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Effective treatment of Alzheimer disease and its complications

ABSTRACT

In Alzheimer disease, therapies to improve the core symptoms and perhaps even slow disease progression include cholinesterase inhibitors, receptor agonists, anti-inflammatory drugs, and antioxidants. Neuroleptics, antiepileptics, and nondrug approaches are used to control and relieve complications such as delusions, hallucinations, paranoia, and agitated behavior. We outline a practical approach to the use of these therapies.

KEY POINTS

Three cholinesterase inhibitors are currently approved by the FDA for treating Alzheimer disease: tacrine, donepezil, and rivastigmine. Of these, the latter two have some advantages in that they can be given once daily and produce fewer side effects.

Management of the behavioral and neuropsychiatric complications of Alzheimer disease is largely empiric. Try to simplify the regimen as much as possible.

If a new, significant behavioral disorder such as agitation arises, look for a medical cause such as pain, infection, urinary retention, or an adverse effect from a new medication.

Depression is common in Alzheimer disease. Selective serotonin reuptake inhibitors can help, but can cause agitation, anxiety, and akathisia.

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WE CAN RELIEVE symptoms and complications and substantially improve the Alzheimer patient's quality of life through prompt and careful use of current treatments, although we cannot as yet cure the disease or arrest its progression.

This article outlines practical use of the best of currently available therapies and discusses treatments for behavioral and neuropsychiatric complications such as anxiety, depression, agitation, and aggression.

OVERVIEW OF ALZHEIMER DISEASE

Alzheimer disease has evolved from a rare curiosity to a major health problem. It is the most common cause of dementia in Europe and North America. In the United States it affects about 4 million people, with estimated indirect and direct costs approaching $100 billion per year.

The **prevalence** of Alzheimer disease rises exponentially with age, approximately doubling every 5 years from 1% at age 60 to 50% by age 90. In addition to age, other established risk factors are a positive family history, the apolipoprotein E4 genotype, and Down syndrome.

The **diagnosis** of Alzheimer disease has been considerably refined in the past 15 years and can be achieved with 80% to 90% accuracy by adhering to proper clinical criteria supplemented by the judicious use of radiologic and laboratory studies. Contrary to common belief, the diagnosis of Alzheimer disease is one of inclusion, not exclusion.[1]

The **prognosis** is one of progressive decline. The course is roughly divided into early, middle, and late stages, each lasting about 3 years, over a period of 8 to 10 years.

Experience shows that if we are going to influence the outcome of Alzheimer disease, it is likely to be in the earlier stages. Therefore, early diagnosis is critical.

Treatments that target the Alzheimer disease process (ie, primary treatments) include:

- Cholinesterase inhibitors
- Receptor agonists
- Estrogen
- Anti-inflammatory drugs
- Antioxidants
- Various experimental agents.

Treatments that target the behavioral and neuropsychiatric complications of the disease process (ie, secondary treatments) include nondrug techniques, neuroleptics, and antiepileptics.

CHOLINESTERASE INHIBITORS

Of the primary treatments for Alzheimer disease, the cholinesterase inhibitors are the best understood. The basis for their use is that patients with Alzheimer disease lose cholinergic function in the brain, specifically losing neurons and choline acetyltransferase in the nucleus basalis, entorhinal cortex, hippocampus, and temporoparietal neocortex—all regions heavily affected by Alzheimer disease and highly correlated with memory loss and other cognitive dysfunction.

The diagnosis of Alzheimer disease is one of inclusion, not exclusion

The cholinergic presynaptic bouton contains the enzyme choline acetyltransferase, which forms acetylcholine from mitochondrial acetyl-CoA and choline (FIGURE 1). Acetylcholine is packaged in synaptic vesicles, transported to the synaptic membrane, and released with depolarization, traveling to the postsynaptic cholinergic receptors where it undergoes hydrolysis to acetate and choline by acetylcholine esterase at the postsynaptic cleft. Cholinesterase inhibitors act by binding at these sites, preventing hydrolysis and increasing acetylcholine availability.

Cholinesterase inhibitors now available are:

- Tacrine (Cognex)
- Donepezil (Aricept).
- Rivastigmine (Exelon)

Under development are:

- Metrifonate
- Physostigmine
- Eptastigmine.

