Alzheimer's Agents Review

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FDA-Approved Indications

Drug	Manufacturer	Dementia Type		
		AD – mild to moderate	**AD – moderate to severe**	**PD – mild to moderate**
Acetylcholinesterase Inhibitors (AChEIs)				
donepezil (Aricept®, Aricept® ODT)	Eisai	X	X	--
galantamine (Razadyne®, Razadyne ER®)	Ortho-McNeil	X	--	--
rivastigmine (Exelon®, Exelon® Patch)	Novartis	X	--	X
tacrine (Cognex®)	Sciele	X	--	--
NMDA receptor antagonist				
memantine (Namenda®)	Forest	--	X	--

AD - Alzheimer's disease
PD – Parkinson's disease

Overview

Alzheimer's Disease (AD) is the most common cause of dementia, accounting for 60 to 70 percent of dementia disorders in the elderly.[1,2] Other forms of dementia include dementia with Lewy bodies, vascular dementia, and fronto-temporal dementia. Dementia may also be associated with Human Immunodeficiency Virus (HIV), Huntington's disease, Korsakoff's syndrome, Multiple Sclerosis, and Parkinson's disease (PD), as well as other less common causes (genetic disease, thyroid deficiency, vitamin deficiency).

AD is characterized by progressive cognitive decline associated with impairment of activities of daily living (ADL) and behavioral disturbances. Patients with AD eventually lose all cognitive, analytical, and physical functioning.

Although the causes of AD have not been completely identified, the etiology of the disease is thought to be multifactorial. The discovery of vast cholinergic cell loss led to the cholinergic hypothesis and the development of drugs that target the cholinergic system. The cholinergic hypothesis suggests that a dysfunction of acetylcholine (ACh)-containing neurons in the brain plays a large part in the decline of cognitive function seen in patients with AD.[3]

Additional abnormalities have been shown to exist in the glutamate pathways. Glutamate is the main excitatory neurotransmitter in the cerebral cortex and hippocampus. The glutamate-gated *N*-methyl-D-aspartate (NMDA) receptor is activated during memory formation. Persistent activation of NMDA receptors due to chronic, excessive glutamate release is toxic to neurons. This over activation leads to deficits in cognitive function and, eventually, neuronal death.[4] Loss of these glutamatergic fibers correlates with the clinical signs of dementia.[5,6]

Finally, there is more recent evidence that a compromise of the serotonergic system contributes significantly to the onset and progression of AD. Specifically, data suggest that serotonin receptors modulate ACh, as well as other neurotransmitters, including glutamate, dopamine, and norepinephrine.[7,8] Regardless of the specific cause, the characteristic features of tangle pathology and neuronal death are noted in all cases.

The degree of cognitive impairment due to AD is related to the amount of cholinergic loss and the density of amyloid plaques, a hallmark of AD.[9] These extracellular amyloid plaques significantly interfere with neuronal transmission. Likewise, intracellular neurofibrillary tangles cause a disruption in cell function that eventually leads to cell death. Although damage exists in other neuronal pathways, the most significant damage is to the cholinergic pathway at the base of the forebrain. This collection of neurons extends projections to the frontal cortex and hippocampus, areas strongly associated with memory and cognition.

There is no validated method for screening for dementia. Use of the Mini-Mental State Examination (MMSE) in patients over 75 years of age may be recommended to improve earlier detection, but data supporting the efficacy or benefit of using this screening instrument are lacking.[10] Positron emission tomography (PET) and single photon computed emission tomography (SPECT) may have a use in the diagnosis of Alzheimer's disease, according to preliminary evidence. Studies using volumetric magnetic resonance imaging (MRI) to measure the size of key brain structures such as the hippocampus, amygdale, cingulated gyrus, ventricles and entorhinal cortex, have suggested that reduction in size of these structures in persons with only minor cognitive complaints can identify individuals who will have diagnosable Alzheimer's dementia within three years. Significant advances in the use of biological markers for diagnosis of dementia have not been made.[11]

Three acetylcholinesterase inhibitors (AChEIs); galantamine (Razadyne, Razadyne ER), rivastigmine (Exelon, Exelon Patch), and donepezil (Aricept, Aricept ODT); are approved by the FDA and widely used for treatment of AD. Tacrine is a fourth AChEI approved by the FDA for treatment of AD but is rarely used because of its potential for hepatotoxicity. Each of these drugs has shown cognitive benefit over placebo; however, it remains unclear if their use slows disease progression, delays placement in nursing homes, or alters mortality. Memantine (Namenda), an NMDA receptor antagonist, has been shown to improve cognition in moderate to severe dementia and is approved by the FDA for treatment of AD.[12] Management objectives for treatment of AD include improving cognition and delaying disease progression as well as promoting quality of life and social functioning, treating with dignity, educating and supporting caregivers, and assisting with decision-making and competency determinations.

The three commonly used AChEIs should be prescribed by specialists in the care of people with dementia including psychiatrists and those specializing in learning disability, neurologists, and physicians specializing in the care of the elderly. Caregivers' input on patient conditions at baseline should be obtained. Patients should be evaluated every six months by MMSE score and global, functional and behavioral assessment if they remain on a medication. Again, caregivers' input on the patient's condition at follow-up should be obtained. Medication should only be continued if it is felt to be having a beneficial effect. MMSE assessment should be

handled by an appropriate specialist team, unless protocols for shared care are agreed upon. Clinicians should be mindful of equality of access to treatment.[13]

Dementia associated with PD is similar in nature to AD in that, in most cases, amyloid plaques and neurofibrillary tangles are present.[14] In dementia associated with PD, cholinergic deficits are the most consistent findings associated with cognitive and neuropsychiatric symptoms.[15,16,17] Because of these similarities, the treatments for dementia of the Alzheimer's type may have some therapeutic benefit in the treatment of PD-related dementia. Rivastigmine (Exelon, Exelon Patch) is FDA-approved for mild to moderate dementia associated with Parkinson's disease.

