Multiple neurochemical pathways are involved in the pathology of Alzheimer’s disease (AD). The following factors have been implicated in the development of AD: β-amyloid; tau proteins; apolipoprotein E (APOE); degeneration of cholinergic, serotonergic, and dopaminergic neurons; oxidative damage; inflammation; estrogen deficiency; and glutamatergic neurotransmission.

**Neurochemical pathways for AD**

**β-Amyloid**

It has been suggested that deposits of β-amyloid proteins appear to be the earliest morphological changes in the formation of neuritic plaques. These plaques ultimately lead to the death and destruction of surrounding axons and dendrites.

**Tau proteins**

Tau proteins are highly phosphorylated microtubule proteins that form neurofibrillary tangles. These abnormal filaments form either parallel bundles or randomly arranged paired helical filaments that extend to the dendritic processes. These tangles lead to dysfunction and degeneration of nerve cells.

**Apolipoprotein E**

APOE is a cholesterol transport protein that has been linked to late-onset familial and sporadic AD. The gene for this protein is found on chromosome 19 and is inher-


Deletion of cholinergic, serotonergic, and dopaminergic neurons

It is known that normal memory functions involve cholinergic systems and that cholinergic deficiency is present in AD. Choline acetyltransferase activity and acetyltransferase are significantly reduced in the cerebral cortex, hippocampus, and amygdala in AD patients. Many of our current treatments are attempts to increase cholinergic neurotransmission. Acetylcholine precursors, cholinergic agonists, and acetylcholinesterase inhibitors have all been used in the treatment of AD. Serotonergic and dopaminergic neurotransmission is decreased in AD, hence promoting the idea that antidepressants and antipsychotics are beneficial in treatment.

Oxidative damage

Oxidative damage is also believed to play an important role in AD. Free carbonyls and thiobarbituric acid–reactive products are significantly increased in AD brain tissue. Plaques and tangles have also been shown to display immunoreactivity to antioxidant enzymes. A number of medications appear to counteract oxidative stress. Vitamin E (an antioxidant) and selegiline (an inhibitor of monoamine oxidase B and thought to act as a free radical scavenger) have both been used in AD treatment. Both were found to delay time of death, institutionalization, and loss of the ability to perform the activities of daily living. Ginkgo biloba has also been shown to have antioxidant properties and will be explored later in this paper.

Estrogen

Studies have shown that estrogen loss predisposes to cognitive decline and neuronal degeneration. Several epidemiological studies have indicated that women taking estrogen supplementation have a lower risk of AD than those who do not. At least one multicenter, randomized, double-blind, placebo-controlled study is underway to determine whether estrogen can delay the onset of AD and memory loss in women 65 years of age or older with a family history of AD (Sano M, personal communication). The role of estrogen in cholinergic pathways has also been demonstrated by basic research. For example, neuronal choline uptake and choline acetyltransferase have been shown to be reduced in the brains of ovariec-
tomized female rats.

Glutamatergic neurotransmission

Glutamate is believed to be the major fast excitatory neurotransmitter in the brain. Glutamate activates three major classes of receptors, and its activation of N-methyl-D-aspartate (NDMA) receptors plays a critical role in learning and memory.

Cholinergic pathways: donepezil

All of the acetylcholinesterase inhibitors act by inhibiting the breakdown of acetylcholine, thus allowing the neurotransmitter to continue its action at the synapse. Donepezil, a reversible cholinesterase inhibitor, has been shown to have a greater specificity for acetylcholinesterase and a longer duration of activity than tacrine or physostigmine. In a double-blind, placebo-controlled trial of donepezil, AD patients were randomly assigned to placebo, 5 mg, or 10 mg donepezil for 24 weeks followed by a 6-week, single-blind placebo washout. The primary measure of efficacy was the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog). Cognitive function improved in the 5 and 10 mg donepezil groups compared with the placebo groups at 12, 18, and 24 weeks. The washout period showed a decline in ADAS-Cog score in both groups.