The various cholinesterase inhibitors differ mainly in their inhibition mechanisms, half-lives, metabolism, elimination, and side effect profiles. Tacrine, donepezil, and rivastigmine are currently approved by the US Food and Drug Administration (FDA) for use in Alzheimer disease. Metrifonate is likely to be released soon. The others are undergoing testing in phase II and III trials. So far, all of these drugs have demonstrated beneficial effects—albeit modest and unsustained—on cognition, behavior, and ability to perform activities of daily living. They should be prescribed once the diagnosis is reasonably secure and when short-term memory loss is most evident. They are also useful when apathy is a major behavioral feature. Warn patients' families that these drugs are given to improve memory and do not alter the ultimate outcome.

Tacrine

Tacrine, the first cholinesterase inhibitor approved by the FDA for treatment of Alzheimer disease, is a centrally acting reversible inhibitor of acetylcholinesterase and butyrocholinesterase. Limitations to its use include frequent dosing, risk of liver damage, and side effects.

Efficacy. Knopman et al,[2] in a well-designed clinical trial, found that taking tacrine for at least 2 years delayed nursing home placement and death. However, the data suggest that tacrine offers little or no benefit in patients with advanced Alzheimer disease, and that patients with moderate disease have the best responses.

Pharmacokinetics and metabolism. Tacrine is well absorbed, with peak plasma levels in 2 hours and an elimination half-life of 2 to 3 hours. It is hydroxylated and conjugated in the liver by the cytochrome P450 isoenzyme system, particularly cytochrome P450 IA2.

Side effects. The most common side effects of tacrine are nausea, vomiting, anorexia, abdominal pain, and diarrhea.

Owing to a risk of liver damage with tacrine use, the serum transaminase level should be checked every other week starting by the fourth week of therapy and continuing until the 16th week.