Pharmacology

Acetylcholinesterase Inhibitors (AChEIs)

AChEIs exert their therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of ACh through reversible inhibition of its hydrolysis by AChE. Some AChEIs also inhibit butyrylcholinesterase (BuChE), another cholinesterase enzyme. Centrally, the resulting increase in ACh improves cognition. Peripheral enhancement of Ach causes the gastrointestinal side effects noted with AChEIs. As the disease progresses, the therapeutic effect of the AChEIs may lessen as fewer cholinergic neurons remain functionally intact.

Tacrine was the first AChEI to be approved. This agent been associated with significant liver toxicity. As a result, the use of tacrine has been nearly completely replaced by the three newer AChEIs, donepezil, rivastigmine, and galantamine.

Rivastigmine, like tacrine, is a carbamate-based AChEI that inhibits AChE and, in a more variable manner, BuChE.[18] Rivastigmine readily penetrates into the central nervous system and has a ten-fold greater affinity for central AChE over peripheral AChE.

Donepezil is a specific inhibitor of AChE, having a 1,250-fold greater affinity for this enzyme than for BuChE.[19]

The remaining AChEI, galantamine, is a phenanthrene derivative. In addition to inhibiting AChE, galantamine modulates nicotinic receptors, resulting in the release of other neurotransmitters throughout the brain.[20] The clinical significance of this effect is unknown.

NMDA receptor antagonist

Memantine (Namenda) is a low to moderate affinity, non-competitive NMDA receptor antagonist that binds preferentially to NMDA receptor-operated cation channels. Memantine allows the NMDA receptor to be activated during physiological memory formation but blocks the receptor during pathological (excitotoxic) activation.[21] Memantine also demonstrates antagonistic effects at the serotonin and nicotinic receptors.[22]

Pharmacokinetics

Drug	Half-Life (hr)	Metabolism	Protein Binding (%)
Acetylcholinesterase Inhibitors (AChEIs)			
donepezil (Aricept, Aricept ODT)[23,24]	70	CYP2D6, 3A4	96
galantamine (Razadyne, Razadyne ER)[25,26]	7	CYP2D6, 3A4	19
rivastigmine (Exelon, Exelon Patch)[27]	1.5	hydrolysis by esterases	40
tacrine (Cognex)[28]	2-4	CYP1A2	75
NMDA receptor antagonist			
memantine (Namenda)[29]	60-80	renal tubular secretion	45

Contraindications/Warnings

CONTRAINDICATIONS

Drug	Pregnancy	Breast feeding	Children	GI bleeding	Jaundice	Hepatic disease	Renal failure
Acetylcholinesterase Inhibitors (AChEIs)							
donepezil (Aricept, Aricept ODT)[30,31]		X	X	X	X		
galantamine (Razadyne, Razadyne ER)[32,33]		X	X	X	X		X
rivastigmine (Exelon, Exelon Patch)[34,35]			X	X	X		
tacrine (Cognex)[36]			X	X	X	X	
NMDA receptor antagonist							
memantine (Namenda)[37]	X	X					X

Rivastigmine (Exelon, Exelon Patch) is also contraindicated in carbamate hypersensitivity.

Contraindications/Warnings

Cholinesterase inhibitors (donepezil, galantamine, rivastigmine and tacrine) are contraindicated for patients with known hypersensitivity to the primary ingredients or any excipients. Similarly, the NMDA receptor antagonist memantine is contraindicated in patients with known hypersensitivity to the primary ingredients or any excipients.

Cholinesterase inhibitors (donepezil, galantamine, rivastigmine and tacrine) are likely to exaggerate muscle relaxation under general anesthesia, resulting in prolonged neuromuscular blockade and potentially extended respiratory depression.[38]

As a result of their primary action, cholinesterase inhibitors, (donepezil, galantamine, rivastigmine and tacrine) may increase gastric acid secretion due to increased cholinergic activity. Patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding.

Cholinesterase inhibitors may have vagotonic effects that may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported with the use of donepezil and rivastigmine. In randomized controlled trials, bradycardia was reported more frequently with galantamine patients than with those receiving placebo. However, this was rarely severe and rarely required treatment discontinuation.

Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease due to their cholinomimetic effects.

Patients taking rivastigmine, either capsules and patches at higher doses (greater then 9mg/day), experienced weight loss equal to or greater then seven percent of their baseline weight as compared to six percent in the placebo groups. Neither the time course nor the severity of the anorexia is known.

Drug Interactions

Antimuscarinics are functional antagonists of the AChEIs and, as such, reduce the effectiveness of the latter when co-administered.[38,39] Drugs with anticholinergic effects that have been shown to interfere with the activity of the AChEIs include amantadine, cyclobenzaprine, orphenadrine, disopyramide, and sedating antihistamines.

Parasympathomimetics produce additive pharmacologic effects when used with AChEIs.[40] Concurrent use is unlikely to be tolerated and should be avoided.

