Alzheimer's disease

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Alzheimer's disease is one of the most devastating brain disorders of elderly humans. It is an undertreated and underrecognized disease that is becoming a major public health problem. The last decade has witnessed a steadily increasing effort directed at discovering the etiology of the disease and developing pharmacological treatment. Recent developments include improved clinical diagnostic guidelines and improved treatment of both cognitive disturbance and behavioral problems. Symptomatic treatment mainly focusing on cholinergic therapy has been clinically evaluated by randomized, double-blind, placebo-controlled, parallel-group studies measuring performance-based tests of cognitive function, activities of daily living, and behavior. Cholinesterase inhibitors, including donepezil, tacrine, rivastigmine, and galantamine are the recommended treatment of cognitive disturbance in patients with Alzheimer's disease. The role of estrogen replacement, anti-inflammatory agents, and antioxidants is controversial and needs further study. Antidepressants, antipsychotics, mood stabilizers, anxiolytics, and hypnotics are used for the treatment of behavioral disturbance. Future directions in the research and treatment of patients with Alzheimer's disease include: applying functional brain imaging techniques in early diagnosis and evaluation of treatment efficacy; development of new classes of medications working on different neurotransmitter systems (cholinergic, glutamatergic, etc), both for the treatment of the cognitive deficit and the treatment of the behavioral disturbances; and developing preventive methods (amyloid β-peptide immunizations and inhibitors of β-secretase and γ-secretase).

Alzheimer's disease (AD) is a significant public health problem secondary to the increased life expectancy of the general population and a better appreciation of the socioeconomic consequences of the disease. It was defined by Alois Alzheimer in 1906 using criteria of progressive memory loss, disorientation, and pathological markers (senile plaques and neurofibrillary tangles).

Initially it was assumed that AD was a rare condition, and later it was considered to be an inevitable consequence of aging. The stigma attached to aging and other factors delayed aggressive research into, and treatment of, patients with AD, but these misconceptions are fading away, and treatments, though initially modest in efficacy, are becoming available.

In this paper we will review the diagnosis, etiology, genetics, epidemiology, course, and treatment of AD.

Diagnosis and course

The clinical manifestations of AD include disturbances in the areas of memory and language, visuospatial orientation, and higher executive function. Noncognitive changes include personality changes, decreased judgment ability, wandering, psychosis, mood disturbance, agitation, and sleep abnormalities.

The diagnostic evaluation of patients suspected of having AD comprises (i) a history from a reliable informant (containing general medical history, neurological history, neuropsychiatric history, family history); (ii) physical and neurological examination; (iii) routine laboratory examinations (complete blood count, sequential multiple analysis–21, thyroid function tests, vitamin B12,

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Selected abbreviations and acronyms

Aβ	*amyloid β-peptide*
AD	*Alzheimer's disease*
ADAS-cog	*cognitive subscale of the Alzheimer's Disease Assessment Scale*
APOE	*apolipoprotein E*
APP	*amyloid precursor protein*
CIBIS	*Clinician Interview–Based Impression Scale*
COX-2	*cyclooxygenase-2*
ERT	*estrogen replacement therapy*
MMSE	*Mini-Mental State Examination*
NSAID	*nonsteroidal anti-inflammatory drug*
PS 1 & 2	*presenilin-1 & -2*
SSRI	*selective serotonin reuptake inhibitor*

folate, rapid plasma reagin); optional laboratory examinations (erythrocyte sedimentation rate, human immunodeficiency virus (HIV) serology, serology for Lyme's disease, urinalysis, urine drug screen, lumbar puncture, electroencephalography); and (iv) neuroimaging (computed tomography or magnetic resonance imaging).