How cholinesterase inhibitors work in Alzheimer disease

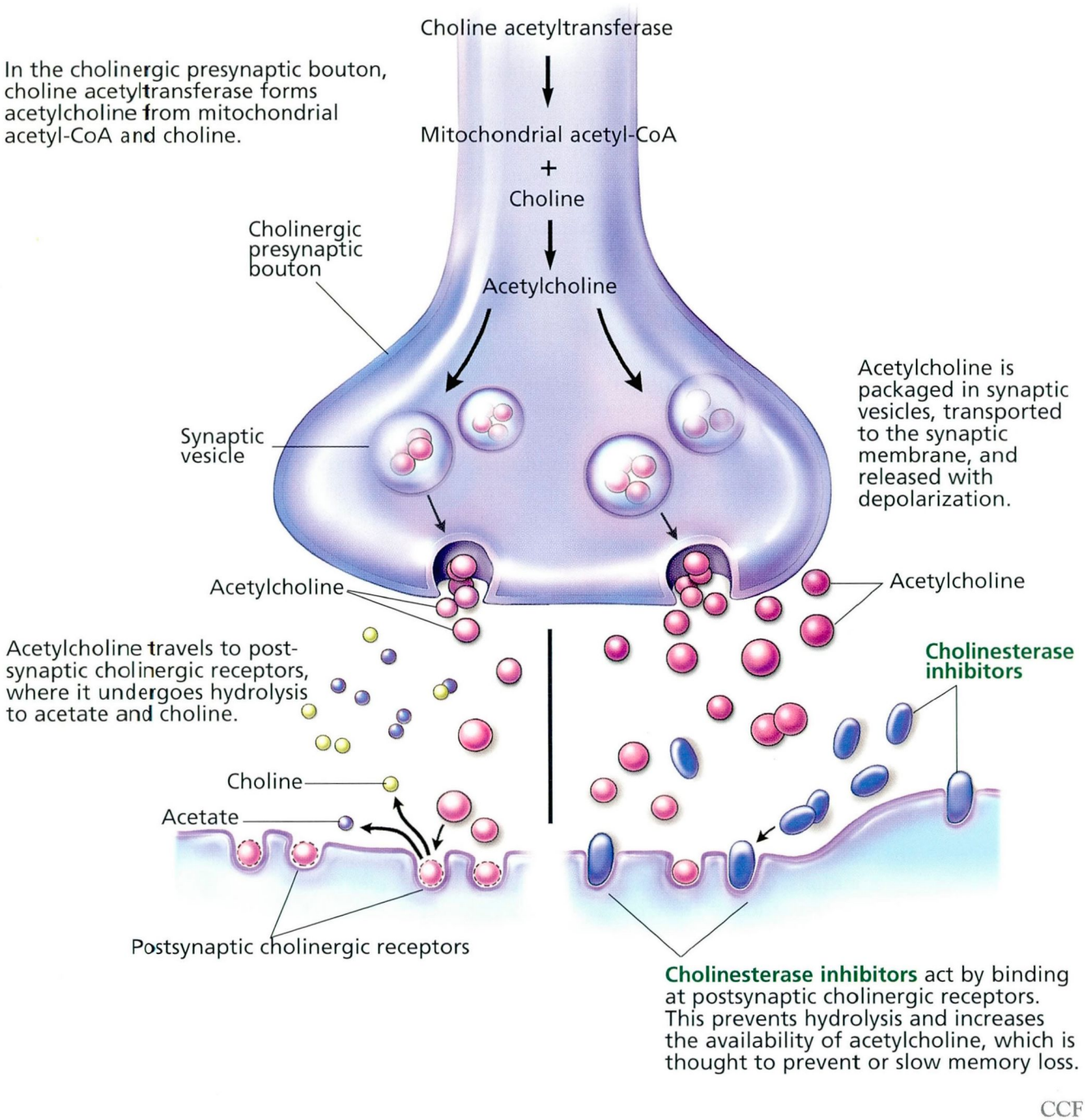

FIGURE 1

Cautions. Use caution if giving tacrine to patients who are taking theophylline or cimetidine, since both will be increased due to competing enzyme degradation. Since tacrine inhibits butyrylcholinesterase, which metabolizes succinylcholine, prolongation of neuromuscular blockade may occur. Also, use tacrine with caution in patients with peptic ulcer disease and supraventricular cardiac arrhythmia, as it enhances parasympathetic activity.

Dosage. Owing to its relatively short elimination half-life, tacrine requires a four-times-daily dosing schedule, beginning at 10 mg four times a day and gradually increasing over 6 weeks to 30 to 40 mg four times a day.

Donepezil

Donepezil, like tacrine, is a reversible cholinesterase inhibitor, but has a much longer elimination half-life (70 hours).

Advantages over tacrine are substantial. The long elimination half-life permits once-daily dosing. Rapid absorption (peak plasma levels at 4 hours) and high affinity for plasma protein, especially albumin, enable immediate dosing at therapeutic levels. Monitoring of liver enzymes is not necessary as there is no risk of hepatotoxicity.

So far, no reliable data support a benefit of nicotinic agonists

Efficacy. Several trials have shown significant improvements in cognition and functional capabilities.[3,4] In addition, pooled data suggest improvements in psychiatric and behavioral disturbances, especially anxiety, apathy, hallucinations, and motor restlessness.

Side effects. As with tacrine, the principal side effects are cholinergic: diarrhea, nausea, vomiting, anorexia, cramps, and fatigue. These are generally mild and resolve with continued administration.

Cautions. Caution is required for patients with supraventricular arrhythmias and peptic ulcer disease.

Dosage. Either 5 or 10 mg daily at bedtime. While there is a trend toward improved cognitive results at the higher dose, this does not reach statistical significance, and the side effects are greater at higher doses. Current recommendations are to begin with 5 mg and increase to 10 mg in 6 weeks if there is no response or only a marginal response.[5]

We begin donepezil 5 mg at bedtime in Alzheimer patients with mild to moderate impairment. If the patient tolerates the drug but shows no improvement, we increase the dose to 10 mg at bedtime. If a patient is already taking tacrine, is tolerating it well, and is either stable or improving, we do not switch to another cholinesterase inhibitor.

Use of donepezil for memory loss alone. Donepezil is widely used "off-label" in patients who have memory loss but do not meet current Alzheimer disease diagnostic criteria. However, no data support this practice, although in one study[6] a substantial percent of patients with mild cognitive impairment developed Alzheimer disease within 2 years.

Rivastigmine

Rivastigmine, another second-generation cholinesterase inhibitor, is described as a pseudo-irreversible inhibitor, which forms carbamylated complexes with cholinesterase, delaying hydrolysis and resulting in a prolonged inhibition half-life. It is specific for acetylcholinesterase and is excreted in the urine with no hepatic involvement.

