CHAPTER 31. BIOLOGICAL THERAPIES

31.15 CHOLINESTERASE INHIBITORS

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Alzheimer's disease is a progressive neurodegenerative disease that gradually destroys brain function. Symptoms of the disease include cognitive deterioration involving memory, language, praxis, higher executive functioning and behavioral changes. In the United States, 4 million patients are afflicted with the disease, with direct and indirect costs for the disease approaching 100 billion dollars annually. The disease is age related with the prevalence of 3.0 percent at age 65, approaching 50 percent by age 85 years and leveling off at 40 percent by age 95. As the population ages, increased numbers of people will develop Alzheimer's disease. Cautious optimism stems from the recent availability of cholinesterase inhibitors that may slow down the progression of this terrible disease, but much more research is required before the disease can be arrested or reversed or those at risk for the disease can be reliably identified and prevented from developing it.

Several lines of evidence suggest that cholinergic function has a substantial role in Alzheimer's disease. Cholinergic transmission is involved in learning and memory. Anticholinergic agents cause memory and attention deficits in animals and humans. Destruction of the basal forebrain in animals or cholinergic circuitry in humans results in cognitive deficits. In clinical trials, cholinergic agents have restored cognitive function and decreased decline in Alzheimer's disease patients. The correlation between cholinergic abnormalities and the degree of cognitive impairment in Alzheimer's disease is a consistent finding in a number of studies. The significance of the cholinergic changes in Alzheimer's disease was eloquently described in a comprehensive examination of neuropathological and neurochemical changes in brains of those afflicted. The strongest correlations between clinical measures of dementia severity and neurochemical changes involved choline acetyltransferase, the enzyme necessary for the formation of acetylcholine.

The cholinergic hypothesis in Alzheimer's disease led to research and development of a number of potential therapeutic agents. These agents are in various stages of preclinical and clinical development in

animals and humans. The agents currently approved by the Food and Drug Administration (FDA) for Alzheimer's disease are predominantly cholinesterase inhibitors. Attempts to alter cholinergic transmission have included increasing presynaptic precursors to acetylcholine, stimulating muscarinic receptors with selective muscarinic agonists and decreasing the enzymatic degradation of acetylcholine by blocking acetylcholinesterase or butylcholinesterase with cholinesterase inhibitors.

Lecithin and choline, the precursors to acetylcholine, have been extensively studied and shown not to be beneficial in Alzheimer's disease. Muscarinic agonists have demonstrated benefit in preclinical studies, and some compounds are now in clinical trials. Although tonic stimulation may be relevant in arousal and attention, continuous stimulation of receptors by cholinergic agonists may result in receptor downregulation because the physiological stimulation is not pulsatile. This downregulation may limit the effectiveness of the muscarinic agonists. Advancing age and Alzheimer's disease progression are associated with a decrease in number and function of cholinergic neurons, possibly explaining the failure of precursors affect the disease. Moreover, this decline in cholinergic neuron number and function may also decrease the effectiveness of the muscarinic agonists and the cholinesterase inhibitors.

TACRINE

Tacrine (Cognex), the first FDA-approved cholinesterase inhibitor for the treatment of dementia of the Alzheimer's type, is a centrally acting, noncompetitive, reversible inhibitor of acetylcholinesterase and butyrylcholinesterase. Originally synthesized in 1945, tacrine was not recognized as a cholinesterase inhibitor until 1953. Tacrine was initially used to attenuate morphine withdrawal in patients with cancer and pain syndromes. Tacrine is effective in slowing the apparent progression of dementia in a subgroup of patients with Alzheimer's disease who can tolerate the medication for sufficient duration. Tacrine's use in Alzheimer's disease is limited by four-times-a-day dosing, gastrointestinal adverse effects, the potential for hepatic toxicity, and the need for frequent serum monitoring.

Chemistry The molecular structure of tacrine (9-amino-1,2,3,4-tetrahydroacridine) is shown in Figure 31.15-1. Tacrine is metabolized to a number of hydroxylated products, including 1-OH-tacrine (which itself was being developed for the treatment of dementia of the Alzheimer's type) as velnacrine.

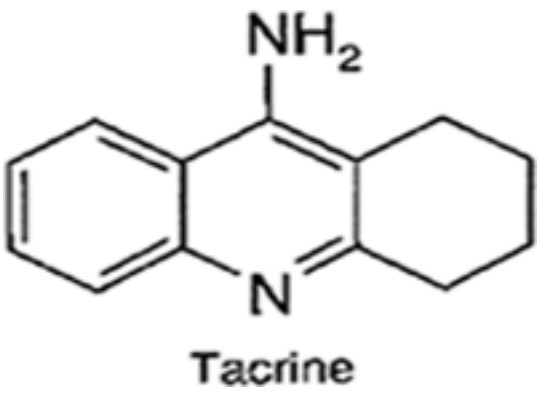


FIGURE 31.15-1 Molecular structure of tacrine.

Pharmacological Actions

Pharmacokinetics Tacrine is well absorbed from the gastrointestinal tract; however, intake with food reduces its bioavailability by 30 to 40 percent. Peak plasma concentration is reached 1 to 2 hours after oral dosing. Steady-state tacrine concentrations are reached after dosage initiation or change in 24 to 36 hours. The steady-state volume of distribution is about 300 L. The elimination half-life of tacrine is 2 to 3 hours. Tacrine is hepatically metabolized by the cytochrome P450 (CYP) is 0 enzymes 1A2 (CYP 1A) and CYP 2D6 and undergoes hydroxylation and conjugation. A small percentage of the drug is excreted in the urine, and dose adjustments are not necessary in patients with renal impairment.