Donepezil is metabolized by CYP2D6 and 3A4; therefore, there is potential for an interaction with drugs that are metabolized by, or inhibit, these isoenzymes. Although clinically significant interactions of this nature have not been demonstrated, patients taking such interacting drugs should be monitored. Donepezil is highly (96 percent) protein bound, but interactions where donepezil displaces, or is displaced by, other protein bound drugs have not been reported.

Galantamine is a primary substrate for CYP3A4 and is metabolized to a lesser extent by CYP2D6. Co-administration with drugs that inhibit these isoenzymes, such as erythromycin, fluoxetine, paroxetine, and ranitidine, increases the bioavailability of galantamine by 25 to 40 percent. Galantamine has not been shown to have a significant effect on other drugs metabolized by the CYP450 enzyme system.[41,42]

Rivastigmine is hydrolyzed by esterases and no significant drug interactions have been reported.

Tacrine is an inhibitor of CYP1A2 and may increase the plasma concentrations of drugs metabolized by this enzyme such as chlordiazepoxide, diazepam, haloperidol, ramelteon, and theophylline.[43] Concomitant administration of other hepatotoxic drug, such as methotrexate and leflunomide, may increase the risk for hepatotoxicity.

Memantine is partially excreted by renal tubular secretion.[44] Co-administration of memantine with other drugs that are excreted in this manner, such as hydrochlorothiazide, nicotine, and ranitidine, may result in increased serum concentrations of one or both drugs. Significant interactions of this type have been documented for several antiarrhythmic agents, including dofetilide, procainamide, and quinidine. When given with metformin, competition between the two drugs for renal elimination may increase the risk of lactic acidosis due to accumulation of metformin. Conditions that raise urine pH may decrease urinary elimination on memantine resulting in increased plasma levels.

Adverse Effects

Drug	Nausea	Vomiting	Anorexia	Diarrhea	Dizziness	Headache	DC due to Adverse Event
Acetylcholinesterase Inhibitors (AChEIs)							
donepezil (Aricept, Aricept ODT)[45]	11 (6)	5 (3)	4 (2)	10 (5)	8 (6)	10 (9)	5-13 (5)
galantamine (Razadyne)[46]	24 (9)	13 (4)	9 (3)	9 (7)	9 (6)	8 (5)	7-10 (7)
galantamine ER (Razadyne ER)*[47]	nr	nr	nr	nr	nr	nr	nr
rivastigmine (Exelon)[48]	29 (11)	17 (2)	6 (3)	7 (4)	6 (1)	4 (3)	18.2 (11.2)
rivastigmine (Exelon Patch)[49]	7-21 (5)	6-19 (3)	3-9 (2)	6-10 (3)	0-2 (1)	3-4 (2)	8.6-9.6 (5)
tacrine (Cognex)[50]	28 (9)	28 (9)	9 (3)	16 (5)	12 (11)	11 (15)	17 (5)
NMDA receptor antagonist							
memantine (Namenda)[51]	nr	3 (2)	nr	nr	7 (5)	6 (3)	nr

*In clinical trials, once daily treatment with Razadyne ER was well tolerated and adverse events were similar to those seen with Razadyne.

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

In general, the incidence of adverse events for the agents in this class is directly related to the dosage being administered.

Hepatotoxicity has been reported with tacrine, but not with the other agents in this class. In a review of tacrine trials involving nearly 2,500 AD patients, 49 percent of patients treated with tacrine developed elevated ALT levels.[52] Elevations in ALT three times the upper limit of normal (ULN) occurred in 25 percent of patients while levels 20 times ULN were reported in two percent of patients. Most cases of elevated ALT were asymptomatic with occasional eosinophilia, fever, and rash. Elevated transaminases returned to normal four to six weeks after discontinuing the drug. There were few reports of jaundice and no reports of death due to hepatotoxicity. The manufacturer recommends that transaminase levels be monitored every other week from weeks four through 16, then every three months thereafter.

Other adverse reactions occurring in $\geq$10 percent of patients at a rate higher than placebo:

Special Populations[53,54,55,56,57,58,59,60]

Pediatrics

No published studies on the use of these agents in the pediatric population were identified. AChEIs are contraindicated for use in children. For the NMDA receptor antagonist, memantine there are also no well-controlled trials demonstrating safety and efficacy in children

Pregnancy

Donepezil and tacrine are classified as Pregnancy Category C. Galantamine, rivastigmine and memantine are classified as Pregnancy Category B.

Renal Impairment

The dose of galantamine should be titrated cautiously in patients with moderate renal impairment, and galantamine use is not recommended in patients with severe renal impairment. The dose of memantine requires dosage adjustment in patients with severe renal impairment.

Hepatic Impairment

The dose of galantamine should be titrated cautiously in patients with moderate hepatic impairment, and galantamine use is not recommended in patients with severe hepatic impairment. Tacrine should rarely, if ever, be used because of its potential for severe hepatotoxicity. Memantine should be used with caution in patients with severe hepatic impairment.