In a study involving 699 patients,[7] the beneficial results compared with placebo were more robust than those for tacrine or donepezil, although none have been compared with each other in clinical trials.[7] The principal side effects are gastrointestinal (nausea, vomiting, anorexia, diarrhea).

Metrifonate

Metrifonate is an irreversible cholinesterase inhibitor of the organophosphate class. It does not start out as a cholinesterase inhibitor, but is metabolized into one, resulting in stable, enduring cholinesterase inhibition. Its long inhibition half-life enables a simple dosing schedule. Whether it will have any advantage over other cholinesterase inhibitors remains to be seen. It is not likely to be released in the near future due to toxicity.

CHOLINERGIC RECEPTOR AGONISTS

Muscarinic receptor agonists

Muscarinic receptor agonists such as xanomeline and milameline were evaluated in Alzheimer disease after dopamine receptor agonists showed benefit in Parkinson disease.

Muscarinic receptors are postsynaptic areas that receive the packages of acetylcholine. While the rationale for using muscarinic receptor agonists seems logical, results have thus far been disappointing: modest benefit only, and a high dropout rate due to adverse side effects. The future of muscarinic receptor agonists in the management of Alzheimer disease is uncertain.

Nicotinic receptor agonists

Interest in nicotinic receptor agonists arose from an earlier, unconfirmed observation that cigarette smoking may reduce the risk of developing Alzheimer disease. Neurochemical studies suggested that nicotinic receptors located presynaptically resulted in acetylcholine release when stimulated. A small controlled trial of transdermal nicotine was negative, and no reliable data support benefit with nicotinic agonists at present.

ESTROGEN

There is evidence of estrogen receptors on hippocampal and cholinergic neurons, and observational and epidemiologic studies suggest estrogen is beneficial in memory enhancement in women. Recently, a large placebo-controlled study[8] sponsored by the National Institute on Aging and the National Institutes of Health determined that a year of estrogen replacement therapy did not improve cognition or functional ability in women with mild to moderate Alzheimer disease, nor did it appear to slow disease progression. The investigators added that estrogen's role in the prevention of Alzheimer disease merits further study.[8]

ANTI-INFLAMMATORY AGENTS

Several epidemiological studies showed a reduced risk of acquiring Alzheimer disease in patients with arthritis taking nonsteroidal anti-inflammatory drugs (NSAIDs). One meta-analysis suggested that the risk may be reduced by as much as 50%.[9] These observations are supported by neuropathologic evidence of inflammation in patients with Alzheimer disease, such as cytokines, complement, and activated microglia—all known to be involved in central nervous system dysfunction. In addition, beta-amyloid, one of the hallmarks of Alzheimer disease pathology, may induce central nervous system inflammation.

Despite these reports, only one clinical trial[10] supports the use of anti-inflammatory drugs in Alzheimer disease. This was a small trial with a high dropout rate due to side effects. NSAIDs cause a high incidence of gastrointestinal toxicity, posing a formidable barrier to their long-term use; however, a novel class of NSAIDs, the cyclo-oxygenase-2 inhibitors, may allow for more productive trials in Alzheimer disease. Still, at best, anti-inflammatory drugs are not expected to reverse the disease, but rather to retard its progression.

ANTIOXIDANTS

Considerable direct and indirect evidence indicates that oxidative stress (lipid peroxidation, DNA injury) is involved in the pathogenesis of Alzheimer disease. Both iron deposition and beta-amyloid induce the generation of free radicals, which injure cells, including neurons.[11]

NSAIDs may slow Alzheimer disease, but not reverse it

Putative antioxidants include vitamins E, C, and A, selegiline, coenzyme Q, glutathione peroxidase, catalase, and superoxide dismutase. Only vitamin E (alpha-tocopherol) and selegiline have undergone investigation in the treatment of Alzheimer disease. A study by Sano[12] suggested that either selegiline or vitamin E, but not both, delays progression of Alzheimer disease, and that vitamin E delays the need for nursing home placement. These findings need to be verified. The dosage of selegiline is 5 mg twice daily. As for vitamin E, the results with antioxidants are still only modest, and it seems prudent to treat newly diagnosed patients with 1,000 IU.

OTHER THERAPIES

Other putative therapies for Alzheimer disease—but still of uncertain benefit—include ginkgo biloba, noncholinergic neurotransmitter modulators, anti-amyloid agents, and neurotrophic (nerve growth) factors. While promising, further investigation is necessary.