Pharmacodynamics Tacrine's mechanism of action in Alzheimer's disease appears related to acetylcholinesterase inhibition resulting in increased acetylcholine availability. The relation between plasma concentration and oral dosing is nonlinear. Plasma concentrations of tacrine in women are double those of men, possibly related to decreased CYP 1A2 activity in women. Cigarette smokers have up to one-third lower serum tacrine levels than nonsmokers, probably related to induction of CYP 1A2 in smokers. Age and tacrine clearance are not directly related.

Design and Interpretation of Clinical Drug Studies Clinical trials using tacrine for Alzheimer's disease have variable methodological strength. Early studies demonstrating remarkable promise of tacrine for dementia were not well controlled. Additional studies in the 1980s had mixed results and continued methodological problems including inadequate dosing strength and duration of treatment. These concerns limited generalizations that could be made about effectiveness. Improved methodology in one 12-week study and 30-week study were pivotal in the ultimate FDA approval of tacrine.

Tacrine and Functional Brain Studies Brain single photon emission computed tomography (SPECT) and xenon (Xe)-inhalation have been used to examine brain function in Alzheimer's disease patients who received tacrine. These studies revealed correlations between clinical response to tacrine and functional imaging changes. Tacrine may improve technetium-99 (^{99m}Tc)-labeled ethylene dicysteinate retention abnormalities (a measure of cerebral blood flow) in patients with mild-to-moderate dementia of the Alzheimer's type. The results were dose dependent; patients who received 75 mg of tacrine a day demonstrated improvement, while those receiving 25 mg of tacrine a day did not show functional change in brain SPECT. In an open-label 14-month trial of tacrine with maximum dosage of 125 mg a day, Xe-inhalation methodology was used to measure regional cerebral blood flow (rCBF) in probable Alzheimer's disease patients before and after tacrine treatment. Patients who responded favorably to tacrine showed improvement or stabilization in rCBF compared with those who did not receive tacrine. The results support a dosage-dependent response to tacrine. The possibility of using functional measures as predictors of clinical response to pharmaceuticals is intriguing, and further research is required in this area.

Pharmacoeconomic Considerations Tacrine has been estimated to generate potential savings up to 17 percent of the current costs of Alzheimer's disease, or a total 3.6 billion dollars annually. These calculations were based upon an improvement of 1 point on the Mini-Mental State Examination

(MMSE) by patients tolerating 80 to 160 mg a day and a 2 point increase in patients who tolerated 160 mg a day. Patients with 1 to 2 points of improvement on the MMSE are estimated to have 9.5 to 12.1 months of reduced community and institutional costs. Industry-sponsored studies examining the effects of various agents on the direct and indirect costs of Alzheimer's disease are ongoing, and justification for choosing one pharmacotherapeutic agent over another may become closely tied to a drug's pharmacoeconomic profile.

Quality of Life In addition to pharmacoeconomic considerations, tacrine's effects on quality-of-life measures have been examined. The effect of tacrine on mortality and placement into a long-term care facility was examined in about 90 percent of the 663 patients from the 30-week clinical trial. Patients were followed for 2 years or until they died or were placed in a nursing home. Patients receiving more than 80 mg of tacrine daily were less likely to die or be placed in a nursing home than patients on a lower tacrine dose (odds ratio > 2.7). The absence of a control group and the retrospective nature of the study limit generalizations, but the dose-response nature of the findings is intriguing.

Effects on Specific Organs and Systems Tacrine dosages of 80 to 160 mg a day appear necessary for clinical response. At least 12 weeks of dose titration are required to achieve a dosage of 120 mg a day. More time is often required because the patient has gastrointestinal side effects or elevated hepatic transaminases. Transaminase elevations exceeding five times the upper limit of normal should result in tacrine discontinuation. Even with transaminase elevations, patients may still be rechallenged with tacrine after the transaminase levels normalize. In the clinical trials, no deaths associated with hepatitis in these patients were reported. A significant number of patients may tolerate rechallenge with tacrine, often at higher dosages than those that initially led to temporary discontinuation of the drug. Tacrine may have vagotonic effects on the heart rate and should be used with caution in patients with supraventricular cardiac arrhythmias. Gastrointestinal effects secondary to the parasympathetic effects of tacrine necessitate caution in patients at risk for peptic ulcer disease.

Therapeutic Indications Tacrine is indicated for the treatment of mild-to-moderate Alzheimer's disease.

Precautions and Adverse Reactions The clinical trials described above reported frequent adverse effects from tacrine. Hepatic abnormalities, although most often asymptomatic, require frequent monitoring of alanine transaminase (ALT) in serum. Dyspepsia, nausea, vomiting, diarrhea, anorexia, and abdominal pain are the most common adverse gastrointestinal effects. Adverse effects occurring in at least 2 percent of patients in clinical trials are reported in Table 31.15-1. Although many of the adverse effects occurred at similar rates in the tacrine and placebo groups, withdrawal from clinical trials occurred at a much higher rate in the tacrine group.

Table 31.15-1 Adverse Events Associated With Tacrine and Placebo Based Upon Clinical Trial Data

Adverse Event	Tacrine (%) (N = 634)	Placebo (%) (N = 342)
Laboratory interferences		
Elevated transaminase	29	2
Digestive system		
Nausea and/or vomiting	28	9
Diarrhea	16	5
Dyspepsia	9	6
Anorexia	9	3
Abdominal pain	8	7
Flatulence	4	2
Constipation	4	2
Body as a whole		
Fatigue	4	3
Weight loss	3	1
Musculoskeletal system		
Myalgia	9	5
Nervous system		
Dizziness	12	11
Ataxia	6	5
Insomnia	6	5
Somnolence	4	3
Tremor	2	<1
Psychobiological function		
Anxiety	3	2
Respiratory system		
Rhinitis	8	6

Adapted from tacrine package insert.