Neuropathological examination (looking for the hallmark senile plaques and neurofibrillary tangles) from autopsy studies suggest a 90% accuracy rate in the clinical detection of AD—if it is done by using standardized criteria such as those of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition *(DSM IV)* criteria[1] *(Table I)* and the National Institute of Neurological and Communicative Diseases and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria *(Table II)*.[2]

The course of AD tends to be slowly progressive, with a loss of 3 to 4 points per year on a standard assessment instrument such as the Mini-Mental State Examination (MMSE). Various patterns of deficit are seen, with the most common being an insidious onset, with recent memory loss followed by the development of aphasia, apraxia, and agnosia after several years. Some patients present with irritability and personality changes in the early stages. In the later stages, patients usually develop gait and motor disturbances, eventually becoming mute

A. The development of multiple cognitive deficits manifested by both:
(1) Memory impairment (impaired ability to learn new information or to recall previously learned information)
(2) One (or more) of the following cognitive disturbances:
(a) Aphasia (language disturbance)
(b) Apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) Agnosia (failure to recognize or identify objects despite intact sensory function)
(d) Disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
C. The course is characterized by gradual onset and continuing cognitive decline
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
(1) Other CNS conditions that cause progressive deficits in memory and cognition (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
(2) Systemic conditions that are known to cause dementia (eg, hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
(3) Substance-induced conditions
E. The deficits do not occur exclusively during the course of a delirium
F. The disturbance is not better accounted for by another Axis I disorder (eg, Major Depressive Disorder, Schizophrenia)

Table I. Diagnostic criteria for Dementia of the Alzheimer's Type (*DSM-IV*).
Reproduced from ref 1: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC; 1994. Copyright © 1994, American Psychiatric Association.

Definite Alzheimer's disease
• Clinical criteria for probable Alzheimer's disease
• Histopathologic evidence of Alzheimer's disease (autopsy or biopsy)
Probable Alzheimer's disease
• Dementia established by clinical examination and documented by mental status questionnaire
• Dementia confirmed by neuropsychological testing
• Deficits in two or more areas of cognition
• Progressive worsening of memory or other cognitive functions
• No disturbance of consciousness
• Onset between ages 40 and 90
• Absence of systemic or brain diseases capable of producing a dementia syndrome
Possible Alzheimer's disease
• Atypical onset, presentation, or progression of a dementia syndrome without a known etiology
• A systemic or other brain disease capable of producing dementia, but not thought to be the cause of the dementia is present
• Gradually progressive decline in a single intellectual function in the absence of any other identifiable cause
Unlikely Alzheimer's disease
• Sudden onset
• Focal neurological signs
• Seizures or gait disturbances early in the course of illness

Table II. National Institute of Neurological and Communicative Diseases and Stroke—Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for diagnosis of Alzheimer's dementia.

and bedridden. On average, AD patients live for 8 to 10 years after they are diagnosed, although the disease can last for up to 20 years.[3]

Comorbidity

Although still the most common form of dementia, AD can be comorbid with Lewy-body dementia or vascular dementia. There are limited clinical data in treating patients with this type of comorbidity. Patients with AD also have a high degree of medical comorbidity (heart disease, diabetes, cancers).

Etiology

The main neuropathological features of AD appear to be senile plaques and neurofibrillary tangles. The senile plaques seem to develop first in brain areas associated with cognition, and spread to other cortical areas as the disease progresses. The senile plaques consist, among other components, of insoluble deposits of amyloid β-peptide (Aβ), a fragment of the amyloid precursor protein (APP). Aβ peptide is generated from APP by two consecutive cleavage events: proteolytic activity by β-secretase generates one end of the Aβ peptide, while γ-secretase generates the other end, also by proteolysis. There appear to be two types of Aβ: a longer species, Aβ42, and a shorter species, Aβ40. Aβ42 seems to be deposited initially and may have a role in initiating the events that ultimately lead to amyloid deposition. It is still not clear if the senile plaques are the cause or a by-product of AD, although there are increasing data that dysfunction in the metabolism of APP with subsequent increase in the insoluble Aβ is responsible for AD. Aβ seems toxic to the neuron either directly, or indirectly by causing inflammation or increasing the production of free radicals.