Emerging treatments

Many of the latest treatments for AD do not involve cholinergic pathways. For example, Ginkgo biloba is being investigated for the prevention of oxidative dam-

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**Selected abbreviations and acronyms**

- **ADAS-Cog**: Alzheimer’s Disease Assessment Schedule–Cognitive Section
- **AD**: Alzheimer’s disease
- **CGIC**: Clinical Global Impression of Change
- **FAST**: Functional Assessment Staging
- **GDS**: Global Deterioration Scale
- **MMSE**: Mini-Mental State Examination
- **NMDA**: N-methyl-D-aspartate
- **NSAID**: nonsteroidal anti-inflammatory drug
age and inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also being used to treat the inflammatory processes of AD. Atypical antipsychotics and selective serotonin reuptake inhibitors (SSRIs) are potential treatments for the serotonergic and dopaminergic deficiencies seen in AD.

**Ginkgo biloba**

A number of trials have evaluated the efficacy of *Ginkgo biloba* in the treatment of AD. In a study by Le Bars et al., 120 mg *Ginkgo biloba* extract was given in a 52-week, double-blind, placebo-controlled investigation; 309 patients were randomized with 202 patients completing the study. Inclusion criteria selected patients with mild-to-moderate dementia, Mini-Mental State Examination (MMSE) scores ranging from 9 to 26, and Global Deterioration Scale (GDS) scores of 3 to 6. The ADAS-Cog, Geriatric Evaluation by Relative’s Rating Instrument (GERRI), and Clinical Global Impression of Change (CGIC) were used as primary outcome measures. Participants on *Ginkgo biloba* had a slight improvement from baseline on the ADAS-Cog, while the placebo group showed continued worsening, with an increased score from 1.4 at 26 weeks to 2.1 at end point. The mean treatment difference of -2.4 points further favored the *Ginkgo biloba* group. Conversely, not all studies have shown *Ginkgo biloba* to be efficacious in the treatment of AD. In a 24-week, double-blind treatment trial, participants were randomized to either 160 mg/day *Ginkgo biloba*, 240 mg/day *Ginkgo biloba*, or placebo. There were 214 participants with mild-to-moderate dementia as a result of AD, vascular insufficiency, or age-associated memory impairment. Outcome measures included neuropsychological testing, digit memory span, and verbal learning. Intention-to-treat analysis showed no effect on any of the outcome measures for participants assigned to *Ginkgo biloba* compared with placebo for the entire 24-week period. After 12 weeks of treatment, the combined high dose and usual dose groups performed only slightly better with regard to self-reported activities of daily life compared with the placebo groups. No beneficial effects of a higher dose or a prolonged duration of *Ginkgo biloba* treatment were found.

*Ginkgo biloba* has also been compared with cholinesterase inhibitors in the treatment of AD. In one study comparing the efficacy of four cholinesterase inhibitors and *Ginkgo biloba*, the ADAS-Cog scale was used to measure the differences in effects after 6 months of treatment. After accounting for the differing degrees of dementia in the various studies and dropout rates, no major differences were seen in efficacy between the four cholinesterase inhibitors and *Ginkgo biloba*.