Hepatic Monitoring and Rechallenge Current recommendations for patients on tacrine treatment who tolerate the drug without significant elevations in hepatic transaminase concentrations are serum ALT monitoring every other week for 16 weeks, then monthly for 2 months, then once every 3 months. Patients may continue according to the titration schedule with up to twice the upper limit of normal ALT; weekly transaminase monitoring is necessary in patients with two to three times the upper limit of normal. Patients with ALT values three to five times the upper limit of normal should reduce the tacrine dosage by 40 mg a day and begin weekly transaminase monitoring. The dosing titration may resume with every-other-week transaminase monitoring when the ALT concentrations normalize. Patients with ALT concentrations exceeding 5 times the upper limit of normal should stop taking tacrine and be carefully monitored for signs and symptoms of hepatitis. If there is evidence of clinical jaundice, total bilirubin above 3 mg/dl, or clinical signs and symptoms of hypersensitivity such as rash or fever, patients should permanently stop taking tacrine and not be rechallenged. In one study that led to modification of the prescribing guidelines for tacrine, almost 88 percent of patients tolerated tacrine rechallenge, and 72 percent of the patients tolerated higher tacrine dosages than the initial dosage that resulted in discontinuation.

Weekly transaminase monitoring is required for all patients rechallenged with tacrine. After ALT values return to normal, patients may resume taking tacrine 10 mg four times a day. The titration schedule resumes after 6 weeks if the patient tolerates the drug and transaminase levels are acceptable (less than 3 times the upper limit of normal). Patients with initial elevations in ALT up to 10 times the upper limit of normal may be rechallenged after transaminase values normalize, although there is limited clinical experience with rechallenging these patients. Hypersensitivity reactions to tacrine resulting in eosinophilia or granulomatous hepatitis have been reported, and rechallenge of these patients is not recommended.

Drug Interactions Patients on theophylline (Theo-Dur) who also take tacrine show a doubling of theophylline concentration, as both drugs are metabolized by CYP 1A2. Cimetidine (Tagamet) is also metabolized by the same isoenzyme as tacrine, and coadministration of these agents requires judicious monitoring, as both drug concentrations increase. Tacrine prolongs the effect of succinylcholine by inhibiting butylcholinesterase, the enzyme responsible for succinylcholine degradation. There have been no reported drug interactions with digoxin (Lanoxin), warfarin (Coumadin), or diazepam (Valium).

Laboratory Interferences Tacrine does not interfere with urinalysis, spectroscopy, or other laboratory

tests. Elevation of transaminases is associated with tacrine use.

Dosage and Administration Tacrine is available in 10-mg, 20-mg, 30-mg, and 40-mg capsules. After a thorough physical examination and review of transaminase levels, tacrine administration should be started at 10-mg four times a day for 6 weeks. The dosage may then be increased by 10 mg four times a day every 6 weeks until the target dosage of 40 mg four times a day is reached. Titration should proceed unless transaminases are elevated or there is other evidence of intolerance. If transaminase elevations occur, tacrine dosage is maintained at the current level or reduced. Patients who discontinue tacrine for 4 weeks must resume taking it at initial dosages of 10 mg four times a day, with attendant transaminase serum monitoring. Patients with gastrointestinal intolerance of tacrine may benefit from coadministration of tacrine with meals, although the drug's bioavailability may decrease by 30 to 40 percent.

DONEPEZIL

In December 1996, donepezil (Aricept) became the second cholinesterase inhibitor FDA-approved for treating dementia of the Alzheimer's type. This compound has once-daily dosing, lacks significant hepatotoxicity, and does not require serum monitoring. Prolonged dosage titration of the drug is not required. Donepezil was in development for close to four decades; in vitro selectivity of donepezil for acetylcholinesterase compared to butylcholinesterase was studied first in 1961.

Chemistry Donepezil, known chemically as (±) -2,3-dihydro-5,6-dimethoxy-2-1 [[1-(phenylmethyl)-4-piperidinyl]methyl]-1*H*-inden-1-one hydrochloride, is a piperidine-based acetylcholinesterase inhibitor. The empirical formula is $C_{24}H_{29}NO_3HCl$, and the molecular weight is 415.96. The molecular structure is shown in Figure 31.15-2.

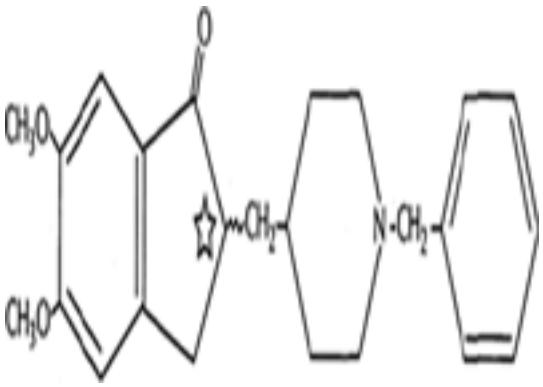


FIGURE 31.15-2 Molecular structure of donepezil.

Pharmacological Actions

Pharmacokinetics Donepezil is well absorbed in the gastrointestinal tract, and has an oral availability of 100 percent. Administration time and intake with food does not influence absorption. Peak plasma concentration is reached 3 to 4 hours after oral dosing. The steady-state volume of distribution is 12 L/

kg. Donepezil is 96 percent bound to human plasma proteins, predominantly albumin (75 percent) and α_1 acid glycoprotein (21 percent). Multiple-dose administration leads to steady state in 15 days with a four- to sevenfold increase in donepezil concentration. The elimination half-life of donepezil is 70 hours. Donepezil is excreted in the urine and hepatically metabolized by CYP 3D4 and CYP 2D6 and undergoes glucuronidation. There are four major metabolites, two of which are active, and a number of minor metabolites. The package labeling reports that patients with hepatic disease (stable alcoholic cirrhosis) had 20 percent less hepatic clearance of donepezil than healthy controls. Patients with renal disease did not differ from healthy subjects in their clearance of donepezil.