The accumulation of neurofibrillary tangles in neurons is a second distinguishing feature of AD. Neurofibrillary tangles are mostly formed by chemically altered (abnormally folded and phosphorylated) tau protein, a protein involved in microtubule formation. Tangle formation is related to the severity of disease; the more advanced the stage of disease, the more tau tangles in the brain. Despite the presence of neurofibrillary tangles in AD, no cases of AD secondary to mutations in the tau gene on chromosome 17[4] have been reported, although frontotemporal dementias with parkinsonism were found in some families with that mutation. The finding that the tau alteration follows Aβ accumulation in patients with AD is supported by recent data.[5]

Genetics

The best support for the central role of amyloid in AD came from the understanding of the possible mechanism of all the four known genes that cause familial forms of the disease.

Three of those specific genetic mutations (APP on chromosome 21, presenilin-1 [PS 1] on chromosome 14, and presenilin-2 [PS 2] on chromosome 1) were

identified in patients with familial early-onset autosomal dominant AD, but these mutations are extremely rare, accounting for fewer than 1% of cases. All these genes appear to increase the cellular production of Aβ42 by selectively increasing the cleavage of APP by β- or γ-secretase.

The fourth AD gene is apolipoprotein E (*APOE*, a gene on the long arm of chromosome 19 that exists in three allelic forms (*APOE-2, -3,* and *-4*) differing in terms of which amino acid is substituted. Multiple studies revealed that the *APOE-4* allele is disproportionately represented among patients with both late-onset and early-onset AD and that the *APOE-4* allele shows a dose-dependent relationship with increasing risk for AD and decreasing age at onset. Conversely, several studies suggested that inheritance of the *APOE-2* allele may be protective. There appears to be an increased risk for the sporadic late-onset form of AD with inheritance of one (2.2 to 4.4 higher risk) or two (5.1 to 17.9 higher risk) copies of the *APOE-4* allele on chromosome 19. *APOE-4* is a risk factor only, its presence is neither necessary nor sufficient for the development of AD. A recent meta-analysis of more than 14 000 patients with AD and controls showed that the *APOE-4* allele represents a major risk factor for AD in both men and women from a large number of racial and ethnic groups across all ages between 40 and 90 years. The genetic risk of AD attributable to *APOE-4* is estimated at 45% to 60%. It appears that *APOE-4* does not act by increasing Aβ production, but by enhancing Aβ aggregation or decreasing its clearance. Another recently identified putative risk factor is lipoprotein(a), which appears to protect against late-onset AD in noncarriers and is an additional risk factor for late-onset AD in carriers of the *APOE-4* allele.[6] A series of retrospective studies—part of the EURODEM (European Studies of Dementia) projects—showed that, compared with men, women had an increased risk for AD, while having equal risk for vascular dementia. Women appear to be at higher risk for developing AD, only in part due to increased longevity. Because women with AD live longer than men with the disease, there are twice as many women as men in the population with this disorder. These studies also showed that low education level significantly increased the risk of AD, while family history of dementia and history of head trauma with unconsciousness did not.[7,8]

At the present time, the only well-established risk factors for AD are age and *APOE-4*. Despite this knowledge, at present, genotyping is not recommended in asymptomatic individuals, with or without a history of AD, because of the uncertain predictive value, lack of treatment to stop progression of the illness, and potential discrimination.[9,10]

Epidemiology

AD can be divided into a familial type and a sporadic type, and also into an early-onset type (younger than 65) and a late-onset type (older than 65). The 6-month prevalence of AD in the general population appears to be 5.5% to 9%.[11] There prevalence of the disease doubles every 10 years. AD currently afflicts nearly half of the people aged 85 years and older.

Individuals with cognitive deficit that do not meet the generally accepted clinical criteria for AD, but have a noticeable decrease from prior levels of cognitive performance with problems in new learning, may have mild cognitive impairment. Recent studies show that 40% of these individuals will develop AD within 3 years.

Early recognition of AD is important for treatment with cholinesterase inhibitors, reduction in caregiver stress, community support, delay in institutionalization, planning of lifestyle, and legal issues.

