Investigational Medications for Treatment of Patients With Alzheimer Disease

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Development of effective treatments for patients with Alzheimer disease has been challenging. Currently approved treatments include acetylcholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine hydrochloride. To investigate treatments in development for patients with Alzheimer disease, the author conducted a review of the literature. New approaches for treatment or prevention focus on several general areas, including cholinergic receptor agonists, drugs to decrease β-amyloid and tau levels, anti-inflammatory agents, drugs to increase nitric oxide and cyclic guanosine monophosphate levels, and substances to reduce cell death or promote cellular regeneration. The author focuses on medications currently in clinical trials. Cholinergic agents include orthostatic and allosteric muscarinic M1 agonists and nicotinic receptor agonists. Investigational agents that target β-amyloid include vaccines, antibodies, and inhibitors of β-amyloid production. Anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs, the natural product curcumin, and the tumor necrosis factor α inhibitor etanercept, have also been studied. Some drugs currently approved for other uses may also show promise for treatment of patients with Alzheimer disease. Results of clinical trials with many of these investigational drugs have been disappointing, perhaps because of their use with patients in advanced stages of Alzheimer disease. Effective treatment may need to begin earlier—before neurodegeneration becomes severe enough for symptoms to appear.

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Although more than 30 years have passed since the discovery of neurochemical alterations in individuals with Alzheimer disease, development of effective treatments remains challenging. Alzheimer disease is characterized by a progressive decrease in cognitive function and loss of short-term memory. Pathologic changes include accumulation of the neurotoxic peptide β-amyloid in plaques and of neurofibrillary tangles containing the protein tau, as well as massive cholinergic degeneration, which correlates closely with decline in cognitive function.[1-2] Thus, initial attempts to treat patients focused on augmenting cholinergic function,[3] and the first successful treatments used acetylcholinesterase inhibitors.[4-6] In 2003, the N-methyl-D-aspartate (NMDA) receptor antagonist memantine hydrochloride became available.[7-9] Although, in many cases, acetylcholinesterase inhibitors and memantine—alone or in combination—have produced improvements in symptoms and in tests of cognition, their effectiveness wanes as Alzheimer disease progresses.

A number of new medications are under investigation for treating patients with Alzheimer disease. The present review focuses on new approaches for Alzheimer disease treatment that are currently being tested in clinical trials or in animal studies. These investigational medications are categorized by therapeutic target or by mechanism of action. Among the drugs discussed are those that interact with cholinergic receptors, those that target β-amyloid, and those that are currently approved for other purposes *(Figure)*.

Drugs That Stimulate Cholinergic Receptors

Muscarinic Agonists

The acetylcholinesterase inhibitors were developed in response to the observation that a severe loss of cholinergic pathways is a consistent finding in patients with Alzheimer disease. These agents

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are effective in many patients, particularly those in early stages of Alzheimer disease. However, because they rely on intact cholinergic nerve terminals, which continue to degenerate as the disease progresses, acetylcholinesterase inhibitors become less effective over time. In addition, acetylcholinesterase inhibitors are incapable of providing receptor selectivity—an inability that is problematic because research has shown that stimulation of M1 receptors, but not M2 receptors, is beneficial in decreasing levels of β-amyloid.[10-11]

Direct-acting muscarinic agonists exert their effects postsynaptically, requiring no cholinergic terminals. Thus, these agonists should be effective much longer than acetylcholinesterase inhibitors. Muscarinic agonists may also slow the progression of Alzheimer disease by decreasing β-amyloid accumulation.