Pharmacodynamics The drug reversibly and noncompetitively inhibits hydrolysis of acetylcholine by acetylcholinesterase in the brain, which results in increased availability of acetylcholine in the synaptic cleft. The inhibitor dissociation constant for donepezil is one or two orders of magnitude lower than that for tacrine, indicating a stronger inhibitory effect by donepezil on acetylcholinesterase. The selective inhibition of donepezil is 1250 times greater for acetylcholinesterase than for butylcholinesterase. The plasma concentration is linearly correlated with daily oral dose in the range of 1 to 10 mg.

Design and Interpretation of Clinical Drug Studies In a double-blind placebo-controlled study, probable Alzheimer's disease patients were treated with donepezil in dosages of 1 mg, 3 mg, and 5 mg a day or placebo for 12 weeks. The donepezil-treated patients demonstrated dosage-related improvements in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the MMSE. The 5-mg donepezil group demonstrated statistically significant improvement in the ADAS-cog compared with the placebo group. Donepezil was not associated with hepatic toxicity and was well tolerated in this study.

In another 12-week double-blind placebo-controlled study with a 3-week placebo washout period, patients received either placebo or 5 mg or 10 mg a day of donepezil. Patients randomized to 10 mg a day received this dosage after 1 week at 5 mg a day. At 12 weeks, the means in ADAS-cog scores in the donepezil-treated groups and placebo group differed significantly. The differences between the 5-mg and 10-mg groups were not statistically significant. After 3 weeks of placebo washout, the donepezil-treated groups demonstrated loss of treatment effect. The difference in ADAS cog scores between donepezil-treated patients and the placebo group was about 3 units at 12 weeks. Studies have reported an expected change of 9 points on the ADAS cog in untreated probable Alzheimer's disease patients. At 12 weeks, patients receiving donepezil also demonstrated statistically significant improvement compared with the placebo group in Clinician's Interview-Based Impression of Change Plus Caregiver (CIBIC-plus) scores, a clinician-based assessment of change after interview with the patient and caregiver.

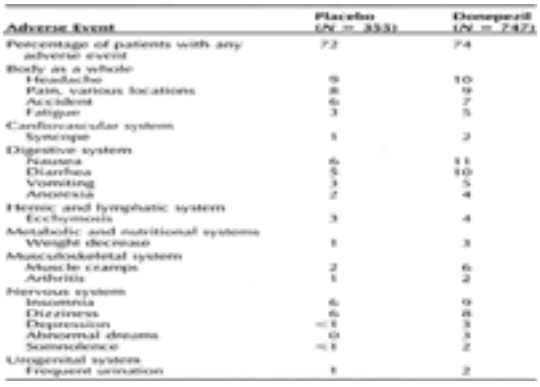
A 30-week study also used the ADAS-cog and CIBIC-plus Assessment as outcome measures. After 24 weeks of active double-blind placebo-controlled treatment, patients had 6 weeks of single-blind placebo-controlled washout. Patients were randomized to receive donepezil at 5 mg a day, 10 mg a day (after 1 week at 5 mg a day), or placebo. After 24 weeks, ADAS-cog scores were higher in donepezil-treated patients than in those in the placebo group, although there was no statistically significant difference between the 5- and 10-mg groups. CIBIC plus scores at 24 weeks also statistically favored the donepezil-

treated groups. There was no difference between the groups receiving 5 and 10 mg a day. After the 6-week placebo washout, the placebo groups and donepezil-treated groups were indistinguishable in ADAS-cog scores, suggesting that donepezil treatment did not change the underlying disease. There have been no direct comparisons of tacrine and donepezil. However, the change in the ADAS-cog scores for donepezil at its best has not been as large as the change in ADAS-cog scores for tacrine at its best.

Effects on Specific Organs and Systems Donepezil does not appear to cause hepatic injury. The drug may have vagotonic effects on the heart rate and should be used cautiously in patients with supraventricular cardiac arrhythmias including sick sinus syndrome. Gastrointestinal effects are secondary to the parasympathetic effects of donepezil. Gastric acid secretion may increase with donepezil. Patients with or at risk of peptic ulcer disease and patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) should be carefully monitored for evidence of gastrointestinal bleeding while receiving donepezil. Nausea, diarrhea, and vomiting may occur more commonly with the 10 mg than the 5 mg a day dosage.

Therapeutic Indications Donepezil is indicated for the treatment of mild-to-moderate dementia of the Alzheimer's type. Other forms of dementia may have some cholinergic depletion but are not currently indicated conditions for prescribing donepezil.

Precautions and Adverse Reactions Table 13.15-2 includes all adverse events reported in clinical trials of donepezil that occurred at a rate of at least 2 percent and at greater frequency than in placebo-treated patients. The most common adverse effects associated with donepezil use were diarrhea, nausea, insomnia, vomiting, muscle cramps, fatigue, and anorexia. These events were frequently mild and transient, resolving during continued treatment with donepezil. Adverse events occurred more frequently in women and the elderly. The most common adverse effects associated with donepezil that led to discontinuation of clinical trials were nausea, diarrhea, and vomiting. Patients who were titrated up to 10 mg a day after 1 week had a higher discontinuation rate than those taking 5 mg a day. An open-label study of the placebo-treated groups revealed that the adverse event rates were lower in the patients titrated up to 10 mg over 6 weeks than in patients titrated to 10 mg a day in 1 week. The rates of adverse effects in the slower-titration group were similar to those in the group receiving 5 mg a day of donepezil.