Treatment

The goals of treatment are to achieve improvement in cognition and to minimize behavioral disturbances (depression, psychosis, agitation, and insomnia).[12]

Psychosocial treatment

Environmental manipulation,[13] family support,[14] and prevention of other medical comorbidities can improve functioning of AD patients. In attempting to maintain patients with AD in their homes for as long as possible, some adjustment of a patient's environment is important. Written daily reminders can be helpful in the performance of daily activities. Prominent clocks, calendars, and windows are important. Patient activities should have minimal changes. Maintaining adequate hydration, nutrition, exercise and cleanliness, is important. Family support is essential, since members are at risk for depression, anxiety syndromes, and insomnia.

Pharmacotherapy

Current pharmacological choices available to clinicians treating AD include cognitive enhancers for the treatment of the cognitive deficit[14] and mood stabilizers, antipsychotics, antidepressants, and hypnotics for the treatment of behavioral disturbance.[15]

Treatment of cognitive disturbance

Cholinesterase inhibitors

The use of cholinesterase inhibitors in AD is based on the cholinergic deficiency observed in the disease. Only cholinesterase inhibitors have shown clinically meaningful responses for patients with AD. By using these compounds, there is an increase in the acetylcholine concentration available for synaptic transmission by inhibiting enzymes responsible for its hydrolysis (ie, acetylcholinesterase). These drugs appear to be useful throughout the disease, but particularly in the middle stage.[16]

The cholinesterase inhibitors *(Table III)* available now worldwide for clinical use are donepezil,[17-21] tacrine,[22-25] galantamine,[26-28] and rivastigmine.[29-31] Physicians and families may not necessarily see an acute improvement in symptoms, but patients on the medications will have the appearance of less loss in cognition compared with controls.

In order to be approved in the US for treatment of AD, any drug must be more effective than placebo as measured by global clinical measures and psychometric testing in a randomized, double-blind, placebo-controlled clinical trial. The trial must last for at least 3 months.

Drug name	Dosage	Side effects
Donepezil	5-10 mg PO qhs	nausea, vomiting, diarrhea
Tacrine	20-40 mg PO qid	nausea, vomiting, diarrhea, hepatotoxicity
Galantamine	8-12 mg PO bid	nausea, vomiting, diarrhea
Rivastigmine	2-6 mg PO bid	nausea, vomiting, diarrhea

Table II. Cholinesterase inhibitors.

The commonly used scales include the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician Interview–Based Impression Scale (CIBIS). The ADAS-cog measures cognition, language, orientation, and performance on simple tasks, word recall, word recognition, object and finger naming, ability to follow commands, and constructional and ideational praxis. The possible scores on the ADAS-cog range from 0 to 70, a higher score indicating greater impairment.

There appears to be a differential response to cholinesterase inhibition based on the severity of AD, with middle-stage AD patients (defined by MMSE scores 11-17) having a better response than patients with mild AD (MMSE scores 18-26). These data are consistent with the notion that the cholinergic defect first becomes statistically significant at this stage of the disease.[32]

Cholinesterase inhibitors may have a role in the treatment of behavioral disturbance in patients with AD. Clinical trials with this class of compounds showed improvement in psychosis, agitation and mood disturbance.[33-36] Unfortunately, there are few studies comparing the safety and tolerability of the cholinesterase inhibitors.[37] Thus, the choice of which cholinesterase inhibitor to use is not aided by clear scientific evidence from head-to-head studies.

Estrogen replacement therapy

Considerable evidence has emerged regarding the role of estrogen on brain development, neuron survival, regeneration, and plasticity. It appears to exert its effect in the brain by enhancing transcription and mediation of nongenomic events. It has been suggested that the abrupt decline of estrogen production in postmenopausal women increases the risk for these women developing AD; men, in contrast, have an intrinsic supply of estrogen by aromatizing testosterone in the brain. There is increasing evidence that estrogen replacement therapy (ERT) in postmenopausal women may have a role in delaying AD by improving cognitive function and reducing the risk for both cognitive impairment and AD, as shown in several open-labeled clinical trials[38-40] and at least one double-blind placebo-controlled trial,[41] although a recent major double-blind controlled study found no effect of estrogen in patients who already had AD.[42,43] In one of the latter studies,[42] estrogen failed to