The M1 muscarinic receptor subtype represents an important therapeutic target, because it is abundant in the hippocampus and cerebral cortex, the brain regions where the cholinergic deficit is most pronounced in Alzheimer disease. This receptor subtype is involved in short-term memory.[12] Furthermore, stimulation of M1 muscarinic receptors decreases production of β-amyloid by activation of α-secretase.[13-15]

The muscarinic agonist AF267B (NGX267; Torrey Pines Pharmaceutical Inc, Del Mar, California) decreased levels of β-amyloid and prevented its accumulation following lesion of cholinergic neurons in rabbits. It also decreased β-amyloid levels in a mouse model of Alzheimer disease.[16-18] Long-term treatment with the selective M1 agonists cevimeline hydrochloride (AF102B) and talsaclidine decreased β-amyloid levels in cerebral spinal fluid (CSF) of patients with Alzheimer disease.[13,19] Conversely, use of cholinergic antagonists in patients

Muscarinic M1 Receptor Agonists
- ☐ Orthostatic
  - —AF267B (NGX267)[16-18,26-27]
  - —Cevimeline hydrochloride (Evoxac, AF102B)[13]
  - —Talsaclidine[19]
  - —Xanomeline with tacrine hydrochloride[22-25]
- ☐ Allosteric
  - —AC-42 (4-*n*-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine)[30]
  - —77-LH-28-1 (1-[3-(4-butyl-1-piperidinyl)propyl]-3,4-dihydro-2(1*H*)-quinolone)[30,33]
  - —AC-260584 (4-[3-(4-butylpiperidin-1-yl)-propyl]-7-fluoro-4H-benzo[1,4]oxazin-3-one)[32]
  - —TBPB (1-(1´2-methylbenzyl)-1,4´-bipiperidin-4-yl)-1*H*-benzo[d]imidazol-2(3*H*)-one)[33,34]
  - —BQCA (benzylquinoline carboxylic acid)[35]

Nicotinic Receptor Agonists
- ☐ ABT-089 (2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride)[42,43]
- ☐ A-582941 (2-methyl-5-(6-phenyl-pyridazin-3-yl)-octahydro-pyrrolo[3,4-c]pyrrole)[49]
- ☐ ABT-107 (5-(6-[(3R)-1-azabicyclo[2,2,2]oct-3-yloxy]pyridazin-3-yl)-1H-indole)[50,51]
- ☐ EVP-6124[52,53]

Vaccines Against b-Amyloid
- ☐ AN1792[54-62]
- ☐ CAD-106[63]
- ☐ ACC-001[52,64]
- ☐ ACI-24[52,64]
- ☐ UB-311[52,64]
- ☐ V-950[52,64]

Humanized Monoclonal Antibodies Against β-Amyloid
- ☐ Bapineuzumab (AAB-001)[66-69]
- ☐ Solanezumab (LY2062430)[70-72]
- ☐ Ponezumab (PF-04360365)[73-75]
- ☐ GSK-933776[52,69]
- ☐ Gantenerumab (R-1450)[52,69]
- ☐ MABT-5102A[52,69]

γ-Secretase Inhibitors
- ☐ Semagecestat (LY-450139)[78-80*]
- ☐ Begacestat (GSI-953)[81,82]
- ☐ BMS-708163[83]
- ☐ PF-3084014 ([(S)-2-((S)-5,7-difluoro-1,2,3,4-tetrahydronaphthalen-3-ylamino)-N-(1-(2-methyl-1-(neopentylamino)propan-2-yl)-1H-imidazol-4-yl)pentanamide])[84]
- ☐ Other secretase inhibitors
  - —Etazolate (EHT-0202)[85,86]
  - —Pioglitazone hydrochloride (Actos)[87,88,115]
  - —Rosiglitazone maleate (Avandia)[87,88,115]

Anti-inflammatory Agents
- ☐ Nonsteroidal anti-inflammatory drugs[89-96]
- ☐ Curcumin[100-104]

Drugs Targeting Tau
- ☐ NAP (Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln; NAPVSIPQ)[106-108]
- ☐ Antibodies to tau[116]
- ☐ Lithium chloride[112,113]
- ☐ Methylene blue (Rember)[117]

Drugs Approved for Other Purposes
- ☐ Latrepirdine (Dimebon)[119-121]
- ☐ Etanercept (Enbrel)[125-127]
- ☐ Sildenafil citrate (Viagra)[128]
- ☐ Lovastatin (Mevacor)[114]

Figure. *Investigational medications for Alzheimer disease in clinical trials or animal studies. *The semagecestat clinical trials (ie, IDENTITY and IDENTITY-2) were stopped in August 2010 because cognitive function appeared to decline more rapidly in treated patients than in control groups.[80]*

with Parkinson disease increased CSF levels of β-amyloid,[20] and M1 receptor knockout in amyloid precursor protein (APP)-transgenic mice also increased β-amyloid deposition.[21] These results indicate that treatments that increase cholinergic function may slow progression of Alzheimer disease by decreasing β-amyloid accumulation.