Adverse Event	Placebo (N = 353)	Donepezil (N = 747)
Percentage of patients with any adverse event	72	74
Body as a whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular system		
Syncope	1	2
Digestive system		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and lymphatic system		
Ecchymosis	3	4
Metabolic and nutritional systems		
Weight decrease	1	3
Musculoskeletal system		
Muscle cramps	2	6
Arthritis	1	2
Nervous system		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal dreams	0	3
Somnolence	<1	2
Urogenital system		
Frequent urination	1	2

Table 31.15-2 Adverse Events Reported in Clinical Trials Comparing Donepezil With Placebo

Drug Interactions The package insert for donepezil reports that the drug is highly protein bound. In

vitro displacement studies with donepezil did not demonstrate displacement of other tightly protein-bound drugs (furosemide [Lasix]), warfarin, digoxin). However, no in vivo drug displacement studies have been performed. Such studies in animals, with rapid infusion of drugs through the intravenous route as might occur under some clinical circumstances, would be revealing. The implications of tight protein binding for donepezil will remain unclear until in vivo studies are performed and potential drug interactions evaluated, especially since the average patient with Alzheimer's disease is taking multiple medications. The company reports that donepezil binding to albumin was not affected by furosemide, warfarin, or digoxin. The effect of donepezil on malnourished or cachectic patients has not been examined. Although there have been no formal studies examining drug interactions, the company reports that donepezil has no significant pharmacokinetic effects on warfarin, theophylline, cimetidine, and digoxin. Donepezil may increase succinylcholine effects on muscle relaxation. Agents that inhibit CYP 2D6 or CYP 3A4 may inhibit donepezil metabolism. Inducers of CYP 2D6 and CYP 3A4 may increase the elimination rate of donepezil. Cholinesterase inhibitors may also interfere with the effects of anticholinergic agents. This concern may be more academic than practical, as anticholinergic agents should generally be avoided in patients with Alzheimer's disease.

Laboratory Interferences There is no current evidence that donepezil interferes with urinalysis, spectrometry, or other laboratory tests.

Dosage and Administration Donepezil is supplied as a round tablet containing either 5 or 10 mg of donezepil hydrochloride. The 5-mg tablets are white, and the 10-mg tablets are yellow. The recommended starting dose is 5 mg daily. The medication is usually administered in the evening so the peak plasma concentration occurs when the patient is sleeping, minimizing adverse effects. The clinical trials demonstrated a dose trend favoring 10 mg over 5 mg a day, although the results were not statistically significant. Based on the clinical trials, it is a matter of prescriber and patient collaboration whether to increase from 5 to 10 mg a day. Open trials with 10 mg titration occurring at 6 weeks demonstrated no significant difference in adverse effects in the 5-mg and 10-mg groups. These authors recommend that patients be given a trial at 10 mg a day after 4 to 6 weeks if they are tolerating the 5 mg a day dosage. The half-life of donepezil is reported to be 70 hours on the basis of studies with younger patients. No half-life studies have been performed with elderly patients. Pharmacokinetic and pharmacodynamic changes in elderly persons may lead to an increased half-life, and it may be preferable to use dosages of 5 mg a day.

INVESTIGATIONAL DRUGS

Physostigmine Physostigmine's molecular structure is shown in Figure 31.15-3. Physostigmine (Antilirium, Eserine), a short-acting reversible cholinesterase inhibitor, has been extensively studied in Alzheimer's disease. Physostigmine improves recognition memory and enhances long-term memory processing. The response is dose dependent with a significant amount of individual variability, requiring a dose-finding phase of treatment to determine a patient's best dosage. Physostigmine is available in parenteral and oral preparations. Studies of oral and parenteral physostigmine in Alzheimer's disease patients have demonstrated variable responses. The drug's effectiveness in dementia appears related to

cholinergic inhibition in serum and cerebrospinal fluid (CSF), and drug concentrations in serum and CSF fluctuate significantly with either parenteral or oral administration. Physostigmine is also associated with peripheral cholinergic side effects that often lead to discontinuation of the drug. More recently, a longer-acting oral preparation, physostigmine salicylate, has demonstrated some benefit in Alzheimer's disease patients in phase III clinical trials.

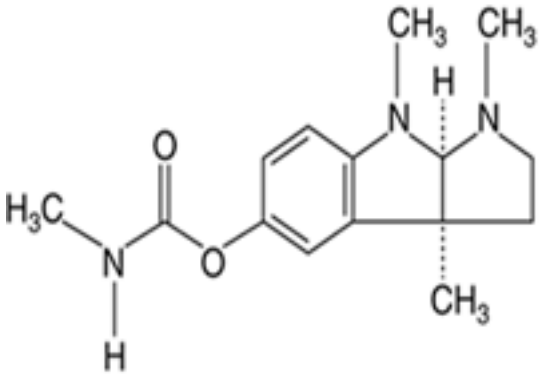
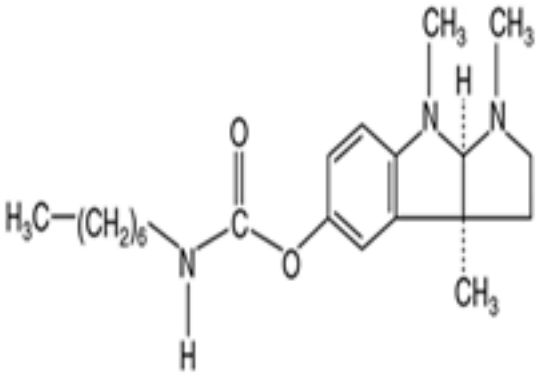


FIGURE 31.15-3 Molecular structure of physostigmine.