Dosages

Drug	Starting Dosage	Minimum Therapeutic Dosage* (minimum time to reach)	Target Dosage** (minimum time to reach)	Special Considerations	Dosage Forms
			Acetylcholinesterase Inhibitors (AChEIs)		
donepezil (Aricept, Aricept ODT)	5 mg daily	5 mg daily (0 weeks)	10 mg daily (6 weeks)	--	tablets: 5, 10 mg tablets, orally disintegrating: 5, 10 mg
galantamine (Razadyne)	4 mg twice daily	8 mg twice daily (4 weeks)	12 mg twice daily (8 weeks)	moderate hepatic and/or renal impairment – reduce Target Dosage	tablets: 4, 8, 12 mg oral solution: 4 mg/mL
galantamine ER (Razadyne ER)	8 mg daily	16 mg daily (4 weeks)	24 mg daily (8 weeks)	moderate hepatic and/or renal impairment – reduce Target Dosage	Capsules: 8, 16, 24 mg
rivastigmine (Exelon)	1.5 mg twice daily	3 mg twice daily (2 weeks)	6 mg twice daily (6 weeks)	--	capsules: 1.5, 3, 4.5, 6 mg oral solution: 2 mg/mL
rivastigmine (Exelon Patch)	4.6 mg/24 hours	9.5 mg/24 hours (4 weeks)	9.5 mg/24 hours (4 weeks)	--	transdermal system: 4.6 mg/24 hours (5 cm^2 size contains 9 mg drug) 9.5 mg/24 hours (10 cm^2 size contains 18 mg drug)
tacrine (Cognex)	10 mg four times daily	nd	40 mg four times daily (12 weeks)	--	capsules: 10, 20, 30, 40 mg
			NMDA receptor antagonist		
memantine (Namenda)	5 mg daily	nd	10 mg twice daily (3 weeks)	moderate renal impairment – consider dosage reduction	tablets: 5,10 mg oral solution: 2 mg/mL

nd = data not available

* Minimum Therapeutic Dosage – the lowest dosage at which a statistically significant improvement in cognition over placebo is noted.

** Target Dosage – The dosage recommended by the manufacturer as showing the best results.

Clinical Trials

<u>Search Strategy</u>

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant of clinical trials; however, there are no randomized, double-blind, directly comparative studies of the drugs in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance and use data analysis techniques consistent with the study question. Due to the paucity of high-quality, active-control, randomized, controlled trials, placebo-controlled studies of these drugs in dementia associated with AD and PD were included in the review. Studies were included if they were of six months (24 weeks) duration or greater and had recognized cognitive and/or functional primary outcome measures. Due to high rates of loss to follow-up in many studies of the drugs in this class, clinical trials with less than 50 percent loss to follow-up were considered in this review. There were no tacrine studies that met these criteria. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

<u>EFFICACY SCALES</u>

Various assessment scales are used to evaluate patient response and efficacy in clinical trials for drugs used in the treatment of dementia associated with AD and PD.

COGNITION

Alzheimer's Disease Assessment Scale (ADAS) – This is a standardized assessment of cognitive function. This scale, in which a trained observer evaluates memory, language, and praxis, is the gold standard for measuring change in cognitive function in drug trials.[61] The FDA has proposed that therapeutic response to drugs used for AD be defined as an improvement of four or more points on the ADAS.[62]

Behavioral Rating Scale for Geriatric Patients (BGP) – This measures observable aspects of cognition, function, and behavior. The total BGP score has a significant association with the level of dependency.[63]

Mini-Mental Status Examination (MMSE) – This is the most widely used measure of cognitive function. It assesses orientation, registration, attention, recall, and language.[64] The MMSE has been shown to successfully differentiate dementia, depression, or a combination of the two.[65]

Severe Impairment Battery (SIB) - This is a cognitive assessment tool that examines elements of attention, orientation, language, memory, visual-spatial ability, construction, praxis, and social interaction.[66]

GLOBAL / FUNCTIONAL

Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) - The ADCS-ADL consists of questions directed at the patient's caregiver and is used to measure the functional capacity of the patient.[67] A subset of 19 items rates the patient's ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores.[68] A modification of this assessment, ADCS-ADL-sev, is used for patients with severe dementia.

Bristol Activities of Daily Living scale (BrADL) - This scale, which assesses 20 daily living abilities, was designed specifically for use in patients with dementia. The validity of this scale was measured by verifying that the items in the scale were important to caregivers and that there is good test-retest reliability.[69]

Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus) - There are a variety of CIBIC formats each different in depth and structure. The CIBIC-plus requires use of caregiver information. Generally, CIBIC results are not comparable across trials.[70]

Disability Assessment for Dementia scale (DAD) - This is a newer functional scale, rated by a trained observer, specifically developed for patients with AD. This scale assesses basic and instrumental ADLs.[71]

Neuropsychiatric Inventory (NPI) - This is a validated instrument that measures disturbed behavior through assessment of ten domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior.[72] In the NPI, each item is rated according to its frequency and severity based on a caregiver interview.

Progressive Deterioration Scale (PDS) – This measures function in both instrumental and basic ADLs by asking the caregiver to assess function using 27 items and to rate the patient's performance on a visual analogue scale that employs a fulcrum line with bipolar descriptions of ADLs at either end. This scale has been shown to be reliable and valid.[73]

Mild to Moderate Dementia of the Alzheimer's Type

donepezil (Aricept) and placebo

In a double-blind study, 473 patients with mild to moderate AD were randomized to receive 24 weeks of donepezil 5 mg/day, donepezil 10 mg/day, or placebo, followed by a six-week single-blind washout period.[74] In the study, cognitive function, as measured by the ADAS-cog, deteriorated significantly less in the active treatment groups compared to placebo (p<0.0001). The CIBIC-plus (p<0.005) and MMSE (p<0.001) also were better in both donepezil groups relative to placebo. There was a 22 percent loss to follow-up in the study.