The M1/M4 agonist xanomeline improved cognition and decreased behavioral disturbances in patients with Alzheimer disease, but adverse gastrointestinal effects limited its use.[22,23] Xanomeline is currently being tested for its usefulness in treating individuals with schizophrenia.[24] Unfortunately, stimulation of M4 receptors by xanomeline might mitigate the drug's beneficial effects on β-amyloid.[11] Nevertheless, a combination of xanomeline and tacrine hydrochloride (the first of the acetylcholinesterase inhibitors to be clincially used for Alzheimer disease) is now being tested.[25]

The orthostatic agonist AF267B is more selective for M1 receptors than is xano-meline.[10,26] It was originally tested in patients with Alzheimer disease, but it caused excessive salivation. As a result, it has since gone through phase 1 and phase 2 clinical trials for treatment of patients with xerostomia.[27]

Allosteric M1 Agonists—Many G protein–coupled receptors contain allosteric binding sites that are separate from the orthostatic binding site for the neurotransmitter.[28] The orthostatic muscarinic binding site is highly conserved, making development of agonists with strong receptor selectivity difficult.[28,29] For this reason, a number of newer agents have been developed to target the allosteric sites associated with M1 receptors.[30,31]

Allosteric sites might differ more between different receptor subtypes than do orthorstatic sites, allowing for the development of highly specific drugs. Stimulation of an allosteric site may enhance the binding of an agonist, or it may have distinct actions of its own to increase signal transduction. Issues that need to be clarified with allosteric M1 agonists include the degree to which they are orally available and the effect of their interaction with the allosteric receptor. Allosteric M1 agonists that have been developed and tested in animal tests or clinical trials include AC-42 (4-*n*-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine; Acadia Pharmaceuticals Inc, San Diego, California) and its analogue 77-LH-28-1 (1-[3-(4-butyl-1-piperidinyl) propyl]-3,4-dihydro-2(1*H*)-quinolone; GlaxoSmithKline, Brentford, England),[30] as well as AC-260584 (4-[3-(4-butyl-piperidin-1-yl)-propyl]-7-fluoro -4H-benzo[1,4]oxazin-3-one; Acadia Pharmaceuticals Inc),[32] TBPB (1-(1´2 -methylbenzyl)-1,4´-bipiperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3H)-one; Merck & Co Inc, Whitehouse Station, New Jersey),[33,34] and BCQA (benzylquinoline carboxylic acid; Merck & Co Inc).[35]

The allosteric agonists AC-42 and 77-LH-28-1 have similar activity in vitro, but 77-LH-28-1 has been shown to have better penetration into the CNS and to stimulate rat hippocampal activity.[33] Also, AC-260584 has been shown to increase cognitive performance in an animal model,[32] but this compound has not yet been tested in humans.

The allosteric agonist TBPB is active in vivo, it is highly selective for M1 receptors,[34] and it does not appear to cause serious peripheral adverse effects, which are often mediated by M3 receptors.[27] This agent also induces NMDA-receptor–mediated receptor currents in the hippocampus, which is important for learning and memory.[34] In vitro studies also show that TBPB decreases the processing of APP into β-amyloid[34]—an effect similar to that produced by previous M1 agonists. The allosteric agonist BCQA produces no direct agonist activity, but it shifts the dose-response for acetylcholine on M1 receptors. It is systemically active and reverses cognitive impairment induced by scopolamine.[35]