Eptastigmine Eptastigmine's molecular structure is shown in Figure 31.15-4. Eptastigmine, or heptylphysostigmine, is another longer-acting preparation of physostigmine. One 13-week controlled clinical trial of eptastagmine included 103 patients with probable Alzheimer's disease. The first 4 weeks were randomized, double-blind placebo-controlled, followed by 1 week of washout and an 8-week open-label phase. Subjects had MMSE scores between 10 and 26. Uniform dosing resulted in nausea and vomiting in some patients, and the methodology was changed to dosing the drug by weight. Outcome ratings included both physician and caregiver global ratings, independent activities-of-daily-living measure, and tests of logical memory, semantic word fluency, and executive functioning. One hundred three patients entered the double-blind phase (81 eptastigmine, 22 placebo). After 4 weeks, 94 remained in the study (74 eptastigmine, 20 placebo). Cholinergic adverse effects, uncooperation, protocol violation, and clinical worsening were all cited as reasons for dropout. At completion of the double-blind phase, the physician global measure and independent activities-of-daily-living measure favored the eptastigmine group. The tests of memory, word fluency, and higher executive functioning demonstrated no between-group differences. Dosage response followed an inverted U shape. Agranulocytosis has been reported with high doses of this drug and may limit its use. More clinical trial data are required with this agent.

FIGURE 31.15-4 Molecular structure of eptastigmine.



Rivastigmine Rivastigmine's molecular structure is shown in Figure 31.15-5.

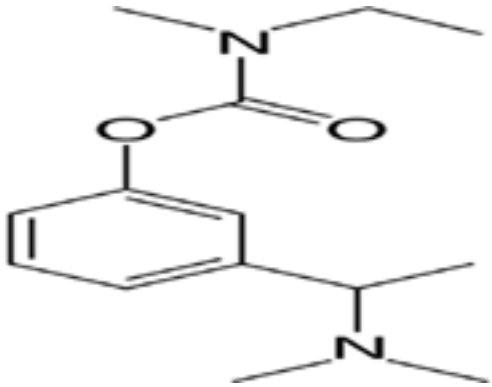


FIGURE 31.15-5 Molecular structure of rivastigmine.

Rivastigmine is a pseudoirreversible carbamate acetylcholinesterase inhibitor that is selective for the hippocampus and cortex. The drug is not metabolized by the liver, and no hepatic toxicity has been reported. It is metabolized by cholinesterase and is not protein bound. Rivastigmine was demonstrated to improve acquisition and retention memory in animals with selective basal forebrain lesions. Phase III clinical trials have been completed, and significant benefits have been reported in the ADAS, CIBIC Assessment and activities-of-daily-living measures. Concern about the possibility of increased deaths in the high-dosage group receiving rivastigmine compared with placebo led to inquiry of the Executive Director of Novartis. He responded that 62 patients died in the clinical trials with rivastigmine (including deaths occurring in patients treated up to 5 years prior to June 30, 1997). No statistical significant difference in the incidence of mortality was seen in placebo-controlled studies in phase I (rivastigmine, 0.8 percent, placebo, 0.5 percent) or phase III (rivastigmine –0.3 percent; placebo –0.1 percent). In phase 3 trials, no difference was found in mortality rates (Kaplan-Meier survival analysis) for patients treated long term with rivastigmine, which was assessed by comparing mortality in patients who were randomized to rivastigmine (13.0 deaths per 1000 patient-years) and treated long term with rivastigmine, with patients randomized to placebo for the first six months and treated long term with rivastigmine (13.5 deaths per 1000 patient-years). Nested case-control analyses were conducted to explore a dosage-response relationship for mortality, based on last prescribed dosage of rivastigmine and post hoc assignment of patients to nonoverlapping dosage ranges of 1 to <4, 4 to 6, >6 to 9, and >9 to 12 mg a day. Analyses comparing the highest to the lowest dose categories yielded a rate ratio of 0.8, indicating the absence of increased risk of mortality at higher dosages of rivastigmine. The causes of

death in the rivastigmine clinical trials were numerous and similar to those reported in the literature for an Alzheimer's disease population.

Galanthamine Galanthamine's molecular structure is shown in Figure 31.15-6. It is a tertiary amine of the phenthrene group that competitively inhibits acetylcholinesterase but not butyrylcholinesterase. The compound is plant derived, naturally occurring, and an allosteric agonist at nicotinic sites without producing desensitization, as well as a cholinesterase inhibitor. This ability to enhance the sensitivity of the acetylcholine receptor is possessed only by galanthamine and physostigmine. The mechanism of action is analogous to that of benzodiazepines at the γ-aminobutyric acid (GABA) A site. Consequently, the drug has an in vivo cholinomimetic activity that is even stronger than its acetylcholinesterase inhibitory properties alone would predict. Galanthamine's properties are interesting because in animals the combination of agonist and cholinesterase inhibitor may have an additive effect with fewer adverse events. Placebo-controlled clinical trials have demonstrated benefit in ADAS, and activities-of-daily-living measures. The usual effective dosage of galanthamine is 20 to 40 mg in divided doses. The drug has been approved in Austria, and multicenter clinical trials are under way in Europe and the United States.

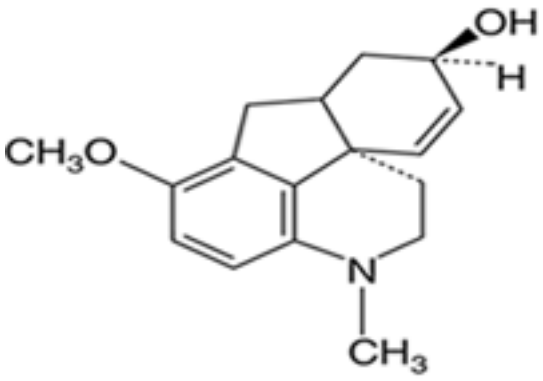


FIGURE 31.15-6 Molecular structure of galanthamine.