Two hundred and seven patients with moderate AD were randomized to donepezil (5 mg/day for four weeks with titration to 10 mg/day based on physician judgment) or placebo for 24 weeks.[75] The double-blind study was completed by over 80 percent of patients in each treatment group. The primary outcome measure, CIBIC-plus, significantly favored active treatment over placebo at week 24 (p=0.0003). The 24-week response rate was 70 percent in the donepezil group and 47 percent in the placebo group (p=0.0007). Both the MMSE and SIB showed improvement in the active treatment group (p=0.0002 and p=0.0026, respectively compared to placebo at 24 weeks). The NPI showed benefit with donepezil treatment with significant differences with placebo in delusions (p=0.0073), apathy (p=0.0131), and aberrant motor behavior (p=0.0232).

In a double-blind study, 565 patients with mild to moderate AD were randomized to donepezil 5 mg/day or placebo.[76] A 12-week run-in period was completed by 486 patients, who were then re-randomized to either donepezil (5 or 10 mg/day) or placebo, with treatment continuing as long as judged appropriate. Over the first two years of the study, cognition (measured by MMSE) and functionality (measured by BrADL) among patients in the active treatment groups were significantly better than in the placebo group (p<0.001 for both comparisons). At three years, there was no significant benefit with donepezil compared to placebo in rates of institutionalization (42 to 44 percent in each group). There was no difference between groups in the progression of disability (measured by BrADL) or in behavioral and psychological symptoms (measured by NPI).

donepezil (Aricept) and galantamine (Razadyne)

In a multicenter, rater-blinded study, 182 patients with AD were randomized to 52 weeks of treatment with galantamine (8 mg/day for four weeks, then 16 mg/day for four weeks with optional titration to 24 mg/day) or donepezil (5 mg/day for four weeks with optional titration to10 mg/day).[77] The study was completed by 78 to 80 percent of patients in each group. At the end of the study, approximately 70 percent of patients in each group were receiving the maximum dose. In each group, the BrADL scores were constant through month nine, then worsened thereafter. At week 52, there was a similar functional responder rate (defined as no increase in BrADL score), 39 percent, in each group. The cognitive response rate (defined as no worsening of MMSE scores from baseline) was higher in the galantamine group (55 percent) than in the donepezil group (33 percent; p≤0.0005) although the between group difference in MMSE was not significant. The ADAS-cog responder rates were not statistically different in the galantamine (45 percent) and donepezil (32 percent; p<0.1) groups at the conclusion of the study.

galantamine (Razadyne) and placebo

A total of 636 patients with mild to moderate AD were evaluated in a six-month, double-blind, trial.[78] Patients were randomized to galantamine at a target dose of either 24 or 32 mg/day or to placebo. Patients randomized to galantamine started therapy with 8 mg/day for the first week. The dose was then increased weekly by 8 mg/day until patients were at their target dose, on which they continued therapy for an additional five months. After a total of six months of treatment, patients receiving either dose of galantamine had significant improvement compared to placebo in ADAS-cog score (p<0.001 for both galantamine groups) and CIBIC-plus (p<0.05 for both galantamine groups). There was no significant difference between the galantamine groups. The loss to follow-up rate in the galantamine groups (32 to 42 percent) was higher than in the placebo group (19 percent). Of 438 patients completing the first phase of the study, 353 entered an open-label phase in which all patients received galantamine 24 mg/day after re-titration. Mean ADAS-cog and DAD scores were unchanged from baseline in patients who received galantamine 24 mg/day for the entire 12-month period.

Patients completing two double-blind, placebo-controlled trials (n=699) were escalated to a 24 mg dose (12 mg twice daily) of galantamine during a period of two weeks and treated for 12 months beyond the initial 6.5-month, double-blind period (total treatment duration: 18.5 months).[79] The primary efficacy measure was the change from baseline in the ADAS-cog score at the conclusion of the study. Patients were maintained close to baseline cognitive ability for 12 months.

In a double-blind, parallel group study, 653 patients with mild to moderate AD were randomized to receive galantamine titrated to 24 mg/day, galantamine titrated to 32 mg/day, or placebo.[80] The six-month study was completed by 525 (80 percent) of the enrollees. At the conclusion of

the study, patients receiving either dose of galantamine had significantly better outcomes as measured by the ADAS-cog, ADCS-ADL, and CIBIC-plus (p<0.05 for all comparisons to placebo). The galantamine 32 mg/day dosage (p<0.05), but not the lower dose (p=0.1), was significantly better than placebo in blunting the progression of dementia as measured by DAD.

galantamine (Razadyne) and galantamine ER (Razadyne ER)

In a double-blind, parallel-group trial, 971 patients with mild to moderate AD were randomized to treatment for six months with galantamine 8 or 12 mg twice daily, galantamine ER 16 or 24 mg once daily, or placebo.[81] The mean change from baseline in ADAS-cog was similar in the galantamine (-1.6 ± 0.4) and galantamine ER (-1.3 ± 0.3) groups, and both treatments were superior to placebo (+1.3 ± 0.3). Compared to placebo, both galantamine regimens were associated with a significant improvement in ADCS-ADL but not in CIBIC-plus or NPI. Galantamine ER had similar tolerability and safety profiles compared with twice-daily galantamine.

rivastigmine (Exelon) and placebo

In a double-blind study, 725 patients with mild to moderately severe AD were randomized to receive either placebo or rivastigmine 1 to 4 mg/day (low dose) or 6 to 12 mg/day (high dose).[82] Doses were titrated up within the assigned dosage range over the first 12 weeks, then continued at that dose for an additional 14 weeks. Patients in the high-dose rivastigmine group demonstrated improvement in the ADAS (p<0.05) and CIBIC-plus (p<0.001) compared to patients in the placebo group. The CIBIC-plus improved more frequently in the high-dose rivastigmine group (37 percent) than in the low-dose (30 percent) or placebo (20 percent) groups.

