clinical trial of donepezil, both the 5- and 10-mg treatment groups had ADAS-Cog (Alzheimer’s Disease Assessment Scale-Cognitive subscale) scores superior to the placebo group throughout the 6-month trial. Moreover, more than 80% of the patients in the treatment group showed either improvement or no decline during the 6-month trial. The long-term efficacy of donepezil treatment has not been evaluated yet. However, the efficacy for up to 2 years was evaluated in patients who completed the 30-week phase 3 trial and who underwent a long-term, open-label study with donepezil. For a mean of 40 weeks, patients maintained performance levels better than their original baseline scores. The ADAS-Cog scores collected for more than 2 years suggested that patients receiving donepezil maintained the same magnitude of benefit as in the beginning of the study, indicating that long-term use of donepezil may be beneficial.11

Table 1. Relevant Drugs for Alzheimer Disease Awaiting Approval or Undergoing Phase 3 Trials*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichlorfon</td>
<td>AChE inhibitor</td>
</tr>
<tr>
<td>Physostigmine salicylate</td>
<td>AChE inhibitor</td>
</tr>
<tr>
<td>Idebenone</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Nebracetam</td>
<td>m1 Muscarinic receptor agonist</td>
</tr>
<tr>
<td>Neffracetam</td>
<td>m1 Muscarinic receptor agonist</td>
</tr>
<tr>
<td>Propentofylline</td>
<td>ACh agonist, calcium channel opener, and phosphodiesterase inhibitor</td>
</tr>
</tbody>
</table>

* AChE indicates acetylcholinesterase; ACh, acetylcholine; and GABA, γ-aminobutyric acid.

Table 2. Individual variability from 2% to 36% (Table 2).

<table>
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<td>ACh agonist, calcium channel opener, and phosphodiesterase inhibitor</td>
</tr>
</tbody>
</table>
Rivastigmine

Rivastigmine is a neuronal selective AChE inhibitor that is still under clinical investigation. Results of phase 2 trials showed that patients with AD tolerated up to 12 mg/d. Adverse effects did not include hepatotoxic effects. The results of a meta-analysis of 3 phase 3 trials demonstrated significant beneficial effects on measures of cognition using the ADAS-Cog scale, global functioning, and activities of daily living. The Swiss regulatory authority approved rivastigmine in August 1997 for the treatment of patients with mild to moderate AD. In May 1998, rivastigmine received marketing approval from the European Medicine Evaluation Agency, London, England, and is currently awaiting approval from the FDA.

Metrifonate

Metrifonate is an AChE inhibitor that acts as a prodrug for the direct, long-acting inhibitor DDVP (2,2-dimethyl-dichlorovinyl phosphate). In blood samples, metrifonate has a mean half-life of 2.3 hours and DDVP has a half-life of 3.8 hours. Thus, prolonged elevation of acetylcholine levels can be achieved. Estimates of the half-life for cholinesterase recovery vary depending on study methods, with a mean ± SD of 26.6 ± 15.2 hours. Recently, after some patients in clinical trials experienced muscle weakness, the request for approval for metrifonate in Europe was withdrawn.

Galantamine

Galantamine, a naturally occurring amaryllidacea alkaloid, is a long-acting, selective, reversible, and competitive AChE inhibitor. Patients with AD who took galantamine had improved performance on memory tests, and it was well tolerated. Galantamine use was approved in Austria.

Nicotinic Cholinergic Strategies

It has been suggested that there is an inverse relationship between smoking and AD. Dose dependency has not yet been shown for this protective action. Subcutaneous administration of nicotine has been claimed to improve attention and information processing in patients with AD. Interestingly, these effects were more evident than memory improvement. Further clinical investigations are clearly required to confirm these results.