So far, only one randomized study of ginkgo biloba has suggested a modest trend in memory improvement, and this has not been replicated. As with all herbal medicines, one never knows what and how much is in a given formulation due to a lack of regulation. We do not recommend it, but we don't actively discourage taking it.

MANAGEMENT OF BEHAVIORAL AND NEUROPSYCHIATRIC DISTURBANCES

From a practical standpoint, managing the complications of Alzheimer disease poses a much greater challenge than treating the disease itself. Complications are largely behavioral and neuropsychiatric and tend to increase in frequency and severity as the disease progresses. Most Alzheimer patients develop at least one such complication. These include anxiety, depression, hallucinations, delusions, vegetative disorders (sleep disorders, appetite disorders, sexual dysfunction), and disturbed psychomotor activity. Patients tend to experience clusters of signs and symptoms of a variety of these disorders.[13]

It seems prudent to give newly diagnosed patients vitamin E, 1,000 IU daily

Management of these complications is hampered by a lack of good randomized trials comparing various therapies. Most guidelines are based on reviews, anecdotal experience, and personal observations. There is some logic in advocating certain approaches, such as using a drug to target a dominant abnormality. Nonetheless, most of the approaches that follow are necessarily empiric.

General management guidelines

Whenever neuropsychiatric disorders emerge or psychopharmacotherapy is considered, some basic guidelines are worth following:

- Look for a concurrent illness that may be modifiable.
- Search for current medications to eliminate, including over-the-counter drugs such as sleep aids, which may have anticholinergic properties that may aggravate confusion and memory loss.
- Try nonpharmacologic alternatives when possible.
- Target the dominant symptom, selecting the drug that is most likely to help and that may address more than one symptom.
- Always begin at low doses (about one third to one half of the usual adult dose) and escalate in small increments, capping at the lowest, effective dose.
- Look for the agent with the best side effect profile.
- Avoid multiple drug regimens.
- Always review compliance and ensure that someone is helping the patient take his or her medications at home.
- Review the treatment program, regularly seeking to simplify where possible.
- Do not anticipate a complete reduction of symptoms. The goal is to improve the quality of life and decrease caregiver stress, and a more aggressive approach often results in intolerable side effects.
- Give clear oral and written instructions.

Management strategies can be separated into nonpharmacologic and pharmacologic, both of which are employed in most instances.

Nondrug treatment of behavioral complications

The general principles of behavioral management are detailed in TABLE 1.[14,15]

In a patient with a new, significant behavioral disorder, especially agitation, look for a medical cause such as pain, infection, urinary retention, or an adverse effect from a new medication, as physical ailments usually manifest as behavioral disturbances in Alzheimer disease patients.

Encourage caregivers to react to the patient in a nonconfrontational manner, maintain consistency in the environment, avoid sensory deprivation, and remove unsafe environmental barriers.

Caregivers need support and encouragement! Acknowledge their stress, and try to get other family members and others to help in the care of the patient. The most common reason for nursing home placement of patients with Alzheimer disease is fatigue, depression, or illness in the primary caregiver.

Drug treatment of behavioral complications

The underlying principle in pharmacotherapy is to deal with a specific target symptom. A "shotgun" approach is not only ineffective but also potentially harmful.

Depression in Alzheimer disease is common, affecting 40% to 50% of patients. It is most easily recognized in the early phase of the illness. Major depressive episodes are less common than more transient elements of depression. Often, depression will manifest only as crying episodes and expressions of worthlessness and low self-esteem. The staged approach to treatment is to use nonpharmacologic approaches followed by antidepressant therapy if the mood disorder persists.

Selective serotonin reuptake inhibitors (SSRIs). Although depressed Alzheimer patients respond to tricyclic antidepressants, the anticholinergic effects of these drugs often increase confusion. SSRIs (fluoxetine, paroxetine, sertraline, citalopram) have simplified management. Side effects of SSRIs include agitation, anxiety, and sexual dysfunction. If anxiety intervenes, a small dose of an anxiolytic with the SSRI can be used. Akathisia, or the desire to move about, may be a complicating side effect of fluoxetine and may give the appearance of increased agitation. Switching to another SSRI may suffice to control this symptom.