The allosteric agonists may provide a highly selective means of activating M1 receptors. This area of research continues to be developed. Some of these drugs, if they directly activate G protein–mediated signal transduction, may overcome the problem of M1 receptor uncoupling, which has been shown to occur in Alzheimer disease and which may limit the effectiveness of orthostatic muscarinic agonists.[36-39]

Nicotinic Receptor Agonists

The early findings of cholinergic loss suggested that nicotinic receptors might be a viable therapeutic target in patients with Alzheimer disease. Indeed, nicotine was shown to produce some improvement in attention and learning in such patients.[40,41] One subtype of nicotinic receptor, the α4β2 receptor, was targeted with a nicotinic receptor agonist called ABT-089 (2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride; Abbott Laboratories, Abbott Park, Illinois), which has been shown to reverse scopolamine memory loss, targets the α4β2 nicotinic receptor subtype.[42] However, ABT-089 produced no statistically significant improvement in patients with Alzheimer disease in clinical trials.[43]

More recently, attention has focused on the α7 subtype of nicotinic receptor, because it is predominant in brain areas showing cholinergic degeneration in Alzheimer disease. β-amyloid binds to this receptor, and its stimulation may improve cognitive function.[44-46] Stimulation of the α7 nicotinic receptor has also been shown to protect cells from β-amyloid–induced degeneration,[47] and chronic administration of nicotine decreases β-amyloid levels and prevents loss of short-term memory in rats receiving long-term β-amyloid infusions.[48] Thus, a number of new selective agonists for the α7 receptor have been developed.

One α7 nicotinic receptor agonist, A-582941 (2-methyl-5-(6-phenyl-pyridazin-3-yl)-octahydro-pyrrolo[3,4-c]pyrrole; Abbott Laboratories), decreased hyperphosphorylation of tau protein in Tg2576-transgenic mice that overproduced APP.[49] Another agonist, ABT-107 (5-(6-[(3R)-1-azabicyclo[2,2,2]oct-3-yloxy]pyridazin-3-yl)-1H-indole; Abbott Laboratories), improved cognition in monkeys, rats, and mice, and it also improved short-term recognition memory when administered with the acetylcholinesterase inhibitor donepezil hydrochloride.[50] Continuous infusion of ABT-107 in tau/APP-double-transgenic mice also reduced spinal tau hyperphosphorylation, suggesting that this approach may be useful in treating patients with Alzheimer disease.[49] This drug has recently been tested in normal

human controls, in whom it appeared to be well tolerated, with good pharmacokinetic findings and only mild adverse effects.[51]

Another α7 nicotinic receptor agonist, EVP-6124 (Elan Pharmaceuticals, Dublin, Ireland), has undergone one clinical trial,[52] and a phase 2 trial of this drug is currently recruiting participants (ClinicalTrials.gov identifier No. NCT01073228). In the initial trial, 48 participants with mild to moderate Alzheimer disease were treated for 1 month with EVP-6124, in addition to an acetylcholinesterase inhibitor that they had previously been taking.[53] No serious adverse effects occurred in the study participants, and some improvement was observed in assessments of attention, verbal fluency, and executive function.[52,53] Thus, agonists of the nicotinic α7 receptor may have potential for treatment of patients with Alzheimer disease.

Agents That Target β-Amyloid

Vaccines

As previously noted, one of the pathologic hallmarks of Alzheimer disease is the presence of neuritic plaques containing the neurotoxic peptide β-amyloid. Thus, reducing levels of β-amyloid in the brain might slow the progression of Alzheimer disease. A vaccine developed against β-amyloid, AN1792, was found to be effective in mouse models in which β-amyloid was overproduced.[54] Transgenic mice with amyloid deposits that were given the vaccine showed a substantial decrease in β-amyloid levels in their brains, as well as improvement in cognitive function.[55,56]

In a human trial with the AN1792 vaccine, levels of β-amyloid appeared to decrease. Unfortunately, meningoencephalitis developed in some patients, leading to termination of the trial.[57-59] Levels of β-amyloid and tau were found to be low in autopsies of 2 patients who had received the vaccine.[59-61] However, cognitive function was not significantly improved in the overall study population.[62] These findings suggest that overproduction of β-amyloid occurs for many years before the onset of Alzheimer disease symptoms, and that—to be effective—vaccine administration would need to occur much earlier in patients deemed to be at high risk.