rivastigmine patch (Exelon Patch) versus rivastigmine capsule (Exelon) and placebo

The efficacy, safety and tolerability of rivastigmine patches was compared to rivastigmine capsules and placebo in the 24-week, double-blind, double-dummy, placebo- and active-controlled IDEAL (Investigation of transDermal Exelon in Alzheimer's disease) study with 1,195 AD participants.[83] Patients with AD were randomized to placebo or one of three active treatment target groups: 10-cm(2) rivastigmine patch (delivering 9.5 mg/24 hours – low dose group); 20-cm(2) rivastigmine patch (delivering 17.4 mg/24 hours – high dose group) or 6 mg rivastigmine capsule administered twice daily. Primary efficacy measures were the ADAS-cog and Alzheimer's Disease Cooperative Study-Clinical Global and Impression of Change. Secondary outcome measures assessed a range of domains, including behavior, cognitive performance, attention, executive functions and activities of daily living. All rivastigmine treatment groups showed significant improvement relative to placebo. The low dose patch group showed similar efficacy to capsules, with approximately two-thirds fewer reports of nausea and vomiting incidences statistically not significantly different from placebo. The high dose patch group showed earlier improvement and numerically superior cognitive scores versus the low dose patch group with similar tolerability to capsules. Local skin tolerability was good.

A prospective outcome of the IDEAL study was to evaluate caregiver preference for rivastigmine patches compared to capsules.[84] Caregivers rated patch adhesion throughout. The AD Caregiver Preference Questionnaire (ADCPQ) assessed patch versus capsule from caregivers' perspective based on expectations, preferences, and satisfaction with treatment. A total of 1,059 caregivers completed the ADCPQ while their respective patients were on study drug. More than 70 percent of caregivers preferred the patch to capsules. It was preferred with respect to ease of use (p<0.0001) and ease of following treatment regimen (p<0.0001).

Caregivers indicated greater satisfaction overall (p<0.0001) and less interference with daily life (p<0.01) with the patch versus capsule.

Moderate to Severe Dementia of the Alzheimer's Type

donepezil (Aricept) and placebo

Patients with moderate to severe AD were randomized to donepezil (5 mg/day for the first 28 days and 10 mg/day thereafter as per the clinician's judgment) or placebo in a 24-week, double-blind study.[85] This 290-patient study was completed by 84 to 86 percent of the patients in each group. Patients receiving donepezil showed benefits on the CIBIC-plus, the primary outcome measure, compared with placebo at all visits up to and including week 24 (p<0.001). All other secondary measures including MMSE, SIB, DAD, and NPI showed significant differences between the groups in favor of donepezil at week 24.

Two hundred ninety patients with moderate to severe AD were randomized to receive donepezil (5 mg/day for four weeks, then 10 mg/day per clinician judgment) for 24 weeks.[86] In this double-blind study, the mean change from baseline in DAD, the primary endpoint, significantly favored donepezil over placebo (p<0.0001) at week 24. The specific components of DAD that favored donepezil were hygiene (p<0.0001), dressing (p=0.0003), and leisure/housework (p=0.0037).

Three hundred forty three patients with severe AD [MMSE scores one to 12 and Functional Assessment Staging (FAST) scores ≥ 6] were randomized to donepezil 10 mg daily (n=176) or placebo (n=167) for 24 weeks in a multinational, double-blind, placebo-controlled trial at 98 sites.[87] Donepezil was superior to placebo on SIB score change from baseline to endpoint (p=0.0001). Donepezil was favored at endpoint for CIBIC-plus and MMSE scores (p=0.0473 and p=0.0267). Donepezil was not significantly different from placebo on the ADCS-ADL-sev, NPI, CBQ (Caregiver Burden Questionnaire or RUSP (Resource Utilization for Severe AD Patients). Adverse events reported were consistent with the known cholinergic effects of donepezil and its safety profile in patients with mild to moderate AD.

donepezil (Aricept) and rivastigmine (Exelon)

Patients with moderate to moderately severe AD were randomly assigned to rivastigmine 3 to 12 mg/day or donepezil 5 to 10 mg/day over a two-year period.[88] In the double-blind study, 994 patients received treatment and 58 percent of these patients completed their assigned treatment regimen. The average decline in SIB, the primary efficacy measure, was similar between the two groups. Approximately 36 percent of patients in each group retained SIB scores that were equal or better than baseline. The two groups were also similar in the secondary measure of cognition, change in MMSE score from baseline, as well as in the change in NPI. At the conclusion of the study, 19 percent of patients receiving donepezil and 25 percent of those receiving rivastigmine retained ADCS-ADL scores that were equal or better than baseline (p=0.047). Fewer patients receiving donepezil (16 percent) than rivastigmine (26 percent) discontinued their assigned treatment due to adverse events.

memantine (Namenda) and placebo

A total of 252 patients with moderate to severe AD were randomized to receive placebo or memantine titrated to 20 mg daily in double-blind fashion for 28 weeks.[89] Seventy-two percent of patients completed treatment. At endpoint (completion or early withdrawal from the study), patients receiving memantine had less deterioration on ADCS-ADL-sev (p=0.02), a primary efficacy variable, and SIB (p=0.002). There were no differences between active treatment and

placebo in CIBIC-plus, MMSE, or NPI. Treatment with memantine (Namenda) did significantly reduce caregiver burden, as measured by BGP, in comparison to placebo (p=0.01). In an open-label, 24-week extension to the trial, 175 patients were allowed to receive memantine per the original study protocol.[90] In the study extension, subjects who had originally received placebo experienced a significantly slower rate of decline in ADCS-ADL-sev in the open-label phase compared to the randomized phase of the trial. Conversely, subjects who received memantine during all 52 weeks experienced a faster rate of decline in ADCS-ADL-sev in the open-label phase. The rate of decline in the CIBIC-plus slowed during the open-label phase in both original randomization groups compared to the randomized phase. While participants who received memantine during the entire 52-week treatment period experienced a similar rate of decline in the SIB during the randomized and open-label study phases, this outcome improved during the open-label phase for those who had received placebo during the randomized phase.