improve cognitive or functional outcomes after 1 year of use, but there was a time-limited benefit (2 months) on the MMSE, similar to previous reports.
At the present time, there are several ongoing investigations regarding primary prevention with estrogen in patients with AD (Women's Health Initiative—Memory Study; Women's International Study of Long Duration Oestrogen for Menopause, Preventing Postmenopausal Memory Loss and Alzheimer's with Replacement Estrogens Study). These studies will hopefully show whether ERT is helpful in preventing AD, while other studies will show whether ERT can delay disease progression.
The selective estrogen-receptor modulators are another interesting class of compounds currently being tested in AD. These act as estrogen agonists in some tissues and antagonists in other tissues (raloxifene, tamoxifen, droloxifene, and tiboline).

Anti-inflammatory agents

The hypothesis that anti-inflammatory therapy can slow the progression of AD has gained support from some retrospective epidemiologic studies.[44-46] There are very few prospective double-blind clinical trials of nonsteroidal anti-inflammatory drugs (NSAIDS) in AD. Nonrandomized studies with NSAIDS (indomethacin,[47] ibuprofen, diclofenac,[48] naproxen), steroids (low-dose prednisone[49]), and other anti-inflammatory agents (hydroxychloroquine, colchicine) showed promising results in modulating the course of the disease. Unfortunately, these studies included small sample sizes. Recent studies have not replicated the previous positive results. A 16-month, double-blind, placebo-controlled, low-dose study in 138 patients with AD receiving prednisone showed that there was no slowing of the rate of cognitive decline compared with placebo.[50] Although some previous high-dose prednisone studies showed improvement, the use of high-dose steroids over a long period of time can cause substantial health problems.[51]
Another class of anti-inflammatory agents is that of the cyclooxygenase-2 (COX-2) inhibitors (celecoxib, rofecoxib). By being more specific for the brain than the currently available NSAIDs, they are now favored in clinical trial use for patients with AD. A major double-blind placebo-controlled trial comparing rofecoxib with naproxen and placebo has now been completed and the results were negative.[52]

Antioxidant agents: selegiline and vitamin E

Current theories suggest that an increase in free-radical formation may occur in AD and have a direct toxic effect. The brain may be vulnerable to the damaging effects of oxidative stress because of an abundance of catecholamines and a relatively low concentration of antioxidative enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase). Furthermore, Aβ has been implicated in increased free-radical formation.
Vitamin E in doses of 1000 IU orally twice daily and selegiline (a monoamine oxidase B inhibitor) in doses of 5 to 10 mg orally every morning,[53-55] seem to minimize free-radical damage by acting as free-radical scavengers. A recent major double-blind study[56] comparing the effect of selegiline alone, vitamin E alone, selegiline and vitamin E with placebo in patient's with AD showed that both delayed nursing home placement and the loss of activities of daily living. However, neither selegiline nor vitamin E improved cognition compared with placebo. There was no additive effect in combining vitamin E with selegiline.

Treatment of behavioral disturbance

A wide range of dementia-associated behavioral disturbances afflict the majority of patients with AD, with depression and psychosis being the most commonly studied from the point of view of treatment. Depression in patients with AD should be treated aggressively, with careful monitoring of cognitive function. With limited clinical trial data, the treatment of depression in AD remains empirical and consists in starting an antidepressant at a low dose and increasing it slowly. Sufficient dosage and duration of treatment are needed for clinical response in depressed patients without dementia. The depressed elderly may take up to 6 weeks to respond to antidepressant medication and patients with AD should be expected to take as long.
Reversible monoamine oxidase inhibitors like brofaromine and moclobemide[57] appear to be also effective in patients with depression and dementia, without the severe potential side effects of the classic monoamine oxidase inhibitors (phenelzine, tranylcypromine).
Use of tricyclic antidepressants is limited to nortriptyline and desipramine, since they have fewer anticholinergic properties than their parent compounds amitriptyline

and imipramine.[58] They were both studied in double-blind, placebo-controlled trials and were effective in treating depression in AD patients.