The CAD-106 vaccine, currently in clinical trials, was found to cause decreases in levels of β-amyloid in animals, and it did not cause CNS inflammation in early trials with humans.[63] Several other Alzheimer disease vaccines (eg, ACC-001, ACI-24, UB-311, V-950) have been developed and are in early stages of clinical trials.[52] Short peptides that mimic parts of β-amyloid are also currently being tested.[64] A nonviral amyloid vaccine has shown promise in animals,[65] but it has not yet been tested in humans.

Humanized Monoclonal Antibodies

Another approach to decreasing levels of β-amyloid is passive immunization with antibodies targeting portions of the β-amyloid molecule. Bapineuzumab (AAB-001) is a humanized monoclonal antibody to the N-terminus of β-amyloid. Two phase 2 trials have been conducted with this drug. In one trial, cortical β-amyloid load was decreased.[66] In the other trial, no statistically significant difference in cognitive function was found between the treatment group and the placebo group.[67] Interestingly, bapineuzumab appeared to produce some beneficial cognitive effects in individuals who did not have the ε4 allelle of the apolipoprotein E (ApoE) gene, but those results were not statistically significant.[66]

The most serious adverse effect in both bapineuzumab studies[66,67] was cerebral vasogenic edema, which occurred in almost 10% of study participants. This adverse effect seemed to correlate with higher doses of bapineuzumab and with presence of the ApoE ε4 allele. This finding is unfortunate, because the ApoE ε4 allele is a risk factor for Alzheimer disease.

Treatment with bapineuzumab has also been found to reduce tau levels in patients with Alzheimer disease in two clinical trials.[68] A phase 3 clinical trial is currently being conducted with bapineuzumab.[69]

Solanezumab (LY2062430), a monoclonal antibody to a fragment of β-amyloid (β-amyloid 13-28), may recognize some variants of β-amyloid that are unrecognized by bapineuzumab.[70] In contrast to bapineuzumab, which targets plaques, solanezumab binds to soluble β-amyloid and should be able to increase clearance of β-amyloid from the body.[71] Early studies suggest that solanezumab decreases the amount of β-amyloid in neuritic plaques.[72]

A number of other monoclonal antibodies are in various stages of development and testing. Ponezumab (PF-04360365), an antibody targeted to the free carboxy terminus of β-amyloid 1-40,[73] has undergone preliminary human trials and has been shown to increase CSF β-amyloid.[74,75] Monoclonal antibodies in earlier stages of development include GSK-933776, Gantenerumab (R-1450), and MABT-5102A, as well as an immunoglobulin G2 antibody to β-amyloid.[52,69]

As with the vaccine approach, it seems likely that drugs targeting β-amyloid would need to be given to patients early in the course of disease—before neurodegeneration becomes severe enough to impair cognitive function.

Secretase Inhibitors

Another area of drug development involves the targeting of γ-secretase, one of the enzymes required for production of β-amyloid from APP.[76,77] Developing specific drugs to inhibit this enzyme is complicated by the fact that γ-secretase has many functions in the body. For example, it interacts with several neuronal factors, as well as with the Notch receptor, which is involved in cell differentiation.[76] Thus, toxicity may be a problem with these drugs. Nevertheless, a number of γ-secretase inhibitors are being tested.

Semagecestat (LY-450139), a γ-secretase inhibitor that reduces β-amyloid levels in the CNS, was being studied in two clinical trials.[78,79] However, these trials (ie, IDENTITY and IDENTITY-2) were recently stopped because cognitive function appeared to decline more rapidly in the treated patients than in the control groups.[80] It is possible that the failure of this drug may also be a result of insufficient selectivity for γ-secretase as opposed to Notch.