TABLE 1

How to manage behavioral disturbances in Alzheimer disease

- Decide which symptoms to treat (ie, depression, anxiety, psychosis, agitation, vegetative disorder, motor hyperactivity)
- Look for a medical cause for the behavioral disturbance(s)
- Establish or revisit neuropsychiatric diagnoses
- Evaluate for other aggravating factors
- Adapt the treatment plan to specific cognitive defects
- Identify psychosocial factors that may contribute to the behavioral disturbance
- Educate caregivers
- Employ behavior management techniques
- Use psychotropic drugs for specific psychiatric syndromes; avoid a shotgun approach
- Treat any symptoms

Drug treatment of neuropsychiatric disturbances

Psychoses pose several unique problems in Alzheimer disease management. Psychoses take several, often concurrent forms, including delusions, hallucinations, paranoia, and agitated behavior. Psychosis is quite common and occurs at some point in about half of Alzheimer disease patients, usually emerging in the middle or late stages, and seems to correlate with the density of plaques and tangles in the medial temporal and medial frontal cortex.

Delusions are classically defined as false beliefs based on incorrect inferences about external reality and firmly held despite evidence to the contrary. Most delusions in Alzheimer disease take the form of belief of personal harm, infidelity, abandonment, and misidentification, as well as in the attribution of negative emotions to one's spouse, significant others, and caregivers. These symptoms, when persistent and accompanied by hallucinations and especially aggression and agitation, are among the most common reasons Alzheimer disease patients are institutionalized.

Hallucinations are false sensory impressions occurring without a corresponding external stimulus. The hallucinations may be visual or auditory. Sensory deprivation is often a cause of hallucination and should be vigorously looked for, particularly visual and auditory deprivation. Hallucinations may also signify delirium, indicating the need for a medical reevaluation.

Treat the problematic symptom—a shotgun approach can be harmful

Agitation and aggression when combined with hallucinations and delusions require aggressive management. Depending on the severity of the symptoms, use of a neuroleptic such as haloperidol 0.5 to 3 mg daily may be warranted. Neuroleptics often produce side effects, particularly parkinsonism, and may not be tolerated for long periods. One alternative therapy is thioridazine 25 to 75 mg daily, which can be effective but is less likely to cause extrapyramidal symptoms. The newer, nonneuroleptic agents such as clozapine and olanzapine are alternatives, but clozapine requires weekly monitoring of the white blood count due to the risk of agranulocytosis. If nighttime hallucinations occur and sleep loss is an issue, trazodone 50 to 100 mg at night

may be quite useful.

When motor restlessness or akathisia is prominent, propranolol 10 to 20 mg three times daily is helpful.

Use of antiepileptics. Finally, if the neuroleptic or atypical neuroleptic agents are ineffective or are accompanied by intolerable side effects, antiepileptics such as carbamazepine or valproic acid may be very useful for agitation and psychosis. Carbamazepine is started at small doses of 100 mg twice daily and is gradually titrated to 200 mg three times daily, while valproic acid is begun at doses of 125 mg twice daily and is gradually titrated to 500 mg three times daily as tolerated, or higher if necessary.

Sleep disturbances in Alzheimer disease are exceedingly common and may contribute to the other behavioral disorders. Traditional sedating medications such as benzodiazepines may increase confusion and daytime drowsiness. A better alternative would be trazodone 25 to 100 mg at bedtime or thioridazine 25 to 75 mg at night.

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CORRECTION

New therapies for allergic rhinitis

In the article "New therapies for allergic rhinitis" by David F. Graft, MD in the March 2000 issue (*Cleve Clin J Med* 2000; 67:165–168), the first paragraph in the section on newer second-generation antihistamines (page 166) did not list all of the available agents, and also indicated that all of the newer agents have no sedating effect. The corrected paragraph should read as follows:

Newer second-generation antihistamines have fewer side effects and are safe. Acrivastine (the antihistamine ingredient in Semprex-D), azelastine, (Astelin), cetirizine (Zyrtec), fexofenadine (Allegra), and loratadine (Claritin) are as effective as older antihistamines. Acrivastine, azelastine and cetirizine have some potential for causing sedation, but much less than with older agents, and fexofenadine and loratadine do not appear to cause sedation at all. All of the newer agents have very little anticholinergic activity, and thus have very low rates of the other side effects.