**Nonsteroidal anti-inflammatory drugs**

NSAID use is thought to protect against the inflammatory reactions that are known to be present in the neurons of patients with AD. A large amount of positive data has been reported on the use of NSAIDs in the treatment of AD. In one study, data were collected from 1648 AD participants in two identical, 26-week, multicenter pharmaceutical trials to examine the distribution of baseline ADAS-Cog scores in relation to certain demographic and clinical variables. ADAS-Cog total scores and NSAID use were evaluated for potential association. NSAID use was associated with higher cognitive performance (ADAS-Cog scores of 26.4±10.6 compared with 28.5±11.0; P=0.0003). Diclofenac, an NSAID, has also been evaluated for the treatment of AD. Scharf et al evaluated the safety and efficacy of diclofenac in combination with misoprostol in patients with AD in a 25-week, randomized, double-blind, placebo-controlled trial: 41 participants were enrolled and 27 completed the study. Selection criteria included mild-to-modestly severe AD and MMSE scores of 12 to 23. Primary outcome measures included the ADAS-Cog, GDS, and CGIC. There were no significant differences between the diclofenac/misoprostol and placebo groups. However, trends toward slower decline in the diclofenac/misoprostol group were noted. The authors cited possible explanations for the absence of significant differences as low sample size, failure of the placebo group to show expected decline, and insufficient observation time.

**Glutamatergic pathways**

Glutamatergic neurotransmission has been implicated in both the symptomatology and pathology of a variety of neurological conditions. In pathological conditions, such as AD, sustained release of glutamate leads to moderate activation of NMDA receptors. As a result, magnesium is displaced from the NDMA receptor and there is a continuous influx of calcium into the cell. This chronic excitotoxicity results in a cognitive deficit due to decrease in
signal-to-noise ratio and neuronal death due to chronic insult. NMDA receptor antagonists block the influx of calcium resulting in a reduction in intracellular calcium. Consequently, the noise is reduced and the signal is processed. Memantine, an NMDA receptor antagonist, is currently being investigated in the treatment of AD.

Memantine

In a 28-week, double-blind treatment trial comparing 20 mg/day memantine with placebo, 252 participants were randomized and 181 completed the study. Participants had MMSE scores between 3 and 14, GDS scores of 5 or 6, and Functional Assessment Staging (FAST) greater than 6a. There was also a 24-week open-label extension for 175 participants who completed the 28-week study. The CIBIC-plus (Clinicians’ Interview-based Impression of Change–plus), ADAS-Activities of Daily Living, Severe Impairment Battery (SIB), and FAST were used to measure outcome. Participants on memantine had a slower rate of decline than those receiving placebo. During the open-label extension, participants switched to memantine showed a more gradual decline compared with the first 28 weeks of placebo treatment.

Serotonergic and dopaminergic pathways: implications for treatment of behavioral disturbances

Newer antipsychotics, such as risperidone, are combined serotonin and dopamine antagonists. Most of the newer antipsychotics exhibit strong antagonistic affinity for the serotonin (5-hydroxytryptamine) receptor 5-HT2. Risperidone has been shown to be efficacious in the treatment of psychosis and behavioral disturbances associated with dementia. Katz et al evaluated 625 participants in a 12-week, double-blind treatment study comparing 0.5 to 2 mg/day of risperidone to placebo. Participants had a diagnosis of AD and/or vascular dementia (73% had AD), FAST scale score of ≥4, MMSE of ≤23, Behavioral Pathology in Alzheimer’s Disease (BEHAVE-AD) rating of ≥8 and a global rating of ≥1. Outcome measures included BEHAVE-AD, Cohen-Mansfield Agitation Inventory (CMAI), and CGI. Significant reductions in BEHAVE-AD total scores, psychosis, and aggressiveness subscale scores were seen in patients receiving 1 and 2 mg/day risperidone, compared with patients on placebo. Adverse events were more commonly seen in the 2 mg/day group and included extrapyramidal symptoms, somnolence, and mild peripheral edema. Antidepressants such as sertraline exert their main effects via the serotonergic system. Sertraline has been evaluated for its efficacy in the treatment of depression in AD (Lyketsos C, personal communication). Twenty-nine patients were assessed with the Neuropsychiatric Inventory (NPI). Average baseline scores were 7.3. After 12 weeks of treatment, patients on sertraline had a reduction in scores by 2.78 points, while the placebo group scores were increased by 0.18 points.