Some types of γ-secretase inhibitors currently under development have less harmful effects on the Notch receptor than previously tested types. One of these

γ-secretase inhibitors, begacestat (GSI-953), decreased plasma levels, but not CSF levels, of β-amyloid in humans.[81,82] Another γ-secretase inhibitor, BMS-708163, decreased CSF levels of β-amyloid in humans.[83] A third γ-secretase inhibitor, PF-3084014 ([(S)-2-((S)-5,7-difluoro-1,2,3,4-tetrahydronaphthalen-3-ylamino)-N-(1-(2-methyl-1-(neopentylamino)propan-2-yl)-1H-imidazol-4-yl)pentanamide]), decreased plasma and CSF levels of β-amyloid in animals, but only plasma levels in humans.[84]

Stimulation of α-secretase leads to non-amyloidogenic processing of APP. Muscarinic agonists increase α-secretase activity, and a number of other drugs are being investigated for this potential.[52] Etazolate (EHT-0202) is a γ-aminobutyric acid ($GABA_A$) receptor modulator that is in a phase 2 trial in patients with Alzheimer disease.[85,86]

Inhibition of β-secretase (β-site APP-cleaving enzyme [BACE1]), which cleaves APP to produce β-amyloid, is another approach to treatment of patients with Alzheimer disease.[52] As with γ-secretase, this enzyme has multiple functions, and selective drugs have not yet been developed. The type 2 diabetes mellitus drugs rosiglitazone maleate (Avandia; GlaxoSmithKline, Brentford, England) and pioglitazone hydrochloride (Actos; Takeda Pharmaceuticals North America, Deerfield, Illinois) inhibit β-secretase, but thus far beneficial effects have not been reported in clinical trials of these drugs for Alzheimer disease.[87,88]

Anti-inflammatory Agents

Inflammation is considered to be an important component of Alzheimer disease, and epidemiologic studies have suggested a beneficial effect from nonsteroidal anti-inflammatory drugs (NSAIDs) in decreasing the risk of Alzheimer disease.[89-91] Some NSAIDs have been shown to decrease β-amyloid and tau levels in animal models[92]—effects that may be the result of inhibition of APP-associated γ-secretase.[76,93] Clinical trials have been conducted with several of these NSAIDs.

The ADAPT study found no improvement from treatment with the NSAIDs naproxen or celecoxib on cognitive function in older adults, and the trial was stopped early because of cardiovascular adverse effects associated with naproxen.[94,95] A trial investigating ibuprofen for use against Alzheimer disease was also disappointing, showing no statistically significant decrease in cognitive decline, though that trial did detect a small, but not statistically significant, beneficial effect in patients who had the ApoE ε4 genotype.[96]

Research results suggest that the neuroprotective effects of NSAIDs occur primarily in younger patients (ie, those younger than 65 years),[89] and that NSAIDs may actually increase neuronal damage in some patients with Alzheimer disease.[97]

Interestingly, the incidence of Alzheimer disease is lower in India than in many developed countries.[98,99] Evidence shows that levels of β-amyloid and tau are lower in people who consume large amounts of curcumin,[100,101] a component of turmeric that inhibits γ-secretase.[102] Evidence further shows that curcumin protects against β-amyloid toxicity,[103] and decreases β-amyloid in Tg2576 transgenic mice.[104] Thus far, however, clinical trials of curcumin have demonstrated no improvement in cognitive function in patients with Alzheimer disease.[105]

These approaches to decreasing β-amyloid production may work best as preventive measures, before symptoms appear, because once the plaques and tangles have formed, neuronal damage is irreversible.

Drugs That Target Tau

Much of the discussion in the present article has focused on drugs that affect production of β-amyloid. However, the other hallmark of Alzheimer disease is the presence of neurofibrillary tangles containing the tau protein. Tau stabilizes microtubules in neurons and is normally phosphorylated. In Alzheimer disease, tau appears to become hyperphosphorylated, which may contribute to destabilization of microtubules.[106] The hyperphosphorylated tau may be incorporated into neurofibrillary tangles.