Metrifonate Metrifonate's molecular structure is shown in Figure 31.15-7. It is an irreversible cholinesterase inhibitor that is currently used to combat schistosomes. Metrifonate preferentially inhibits butyrylcholinesterase over acetylcholinesterase. Metrifonate is the prodrug of dichlorvos, the long-acting irreversible organic cholinesterase inhibitor. Although metrifonate has a short half-life, it achieves long-acting cholinesterase inhibition. Animal and human studies support metrifonate's memory-enhancing effects. Double-blind placebo controlled studies with Alzheimer's disease patients have demonstrated benefits for metrifonate-treated patients in 12- and 26-week trials. The benefits have been in cognitive measures (Alzheimer's Disease Assessment Scale-cog), behavioral measures (Neuropsychiatric Inventory), and global function (Clinician's Interview-Based Impression of Change-plus). The Food and Drug Administration is reviewing metrifonate, but there are no imminent plans for release of this medication because of safety concerns after some patients demonstrated prolonged muscle weakness after receiving the drug.

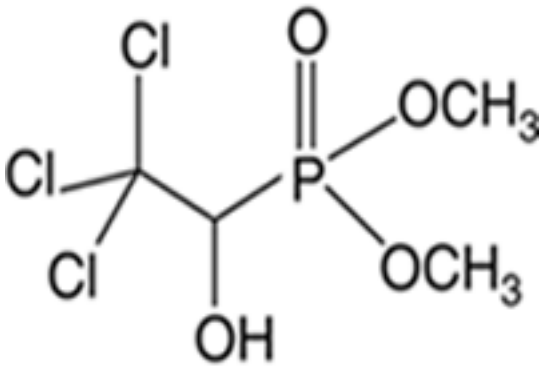


FIGURE 31.15-7 Molecular structure of metrifonate.

FUTURE DIRECTIONS

The concept of a polypharmaceutical approach to Alzheimer's disease has a theoretical rationale, as multiple domains appear to be involved in its pathogenesis. Future therapeutic approaches for Alzheimer's disease may be similar to hypertensive or neoplastic treatment, in which combination therapy is commonplace. Combination treatment with cholinesterase inhibitors and other agents has not been prospectively evaluated in Alzheimer's disease. A retrospective analysis to assess the effects of estrogen replacement therapy on tacrine response was performed using data from the 30-week tacrine study. Women receiving estrogen replacement therapy and tacrine had better measures of cognition and overall function than those not taking estrogen. Although these results are intriguing, prospective studies using cholinesterase inhibitors in combination with other treatments are required prior to recommending combination treatment as a standard of care.

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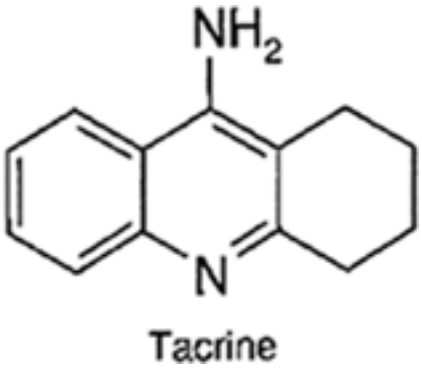

FIGURE 31.15-1 Molecular structure of tacrine.

Table 31.15-1 Adverse Events Associated With Tacrine and Placebo Based Upon Clinical Trial Data

Adverse Event	Tacrine (%) (*N* = 634)	Placebo (%) (*N* = 342)
Laboratory interferences		
Elevated transaminase	29	2
Digestive system		
Nausea and/or vomiting	28	9
Diarrhea	16	5
Dyspepsia	9	6
Anorexia	9	3
Abdominal pain	8	7
Flatulence	4	2
Constipation	4	2
Body as a whole		
Fatigue	4	3
Weight loss	3	1
Musculoskeletal system		
Myalgia	9	5
Nervous system		
Dizziness	12	11
Ataxia	6	5
Insomnia	6	5
Somnolence	4	3
Tremor	2	<1
Psychobiological function		
Anxiety	3	2
Respiratory system		
Rhinitis	8	6

Adapted from tacrine package insert.

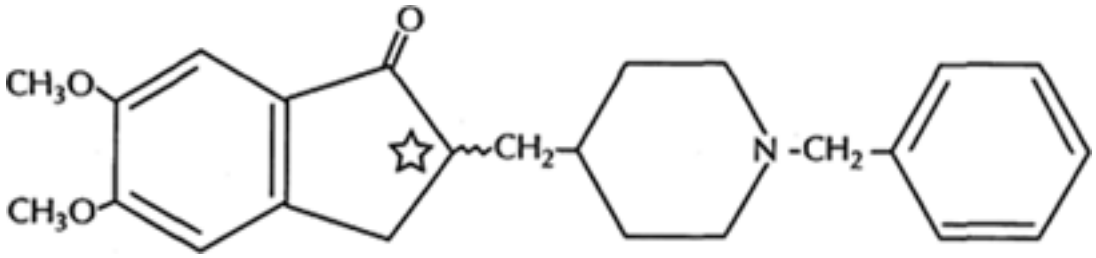

FIGURE 31.15-2 Molecular structure of donepezil.

Table 31.15-2 Adverse Events Reported in Clinical Trials Comparing Donepezil With Placebo

Adverse Event	Placebo (*N* = 355)	Donepezil (*N* = 747)
Percentage of patients with any adverse event	72	74
Body as a whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular system		
Syncope	1	2
Digestive system		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and lymphatic system		
Ecchymosis	3	4
Metabolic and nutritional systems		
Weight decrease	1	3
Musculoskeletal system		
Muscle cramps	2	6
Arthritis	1	2
Nervous system		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal dreams	0	3
Somnolence	<1	2
Urogenital system		
Frequent urination	1	2

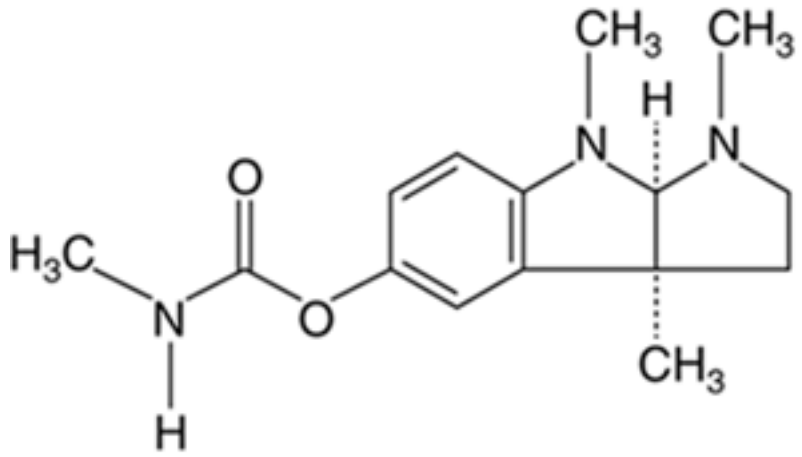

FIGURE 31.15-3 Molecular structure of physostigmine.