All newer antidepressants, including fluoxetine,[59] sertraline, paroxetine,[60] fluvoxamine,[61] citalopram,[62] nefazodone, bupropion, mirtazapine, and venlafaxine appear to have beneficial effects in depression in AD patients, although only fluoxetine, paroxetine, and fluvoxamine were studied in double-blind, placebo-controlled trials.

At the present time, the selective serotonin reuptake inhibitors (SSRIs) are the standard of care for the treatment of depression in patients with AD.[62] Depression in these patients can very often be complicated by psychosis and behavioral disturbances, which can also be an independent feature of the disease. The incidence of psychosis in patients with AD is 25% to 50%.[63] Multiple treatments have been proposed, but very few controlled trials are available. Treatment of psychosis[64] in patients with AD should rely on atypical antipsychotics such as risperidone[65,66] and olanzapine,[67] which have been used in double-blind placebo-controlled trials.

Risperidone[63] was studied in a large (625 patients) double-blind, placebo-controlled study evaluating the efficacy and safety of an atypical antipsychotic in the treatment of psychosis and behavioral symptoms in patients with AD. This trial showed that 1 mg of risperidone per day significantly improved psychosis without the emergence of the side effects associated with typical antipsychotics. Another recent double-blind, placebo-controlled study[66] compared the effects of risperidone with those of haloperidol and placebo in patients with AD, and showed equal efficacy of risperidone with haloperidol (similar 1-mg dose of each of the compounds), but with significantly fewer extrapyramidal side effects with the atypical agent.

A double-blind, placebo-controlled trial of olanzapine[67] has also shown significant improvement in psychosis in patients with AD compared with placebo, with no significant side effects.

Recent findings appear to favor the use of a new agent, quetiapine, for the treatment of psychosis; however, the trial was not controlled.[68]

If typical antipsychotics are used, low dosages should be employed to avoid extrapyramidal symptoms; this risk can further be decreased by using atypical agents.[69]

Treatment of both the cognitive disturbance and the behavioral disturbance appears to delay nursing home placement and improve morbidity and mortality, thus resulting in a significant economic impact on AD.[70,71]

Economic impact

Although half of patients with AD are treated at home, AD is becoming a leading cost of medical care with annual national costs of $50 billion in the United States. Considering that in 1988 there were nearly 70 million people worldwide aged 80 or above, and that recent projections estimate this number will soar to 370 million in 2050, the potential financial burden of AD treatment is enormous. AD also exacts a severe indirect toll on caregivers who experience emotional, physical, and financial stressors.

To date, no prospective studies exist regarding the economic weight of AD treatment, especially with respect to cholinesterase inhibitors. Only uncontrolled data are available. A recent retrospective cost-analysis study[70] showed that use of tacrine resulted in savings of $10 000 per patient, from diagnosis to death. Another recent study[71] showed that 5% of donepezil-treated AD patients were institutionalized at the end of a 6-month period, compared with 10% of those not receiving donepezil.

Future directions

Future therapeutic approaches[72] to the treatment of patients with AD include applying functional brain imaging techniques in early diagnosis and evaluation of treatment efficacy (in vivo measurements of cholinesterase function,[73] and developing preventive methods, such as Aβ immunizations[74] and inhibitors of β-secretase[75] and γ-secretase.[76] Repetitive immunizations of APP transgenic mice with Aβ produces antibodies that seem to promote the clearance of Aβ deposits from the brain. This approach is now being used in phase 1 clinical trials.