One approach used with transgenic mice has involved NAP (Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln; NAPVSIPQ), an octapeptide that prevents disruption of microtubules by binding to tubulin. Administration of this compound decreased hyperphosphorylation of tau and improved cognitive function in mice.[107,108] This drug has entered a clinical trial.[106]

Another approach focuses on enzymes involved in phosphorylating tau. One kinase, glycogen synthase kinase-3 (GSK-3), has been shown to cause hyperphosphorylation of tau when overexpressed in transgenic mice,[109,110] and inhibition of this enzyme decreases levels of β-amyloid.[111] Lithium chloride inhibits GSK-3, and chronic administration of this substance has been shown to decrease hyperphosphorylation of tau and improve cognition.[112,113] Lovastatin (Mevacor; Merck & Co Inc)[114] and the thiadiazolidinones[115] may also inhibit GSK-3.

Inhibition of tau aggregation is yet another approach. Immunotherapy with antibodies directed at tau decreased tangles in the Tg P301L mouse model.[116] Methylene blue (Rember), which may prevent aggregation of tau, displayed promising results in a phase 2 clinical trial,[117] and it decreased levels of β-amyloid and cognitive deficits in 3xTg-AD-transgenic mice.[118] Other drugs are being investigated for their ability to inhibit tau aggregation, to target heat shock protein and increase clearance of tau, or to stabilize the microtubules.[106]

Tau clearly presents a potential therapeutic target in Alzheimer disease. However, as with other medications, treatment would be most useful if initiated early in the course of disease, before the onset of massive neurodegeneration.

New Uses for Old Drugs

Latrepirdine

Latrepirdine (Dimebon; Medivation Inc, San Francisco, California; Pfizer Inc, New York, New York) is a nonselective antihistamine that was marketed in Russia for a number of years. Latrepirdine inhibits acetylcholinesterase and blocks NMDA receptors, and it has been shown to improve cognitive function in rats with cholinergic loss.[119] Thus, some researchers thought that this drug might combine the beneficial effects of an acetylcholinesterase inhibitor with those of memantine.

Results of a clinical trial of 14 patients with Alzheimer disease in Russia suggested that latrepirdine produced substantial improvement in cognitive function.[119] A subsequent clinical trial in Russia with 89 patients showed statistically significant improvement in cognition and activities of daily living with latrepirdine.[120] These findings led to the establishment of a similar, but larger (598 participants), clinical trial of latrepirdine for Alzheimer disease in the United States. In that US trial, no statistically significant difference was detected between the treatment and placebo groups.[120,121] Ongoing studies are attempting to determine reasons for the discrepancies between the Russian and US studies.

Etanercept

A number of studies have suggested that the inflammatory cytokine tumor necrosis factor α (TNF-α) may play a role in the pathogenesis of Alzheimer disease.[122] TNF-α increases the production of β-amyloid,[123] and blockade of TNF-α decreases toxicity of β-amyloid.[124] Etanercept (Enbrel; Amgen Inc, Thousand Oaks, California), a TNF-α inhibitor, is currently approved by the US Food and Drug Administration for treatment of patients with rheumatoid arthritis. Two reports have found improvement in aphasia, verbal fluency, and cognition in patients with Alzheimer disease after perispinal administration of enteracept.[125-127] Another clinical trial on the use of enteracept for Alzheimer disease is scheduled but has not begun recruiting participants (ClinicalTrials.gov identifier No. NCT01068353).