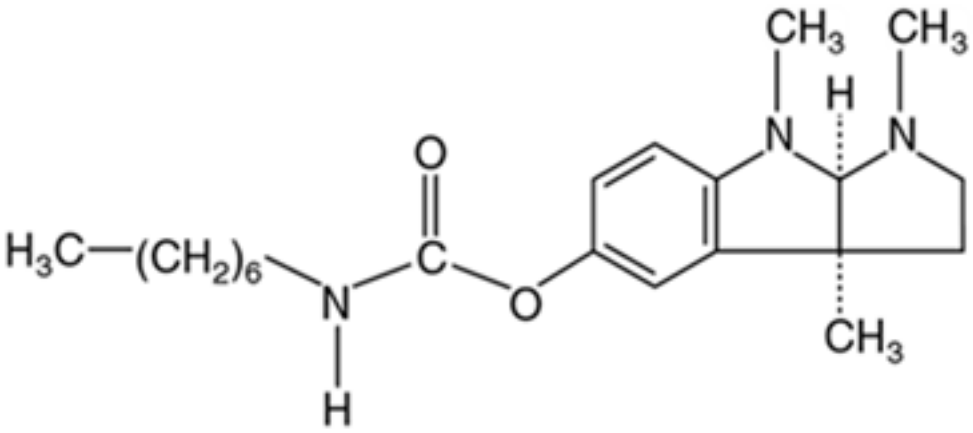

FIGURE 31.15-4 Molecular structure of eptastigmine.

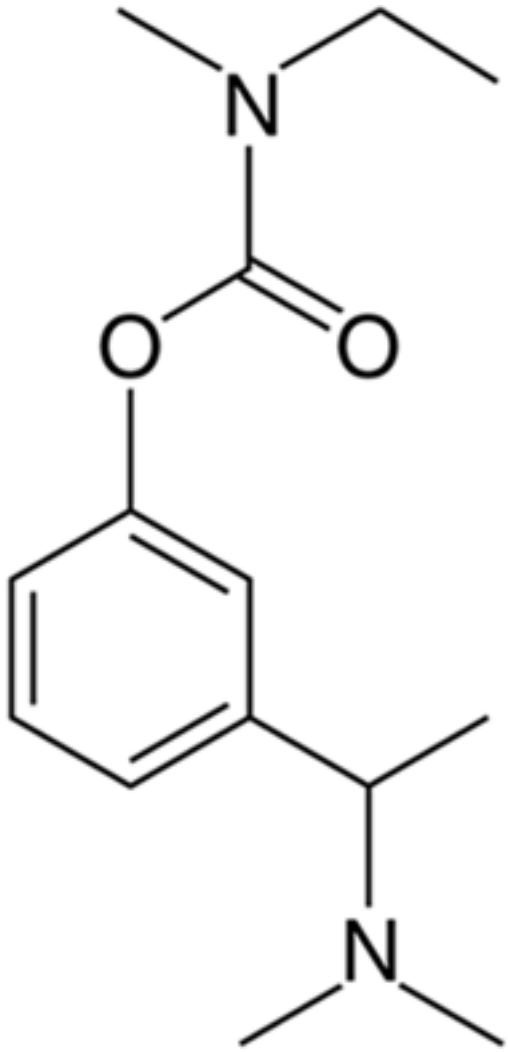

FIGURE 31.15-5 Molecular structure of rivastigmine.

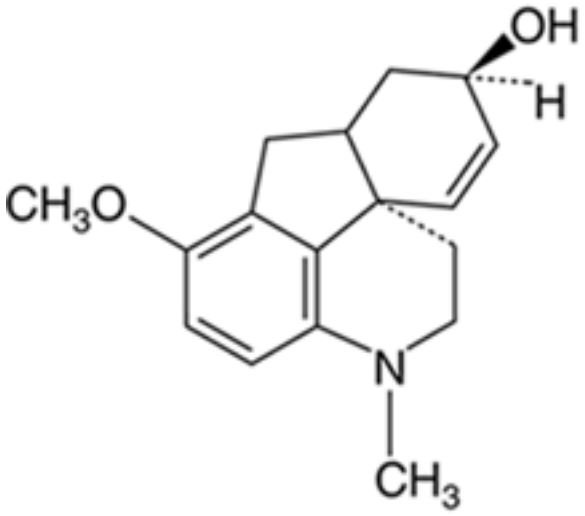

FIGURE 31.15-6 Molecular structure of galanthamine.

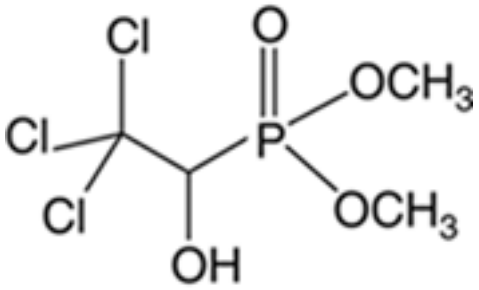

FIGURE 31.15-7 Molecular structure of metrifonate.