MODULATION OF OTHER NEUROTRANSMITTER SYSTEMS

There is a growing body of evidence that disturbances of glutamatergic neurotransmission may underlie a mechanism of neurotoxic excitatory amino acids contributing to cognitive deficits in patients with AD. Age-related changes in NMDA (N-methyl d-aspartate) receptors have been found in cortical areas and in the hippocampus in

Table 2. Pharmacokinetic and Pharmacodynamic Profiles of Some Drugs Used or in Clinical Development for the Treatment of Alzheimer Disease*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Half-life, h</th>
<th>Starting Oral Dosage</th>
<th>Bioavailability, %</th>
<th>Protein Binding, %</th>
<th>Food Effect</th>
<th>Common Adverse Effects Leading to Treatment Discontinuation</th>
<th>Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrine hydrochloride</td>
<td>Cholinesterase inhibition</td>
<td>1.60-2.14</td>
<td>10 mg, 4 times a day</td>
<td>2.4-36.0</td>
<td>75</td>
<td>Decreases effectiveness by 30%-40%, take 1 h before meals</td>
<td>Nausea, vomiting, increased salivation, sweating, lacrimation, and elevated transaminase levels</td>
<td>Registered with the FDA (since 1993) and the EMEA</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Cholinesterase inhibition</td>
<td>50-70</td>
<td>5 mg/d</td>
<td>100</td>
<td>93-96</td>
<td>None</td>
<td>Nausea, diarrhea, insomnia, and vomiting</td>
<td>Registered with the FDA (since 1996) and the EMEA</td>
</tr>
<tr>
<td>Rivastigmine tartrate</td>
<td>Cholinesterase inhibition</td>
<td>NA</td>
<td>2 mg/d, slow titration to 6-12 mg, 2 or 3 times a day</td>
<td>Approximately 35</td>
<td>NA</td>
<td>NA</td>
<td>Nausea, vomiting, diarrhea, dizziness, and headaches were evident at high doses</td>
<td>Awaiting FDA approval and approved by the EMEA (May 1998)</td>
</tr>
<tr>
<td>Trichlorfon</td>
<td>Cholinesterase inhibition</td>
<td>2.3</td>
<td>Daily, possibility of weekly</td>
<td>Low</td>
<td>NA</td>
<td>NA</td>
<td>Gastrointestinal disturbances</td>
<td>Filed with the FDA (November 1997) and the EMEA (October 1997)</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Cholinesterase inhibition</td>
<td>5.7</td>
<td>20-50 mg/d</td>
<td>90-100</td>
<td>NA</td>
<td>Negligible</td>
<td>Nausea, vomiting, agitation, and sleep disturbances Gastrointestinal disturbances, dizziness, headaches, and heartburn</td>
<td>Approved in Austria</td>
</tr>
<tr>
<td>Propentofylline</td>
<td>Adenosine reuptake inhibition</td>
<td>NA</td>
<td>300 mg, 3 times a day</td>
<td>Approximately 32</td>
<td>NA</td>
<td>NA</td>
<td>Gastrointestinal disturbances, dizziness, headaches, and heartburn</td>
<td>Awaiting approval by the FDA</td>
</tr>
</tbody>
</table>

*FDA indicates Food and Drug Administration; EMEA, European Medical Evaluation Agency; NA, data not available.
many species. Based on these findings, several strategies have been developed to improve cognition by the use of NMDA antagonists as neuroprotective agents to slow the progression of dementia. These antagonists include dextromethorphan hydrobromide, memantine (a congener of amantadine hydrochloride),17 and nitroglycerine. Preclinical trials for treatment of women with AD.

### Neurotrophic Growth Factors

Nerve growth factor (NGF) as the prototypic neurotrophic growth factor is intimately related to the maintenance of function of the cholinergic basal forebrain system. Forebrain cholinergic neurons are the only cells in the adult brain that express high amounts of the low-affinity p75 receptors for NGF. The NGF increases hippocampal acetylcholine and prevents cholinergic cell loss and atrophy after fornix lesions, indicating the potential utility of NGF as a neuroprotective treatment for basal forebrain cells in AD.18 An innovation in AD therapy may come from NGF-mimetic drugs. Neotrofin or AIT-082 (an analog of hypoxanthine) (NeoTherapeutics, Irvine, Calif) is an orally active compound that is claimed to enhance the levels of various neurotrophic factors, such as NGF, ciliary neurotrophic factor, and neurotrophin-3, and also potentiate the effects of NGF.