Phosphodiesterase-5 Inhibitors

In a study of double transgenic (ie, human APP/presenilin 1) mice with pathologic characteristics of Alzheimer disease, treatment with sildenafil citrate (Viagra; Pfizer Inc, New York, New York), a drug that increases cyclic guanosine monophosphate (cGMP) levels by inhibiting phosphodiesterase-5, improved memory and decreased β-amyloid levels in the brain.[128] Cyclic guanosine monophosphate levels are also increased by drugs that increase nitric oxide levels. Nitric oxide synthase knockout mice that overexpressed APP showed increased β-amyloid pathologic characteristics.[129]

Cyclic guanosine monophosphate increases phosphorylation of cyclic adenosine monophosphate (cAMP)-responsive element binding factor (CREB). By contrast, β-amyloid inhibits CREB phosphorylation, which may be one of the mechanisms involved in β-amyloid–mediated neuronal stress. The effect of β-amyloid on CREB phosphorylation can be prevented by analogues of cGMP or by medications that increase nitric oxide levels, suggesting that increasing nitric oxide might be another potential therapeutic approach.

Selective inhibitors of phosphodiesterase-5 are being developed for possible use in Alzheimer disease. Because phosphodiesterase-5 inhibitors are widely used in older men for erectile dysfunction, epidemiologic evidence may demonstrate whether the incidence of Alzheimer disease is decreased over time in this population.

Diabetes Mellitus Drugs

A postmortem analysis of patients who were treated with insulin and other medications for diabetes mellitus revealed that levels of neuritic plaques were substantially lower in individuals given a combination of insulin and oral agent than in other individuals.[130] Other research has suggested that patients with Alzheimer disease who take diabetes mellitus medications show less cognitive decline than other patients with Alzheimer disease.[131] The diabetes mellitus drugs rosiglitazone and pioglitazone are known to inhibit the β-secretase that is involved in production of β-amyloid.[88] These findings have led to suggestions that insulinlike hormones might provide a new avenue for treatment of patients with Alzheimer disease.[132] However, as previously indicated, clinical trials of these drugs have not shown any effectiveness for Alzheimer disease.[133]

Statins

The presence of neuritic plaques is correlated with high cholesterol levels,[134] and elevated cholesterol may increase β-amyloid production.[135,136] Several clinical trials have been conducted to determine whether using statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) to decrease cholesterol levels will also reduce the incidence or decrease symptoms of Alzheimer disease. Unfortunately, results of these studies have not been encouraging, though it is likely that the studies initiated drug treatment too late in the course of the disease.[137,138] Perhaps aggressive management of high cholesterol levels, which now occurs commonly in clinical practice, may lead to an overall decline of Alzheimer disease over the next few decades.

Other Approaches

A number of other approaches to the treatment of patients with Alzheimer disease are being pursued. Some of these approaches include drugs to decrease aggregation of β-amyloid; new NMDA antagonists designed to reduce excitotoxicity; various antioxidants; and drugs or cytokines that may stimulate neuronal regeneration.[52,139,140]

Summary

Many of the newer treatments discussed in the present article have not been effective in ameliorating the symptoms of Alzheimer disease. One conclusion that could be drawn is that these treatments do not address appropriate targets in Alzheimer disease. With the exception of the cholinergic receptor agonists, which target neuronal dysfunction, many treatments are designed to affect degenerative processes that probably begin many years before symptoms are seen.

Therefore, a number of approaches are under investigation to develop new treatments for patients with Alzheimer disease. The present review has focused primarily on medications that have entered clinical trials. A key consideration with the majority of approaches discussed in the present review is the importance of initiating treatment early, before clinical symptoms of Alzheimer disease appear. Prevention of the neuropathologic cascade is likely to be more successful than attempts to manage the disease after neurodegeneration is substantial enough to cause impairment of cognitive function.

For this reason, an early diagnostic tool that can reliably predict the likeli-

hood of development of Alzheimer disease is crucial to the success of treatment. Recently, a method was reported that holds great promise for early diagnosis. By analyzing a mixture of β-amyloid 1-42, phosphorylated tau, and total tau in CSF, De Meyer and colleagues[141] were able to classify patients with Alzheimer disease or with mild cognitive impairment that eventually developed into Alzheimer disease. Nevertheless, until such diagnostic markers are widely available, it is imperative that patients begin treatment early—as soon as they begin to manifest symptoms of cognitive impairment.

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