In a 24-week, double-blind, placebo-controlled trial, patients not receiving a cholinesterase inhibitor (n=350) were randomized to receive memantine 20 mg/day or placebo.[91] Prospectively defined analyses failed to demonstrate a statistically significant benefit of memantine treatment compared with placebo on the SIB at the endpoint of 24 weeks although a significant advantage was observed at weeks 12 and 18. The 19-item ADCS-ADL did not differ significantly between groups in any analysis. CIBIC-plus did not significantly favor memantine at week 24 despite a significant advantage for memantine at weeks 12 and 18. Other secondary outcomes showed no significant treatment differences. Post hoc analyses of potentially confounding covariates and alternative methods of imputing missing data did not substantially alter the results. Due to violations of normality assumptions for the SIB and ADCS-ADL19, nonparametric analyses were performed; statistically significant benefit of memantine over placebo was demonstrated at week 24 for the SIB but not the ADCS-ADL19. Type and incidence of adverse events were similar in both groups.

Data from six randomized, double-blind, placebo-controlled, six-month studies were pooled and a subgroup of patients (867 patients on placebo and 959 patients on memantine) with moderate to severe AD (MMSE < 20) was analyzed.[92] "Clinical worsening" was defined as a decline on the ADAS-cog or the SIB and on the CIBIC-plus and the ADCS-ADL and "marked clinical worsening" was defined as ≥ 4 points decline on the ADAS-cog or ≥5 points on the SIB and decline on the CIBIC-plus and the ADCS-ADL. More placebo-treated than memantine-treated patients showed any clinical worsening (28 versus 18 percent; p<0.001) and 21 percent placebo-treated patients compared to 11 percent memantine-treated patients had marked clinical worsening (p<0.001).

In a 24-week, double-blind study, 404 patients with moderate to severe AD who were receiving stable doses of donepezil were randomized to memantine at a starting dose of 5 mg/day increased to 20 mg/day or placebo.[93] The change in total mean scores favored memantine versus placebo for both primary outcome measures, SIB (p<0.001) and ADCS-ADL (p=0.03). Secondary outcomes, including BGP (p=0.001) and NPI (p=0.002), also showed significant benefits of memantine compared to placebo. Improvement in CIBIC-plus occurred in 55 percent of memantine patients and 45 percent of those receiving placebo (p=0.03). Over 25 percent of patients in the placebo group were lost to follow-up, compared to 15 percent of patients in the memantine group.

Dementia Associated with Parkinson's Disease

rivastigmine (Exelon) and placebo

In a 24-week, double-blind study, 541 patients with mild-to-moderate PD-associated dementia were randomized to receive rivastigmine 1.5 mg twice daily, titrated up to 12 mg daily, or matching placebo.[94] Patients in the rivastigmine group had a mean improvement of 2.1 points (8.8 percent) for the ADAS-cog (a primary efficacy variable) compared to a 0.7 point (2.9 percent) worsening in the placebo group (p<0.001). Patients in the rivastigmine group also had more favorable outcomes based on CGI-C, a primary efficacy measure, with moderate or marked improvement noted in 20 percent of patients compared to 15 percent of patients in the placebo group (p=0.02). Marked or moderate worsening of CGI scores occurred in 34 and 43 percent of patients in the rivastigmine and placebo groups, respectively. Rivastigmine also provided benefit compared to placebo in ADCS-ADL (p=0.02), NPI (p=0.02), and MMSE (p=0.03). Nearly 25 percent of patients prematurely discontinued the study with 17 percent of patients in the active treatment group withdrawing due to adverse events (compared to eight percent of patients in the placebo group).

Meta-Analyses

Researchers performed a meta-analysis of randomized, double-blind, placebo-controlled, parallel-group trials of donepezil, galantamine, and rivastigmine published through early 2002.[95] They identified 16 trials of over 8,000 patients in which the drugs were used in therapeutic doses for at least 12 weeks and for which a cognitive outcome was reported. The pooled mean proportion of global responders (improvement in CGI-C or CIBIC-plus) to AChEI in excess of that for placebo was ten percent (95% CI, 4-17 percent; p<0.05). The number needed to treat (NNT) to yield one additional global responder was 12 (95% CI, 9-16). The NNT to yield one additional cognitive responder (four points or greater improvement on ADAS-cog) was ten (95% CI, 8-15). The NNT for one additional patient to experience an adverse event was 12. The rates of adverse events, dropout for any reason, and dropout because of adverse events were all seven to eight percent higher among patients receiving AChEI treatment than among those receiving placebo (p<0.05 for all comparisons). The difference between each of the three AChEIs and placebo in adverse events and dropout rates was similar, with the exception of the dropout rate for galantamine (Razadyne) (14 percent; 95% CI, 8-21 percent) differing from placebo more than that for donepezil (3 percent; 95% CI, 1-6 percent).