### DECREASING THE CELLULAR REACTION TO NEURODEGENERATION

Microglial cells, closely related to the macrophage series of cells in the periphery, increase in size and number in the brain with AD. From this observation and the presence of complement in amyloid plaques, the concept of AD as an inflammatory disease has emerged. It has been reported that individuals taking anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), have fewer cerebral microglia19 and are less likely to develop AD, with a fairly consistent risk reduction of about 50%.20 The greatest protection is observed in those individuals with late onset (>70 years of age) and a strong family history of AD. In one randomized, placebo-controlled study21 with indomethacin sodium in 44 patients with mild

### Table 3. Classes of Drugs in Preclinical or Early Clinical Development for the Treatment of Alzheimer Disease (AD)*

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td>L-701252</td>
<td>Being developed for treatment of AD, epilepsy, and cerebrovascular ischemia</td>
</tr>
<tr>
<td>NMMA antagonist</td>
<td>LY-235599</td>
<td>Competitive antagonist; potential for use in AD and other CNS diseases</td>
</tr>
<tr>
<td>NMMA antagonist</td>
<td>WIN-63480-2</td>
<td>Uncompetitive antagonist; does not produce phencyclidine-like effects in animals</td>
</tr>
<tr>
<td><strong>Neurotrophic</strong></td>
<td>AIT-082</td>
<td>Undergoing phase 2 clinical trials</td>
</tr>
<tr>
<td>NGF agonist</td>
<td>AK-30-NGF</td>
<td>Monoclonal antibody; NGF delivery system</td>
</tr>
<tr>
<td>NGF agonist</td>
<td>NBI-106</td>
<td>Potent immune stimulation and memory-enhancing properties</td>
</tr>
<tr>
<td>NGF agonist</td>
<td>rhNGF</td>
<td>Recombinant protein; also undergoing phase 3 clinical trials for peripheral neuropathy therapy</td>
</tr>
<tr>
<td><strong>Hormonal</strong></td>
<td>ABPI-124</td>
<td>Specific for CNS; does not interact with other tissues</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Neurestrol</td>
<td>An estrogen agonist developed by Endocon Inc, South Walpole, Mass, for treatment of women with AD</td>
</tr>
<tr>
<td><strong>Anti-inflammatory</strong></td>
<td>SC-110</td>
<td>Undergoing phase 1 clinical trials</td>
</tr>
<tr>
<td>Anti-inflammatory agent</td>
<td>GR-253035</td>
<td>IC50 to COX-1 of more than 100 µmol/L and IC50 to COX-2 of 0.14 µmol/L; entering phase 1 clinical trials for treatment of AD</td>
</tr>
<tr>
<td>Cytokine modulator</td>
<td>NBI-117</td>
<td>Reported to bind and activate newly discovered receptors of cytokine activin</td>
</tr>
<tr>
<td><strong>Antioxidants</strong></td>
<td>ARL-16556</td>
<td>Spin-trapping effects that scavenge free radicals and the ability to modulate the effects of nitric oxide</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>MDL-74100DA</td>
<td>Undergoing preclinical trials; analog of vitamin E that inhibits in vitro and ex vivo lipid oxidation and protects mice against CNS trauma</td>
</tr>
<tr>
<td><strong>Antiamyloid</strong></td>
<td>MDL-28170</td>
<td>Dipeptide aldehyde (Z-Val-Phe-H); cysteine protease inhibitor</td>
</tr>
<tr>
<td>γ-Secretase inhibitor†</td>
<td>Calpeptin</td>
<td>Dipeptide aldehyde (Z-Leu-Leu-Leu-H); cysteine protease inhibitor</td>
</tr>
<tr>
<td>γ-Secretase inhibitor†</td>
<td>MDL-132</td>
<td>This tripeptide aldehyde (Z-Leu-Leu-Leu-H) and others at low concentrations inhibit cysteine proteases and the degradation of the cytoplasmic domains of amyloid precursor protein; at higher concentrations they inhibit γ-secretase and proteasome</td>
</tr>
<tr>
<td>Antifibrillogenic</td>
<td>MW-167</td>
<td>Substrate-based difluoroketone, aspartyl protease inhibitor</td>
</tr>
<tr>
<td>Antifibrillogenic</td>
<td>SKF-74652</td>
<td>In a model of τ aggregation, an IC50 of 28 µmol/L</td>
</tr>
</tbody>
</table>