Cholinergic pathways: implications for treatment of behavioral disturbances

Acetylcholinesterase inhibitors have been shown to benefit the cognitive, functional, and behavioral symptoms of patients with AD. For example, one study evaluated 978 patients with mild-to-moderate AD treated with slow dose escalation of galantamine. After 4 weeks of placebo, patients were randomized to one of four treatment groups: placebo or galantamine escalated to final doses of 8, 16, or 24 mg/day. At 5 months, both the 16 and 24 mg/day groups showed very little change from baseline, while the placebo group scores deteriorated. As a result, the 16 and 24 mg/day groups exhibited significantly better NPI total scores as compared to placebo (P<0.05). Improvements were also seen in the ADAS-Cog and CIBIC-plus in the 16 and 24 mg/day groups.

Combination therapy: rationale, efficacy, and safety

A potential treatment regimen may be developed based on the stages of AD.

• The latent stage, which may last for several decades, exists among individuals at known genetic risk of late-life AD. These patients may show changes in functional abilities, early neuroanatomic changes, and regional hypometabolism in temporal and parietal lobes in their middle life. During this stage, neuroprotection with NSAIDs, NMDA receptor antagonists, and estrogen may slow or attenuate progress and prove beneficial.

• During the prodromal stage, early cognitive symptoms appear, and as damage increases substantial impairment develops. Treatment interventions in this stage may slow progression from mild symptoms to disabling
dementia. Cholinesterase inhibitors may work best at this stage of the disease.

- During the symptomatic stage, the goal is to improve existing cognitive functions and prevent current symptoms from worsening. Medications that may be beneficial during this stage include *Ginkgo biloba*, NMDA receptor antagonists, antipsychotics, and antidepressants. Treatment strategies for the immediate future should include therapy with some or all of the following compounds: acetylcholinesterase inhibitors, *Ginkgo biloba*, NSAIDs, NMDA receptor antagonists, atypical antipsychotics, and SSRIs. One study is currently investigating whether the concurrent use of an atypical antipsychotic (risperidone, olanzapine, or quetiapine) and galantamine increases the incidence of adverse events associated with either class of drug. Subjects from the following multicenter, double-blind, placebo-controlled studies of galantamine in the USA were included: GAL-USA-1 and GAL-USA-10. Only the subjects that were either on galantamine 16 or 24 mg, or placebo were included. Subjects who used conventional antipsychotics and subjects who took atypical antipsychotics only during screening were excluded. Specific adverse events outcomes included the following: falls, peripheral edema, rhinitis, somnolence, urinary tract infection, and extrapyramidal symptoms. These adverse events have been described in previous studies of atypical antipsychotic treatment in older adults.

The risk of adverse events linked to atypical antipsychotics and acetylcholinesterase inhibitors was analyzed. There was no overall statistical difference between drug groups for falls, rhinitis, or urinary tract infections. Further, there were no reports in peripheral edema. When an atypical antipsychotic plus galantamine was compared with an atypical antipsychotic only, there was no difference in extrapyramidal side effects (odds ratio [OR]=1.04). There was a higher risk of somnolence, however, in the atypical antipsychotic plus galantamine group, but it was not significant (OR=1.86; \( P=0.305 \)). When an atypical antipsychotic plus galantamine was compared with galantamine only, the risk of any gastrointestinal adverse effect was lower in the atypical antipsychotic plus galantamine group, but not significant (OR=0.75; \( P=0.227 \)). Both nausea and vomiting were lower in the atypical antipsychotic plus galantamine group. Nausea was significantly lower (OR=0.42). Vomiting, however, was noted to be lower in the atypical antipsychotic plus galantamine group (OR=0.53), but not significantly (\( P=0.147 \)). There was no overall statistical difference between the two groups for diarrhea.

Another study analyzed the efficacy and safety of the combination of donepezil and sertraline on behavioral and cognitive symptoms of AD. Participants in this trial were all given 8 weeks of open-label donepezil and were then randomized to double-blind donepezil and sertraline or donepezil and placebo. The goal was 240 participants at 24 sites. This study showed no clear beneficial effects for the combination. Secondary analysis on this data is currently ongoing.