A meta-analysis using both electronic and manual search strategies examined the effect of donepezil, galantamine, and rivastigmine on AD clinical outcomes and completion rates.[96] Regression analyses compared the effect of dose on clinical outcomes and completion rates, using ten donepezil, six galantamine, and five rivastigmine studies. All three drugs showed beneficial effects on cognitive tests, as compared with placebo. For donepezil and rivastigmine, larger doses were associated with a larger cognitive effect; this was not the case with galantamine. The odds of clinical global improvement demonstrated superiority over placebo for each drug with no dose effects noted. Dropout rates were greater with galantamine and rivastigmine. There was little difference in dropout rate for each drug at each dose level, except with high-dose donepezil. This was accounted for by the high dropout rate in two 52-week studies using larger doses.

A meta-analysis that included 22 placebo-controlled clinical trials of donepezil, galantamine, and rivastigmine estimated an average 3.9 point reduction in ADAS-cog scores and a 0.26-0.54 point improvement in CIBIC-plus scores from treatment with these agents.[97]

Summary

There are four cholinesterase inhibitors approved as first-line for treatment of mild to moderate AD. Donepezil (Aricept, Aricept ODT) is also approved for treatment of moderate to severe AD. Rivastigmine (Exelon, Exelon Patch) is also approved for the treatment of mild to moderate dementia associated with PD. Other than the potential hepatotoxicity associated with tacrine (Cognex), these agents have a low incidence of serious side effects. Minor side effects tend to be cholinergically mediated.

Pharmacologic interventions with the five FDA-approved medications addressed in this review have shown statistically significant improvement on the various instruments used to evaluate the changes in patients with dementia due to Alzheimer's. Most of these outcomes are not used in routine clinical practice and the interpretation of their clinical significance is challenging. Many of the improvements demonstrated in clinical trials, while statistically significant, were not clinically important and their importance cannot be determined at this time. Evidence of improvement on global assessment tools was available for donepezil, galantamine, rivastigmine and memantine, although the changes were generally modest. The evidence regarding their effect on quality of life was mixed. The evidence for tacrine was less convincing, especially in the presence of serious adverse effects. No convincing evidence demonstrates that one therapeutic treatment is more effective than another.[98]

The decision to initiate therapy should be based on an evaluation of the benefits and risks associated with an individual patient. All of these medications have known adverse events and the decision to manage patients with Alzheimer's should balance those potential adverse events against modest or even no benefit. [99]

Currently, there is no method to predict which patients might have a clinically important response.[100] There are a high percentage of patients who do not respond to the cholinesterase inhibitors. In patients that do respond, these agents provide only modest symptomatic relief. There are limited data showing evidence for a prolonged duration of effect.[101,102,103,104,105] Currently, there is a lack of evidence that symptomatic treatments can alter the pathological course of dementia associated with AD or PD. It remains unclear if use of these drugs delays nursing home placement or alters mortality.

Tacrine should rarely, if ever, be used because of its potential for severe hepatotoxicity and the availability of equally effective, less toxic agents. The American Association of Geriatric Psychiatry (AAGP) has published their position that tacrine should not be used in light of the alternatives, its complex titration, and associated risk of hepatic toxicity.[106]

The remaining AChEIs have been shown to have similar, albeit small, therapeutic effects at six months, as measured by global and cognitive rating scales. Despite the relatively small treatment effect, the AChEIs are recommended as first-line treatment in patients with mild to moderate AD, primarily due to a lack of effective alternatives.[107]

A common pattern of response to treatment with AChEIs is initial improvement in cognition, followed by maintenance of cognitive gains above baseline and finally a decline in cognition to below baseline levels with the level of cognition remaining above that predicted for those not receiving pharmacologic treatment. There may be benefit in switching cholinesterase inhibitors after treatment failure or intolerability to the first agent tried.

Galantamine (Razadyne) and rivastigmine (Exelon) must be dosed twice daily whereas donepezil (Aricept, Aricept ODT), galantamine ER (Razadyne ER) and transdermal rivastigmine

(Exelon Patch) are administered once daily. Rivastigmine (Exelon) and galantamine (Razadyne) are also available in oral solutions, and donepezil (Aricept ODT) as an orally disintegrating tablet. Rivastigmine (Exelon Patch) is also available as a transdermal patch (for application to the upper or lower back, upper arm or chest) which may improve therapy compliance due to ease of administration for caregivers. The effectiveness of all the cholinergic products is limited by the maximum tolerated dose. All of the cholinesterase inhibitors must be slowly titrated upward to minimize the gastrointestinal effects of the products.

Among galantamine (Razadyne, Razadyne ER), donepezil (Aricept, Aricept ODT), and rivastigmine (Exelon, Exelon ER), the incidence of gastrointestinal complaints (nausea, vomiting, diarrhea, anorexia, and weight loss) is the highest with rivastigmine (Exelon, Exelon Patch) and the lowest with donepezil (Aricept, Aricept ODT). Rivastigmine (Exelon, Exelon Patch) does not have CYP450-mediated drug interactions, which may offer an advantage for some patients.

The NMDA receptor antagonist, memantine (Namenda), is approved for the treatment of moderate to severe AD. Due to conflicting data on the efficacy of memantine (Namenda) in mild AD, the FDA rejected a request to approve memantine (Namenda) for mild AD. There are data showing that memantine (Namenda) in combination with AChEIs is beneficial in moderate to severe AD patients.[108,109] Memantine (Namenda) does not have the gastrointestinal adverse events common among the AChEIs.

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