* NMDA indicates N-methyl-D-aspartate; CNS, central nervous system; NGF, nerve growth factor; rhNGF, recombinant human NGF; Cox, cyclooxygenase; IC50, the inhibition concentration at 50%; and Aβ, β-amyloid.
† γ-Secretase may be one mechanism involved, but further study is needed.
protection of mild to moderate dementia in addition to pro-
tective responses, or even directly reduce A
produce plasma levels of apolipoprotein E, modify inflamma-
estrogen may promote growth of cholinergic neurons, re-
own in progress. In addition to its antioxidant properties,
trapping effects.
16556, an
trapping.
ABPI-124, a compound without the adverse effects of femi-
tation are still too rudimentary. The normal function of APP
also remains uncertain, placing some restriction on our
ability to predict the unintended adverse effects of APP down-regulation.
Most therapeutic research has been devoted to de-
veloping inhibitors of the β- and γ-secretases, which are
responsible for the proteolytic cleavage events that gen-
erate Aβ. While the identity of these enzymes remains
unknown, several pharmaceutical companies have de-
veloped compounds that are efficient inhibitors of γ-secretase (Table 3). Most are still undergoing preclinical de-
velopment, although registration of some compounds may
occur in 2000. Studies26,27 that implicate the presenilins
in the γ-secretase pathway also are introducing new thera-
peutic strategies, although the involvement of presenil-
ins in Notch signaling has caused some concern about the
potential adverse effects of γ-secretase inhibitors.

Compounds directed at inhibiting the toxic effects of Aβ or stabilizing the aggregated forms of Aβ to pro-
mote its clearance from the brain are now undergoing active development. Further insight is required to un-
derstand the roles of other proteins or lipids (eg, cho-
lesterol) that interact with Aβ (such as apolipoprotein E
and α-2-macroglobulin) or with APP as it travels through
the cell toward its biogenesis of Aβ. Recently, a remark-
able approach was described in which transgenic mice
immunized with human Aβ showed attenuation of amy-
loid plaque formation.28 This attenuation may represent a
novel mechanism for promoting the clearance of Aβ from
the brain, as the rates of Aβ production were not altered.
The prospect of large-scale human immuniza-
tions with potential autoantigens raises considerable challenges.

THE EMERGING FIELD
OF PHARMACOGENETICS

As in all complex diseases, many genetic elements are re-
sponsible for the clinical phenotype. Predicting who, in
a mixed population, will respond best to any given therapeu-
tic compound is a challenge for pharmacogeneti-
cists. There are already some indicators that the apo-
lipoprotein E allotype may affect responses to AChE
inhibitor therapy.29

CONCLUSIONS

Much has been learned from the first few years of
specifically targeted therapy for AD. A comparison of
tacrine with other second-generation AChE inhibitors in
clinical studies shows that despite these drugs having mod-
est clinical efficacy, their main differences are in the fre-
cuency of adverse effects, number of dropouts, and per-
centage of patients whose conditions improve. Although
efficacy may be similar between the AChE inhibitors at
effective doses, peripheral cholinergic adverse effects, tol-
erability, and hepatotoxic effects are severe limitations.
The controlled studies using AChE inhibitors have gen-
erally been short-term, from 12 weeks to 6 months, and
use similar kinds of cognitive outcome measures. There-
fore, long-term (>1 year) controlled studies need to be
evaluated. Furthermore, reliable controlled data on mean-
ingful outcomes, such as dependency and institutional-
ization or other aspects of long-term efficacy, are urgently needed. In contrast to the AChE inhibitors, the beneficial effect of estrogen therapy may delay the progression of AD. Since combination therapies may be crucial, it will be interesting to perform trials with combinations of drugs that possess different mechanisms of action; for example, AChE inhibitors and estrogen. Clinical studies are necessary to assess the efficacy and interactive effects of these approaches. With regard to the use of NSAIDs in AD, elderly people with AD are more susceptible to the adverse effects of NSAIDs; therefore, these drugs should be used with caution. The development of COX-2 and leukotriene inhibitors might be very important. The use of antioxidants, such as vitamin E, is worth considering in patients with AD, since they can be obtained over the counter and are relatively nontoxic and inexpensive.

In summary, the knowledge gained to date has served to set the standards by which all future therapies for AD will be measured. Progress in the development of drugs and clinical trials for AD has been remarkable, with every prospect that more effective strategies will emerge in the near future.

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