Adverse events were noted to be similar in the two groups: in 87.1% of patients with donepezil plus sertraline and 81.7% with donepezil plus placebo. Serious adverse events occurred in 8.9% of patients on donepezil plus sertraline and 5.8% of patients on donepezil plus placebo. Discontinuations occurred in 11.3% on donepezil plus sertraline and 9.2% on donepezil plus placebo. Adverse effects related to the digestive system were more common in the donepezil plus sertraline group at 49.2%, compared with 31.7% in the donepezil plus placebo group. The majority of digestive system adverse events were mild. Another potential combination treatment involves the concurrent treatment with acetylcholinesterase inhibitors and NMDA antagonists. One study has evaluated the efficacy of donepezil alone versus donepezil and memantine in a double-blind, placebo-controlled trial. A total of 403 moderately to severely affected AD patients were enrolled in this 6-month trial. At the end of 28 weeks during the double-blind phase, combination therapy showed improvement in the CIBIC-plus score compared with donepezil alone and placebo. Both donepezil and placebo showed a decline in scores, with placebo treatment having the greatest.

**Conclusion**

Combination pharmacotherapy offers optimal management of AD symptoms by targeting various neurochemical pathways. A few studies have found combination pharmacotherapy to be both efficacious and safe in AD patients. More research is needed in the area to further define the benefits as well as the pitfalls of combination pharmacotherapy in this fragile population. 

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La Enfermedad de Alzheimer es una demencia de tipo progresivo y debilitante que afecta a más de 18 millones de personas en el mundo. Al no disponer de tratamiento curativo, muchos pacientes y sus familias deben tomar contacto con establecimientos de estancia prolongada durante las etapas finales de la enfermedad. Los tratamientos actuales sólo retardan la progresión de los síntomas y ayudan al control conductual. En los últimos años la investigación en este campo se ha incrementado y se han incluido muchos ensayos clínicos de potenciales fármacos. Sin embargo, a pesar de los numerosos estudios, persiste el enigma de esta enfermedad. Resulta difícil, aunque es necesario, estar al día sobre la información emergente que pueda justificar cambios en los tratamientos actuales. El fundamento de la terapia combinada resulta evidente al revisar las múltiples vías neuroquímicas comunes para esta enfermedad. Este artículo revisará la información disponible sobre la farmacoterapia de la Enfermedad de Alzheimer y evaluará los datos de la asociación de medicamentos. También serán tratados la eficacia individual, los posibles efectos sinérgicos y la seguridad de la terapia combinada.

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**Farmacoterapia combinada en la Enfermedad de Alzheimer**

**Association médicamenteuse dans la maladie d’Alzheimer**

La maladie d’Alzheimer est une forme de démence progressive, débilitante, qui affecte plus de 18 millions d’individus dans le monde. En l’absence d’un traitement curatif, lors des phases ultérieures de la maladie, de nombreux patients et leur famille doivent se tourner vers des établissements de long séjour. Les traitements actuels ne font seulement que retarder la progression et contribuer au contrôle des symptômes comportementaux. Ces dernières années, la recherche dans ce domaine s’est élargie pour inclure de nombreux essais cliniques sur des traitements médicamenteux potentiels. Cependant, en dépit des nombreuses études, l’énigme posée par cette maladie demeure. Il est difficile, mais pourtant nécessaire d’être au fait des informations émergentes susceptibles d’entraîner des changements dans le traitement actuel. Les arguments pour une association thérapeutique deviennent évidents au vu des multiples voies neurochimiques communes à la maladie. Cet article passe en revue les informations disponibles sur la Pharmacothérapie de la maladie d’Alzheimer et évalue les données sur l’utilisation d’une association médicamenteuse. Efficacité individuelle, possibles effets synergiques et tolérance de l’association thérapeutique sont aussi évoqués.
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