Conclusions

Current treatment approaches to dementia are based on variable degrees of scientific evidence, reflecting an incomplete understanding of the basic pathophysiology of AD. Cholinergic deficits have been well described and evidence is sufficiently consistent to make cholin-esterase inhibitors (donepezil, tacrine, rivastigmine and galantamine) the recommended treatment of cognitive disturbance in patients with AD. Symptomatic treatment mainly focusing on cholinergic

therapy has been clinically evaluated by randomized, double-blind, placebo-controlled, parallel-group studies measuring performance-based tests of cognitive function, activities of daily living, and behavior. Cholinesterase inhibitors may treat behavioral disturbances. Treatments with antioxidants, anti-inflammatory agents, and estrogen replacement therapy are still controversial, although clinical trials exploring their effectiveness are under way. Antidepressants, antipsychotics, mood stabilizers, anxiolytics, and hypnotics are used for symptomatic treatment of behavioral disturbance. ❑

Enfermedad de Alzheimer

La Enfermedad de Alzheimer es uno de los trastornos cerebrales más devastadores de los sujetos de edad avanzada. Es una enfermedad subdiagnosticada y subtratada que se está transformando en un problema importante de la salud pública. La última década ha sido testigo de un esfuerzo creciente dirigido al descubrimiento de la etiología de la enfermedad y al desarrollo de tratamientos farmacológicos. Los progresos recientes incluyen un avance en las pautas del diagnóstico clínico y en el tratamiento tanto de los trastornos cognitivos como de las alteraciones de conducta. El tratamiento sintomático, que se focaliza principalmente en la terapia colinérgica, ha sido evaluado clínicamente a través de estudios randomizados, doble-ciego, placebo controlados y de grupos paralelos mediante pruebas basadas en rendimientos que miden la función cognitiva, actividades de la vida diaria y conductas. Los inhibidores de la colinesterasa como el donepezil, la tacrina, la rivastigmina y la galantamina son los tratamientos recomendados para los trastornos cognitivos en los pacientes con Enfermedad de Alzheimer. El papel de la terapia de reemplazo con estrógenos, el empleo de agentes antiinflamatorios o el uso de antioxidantes constituyen tratamientos en que hay controversia y se requiere de mayor investigación a futuro. Para el tratamiento de las alteraciones de conducta se han utilizado antidepresivos, antipsicóticos, estabilizadores del ánimo, ansiolíticos e hipnóticos. A futuro, la investigación y el tratamiento de los pacientes con Enfermedad de Alzheimer incluirá: a) la aplicación de técnicas de imágenes cerebrales funcionales para el diagnóstico precoz y la evaluación de la eficacia del tratamiento, b) el desarrollo de nuevas clases de medicamentos que actúen sobre diversos sistemas de neurotransmisión (colinérgico, glutamatérgico, etc.) tanto para el tratamiento de los déficits cognitivos como para las alteraciones de conducta, y c) el desarrollo de medidas de prevención (inmunizaciones con beta amiloide e inhibidores de la beta o gama secretasa).

Maladie d'Alzheimer

La maladie d'Alzheimer se situe parmi les plus destructrices des pathologies cérébrales chez le sujet âgé. Elle est devenue un problème de Santé publique majeur, mais reste insuffisamment diagnostiquée et traitée. La recherche étiologique et thérapeutique a constamment progressé au cours de la décennie passée, aboutissant récemment à la mise au point de recommandations pour le diagnostic clinique et à l'amélioration de la prise en charge thérapeutique des troubles cognitifs et du comportement. Les traitements symptomatiques, reposant essentiellement sur les traitements cholinergiques, ont été évalués dans des études randomisées, en double aveugle, contrôlées contre placebo, en groupes parallèles, évaluant les tests de performance cognitive, les activités quotidiennes et le comportement. Les traitements recommandés pour les troubles cognitifs sont les inhibiteurs de la cholinestérase, parmi lesquels le donezepil, la tacrine, la rivastigmine et la galantamine. Le rôle des traitements estrogéniques substitutifs, des traitements anti-inflammatoires et des antioxydants reste controversé et mérite de plus amples recherches. Les antidépresseurs, les antipsychotiques, les médicaments régulateurs de l'humeur, les anxiolytiques et les hypnotiques sont prescrits dans les troubles du comportement. Parmi les objectifs de recherche dans l'avenir, on peut citer : le développement de techniques d'imagerie cérébrale fonctionnelle permettant un diagnostic précoce de la maladie et l'évaluation de l'efficacité des traitements ; la mise au point de nouvelles classes thérapeutiques agissant sur différents systèmes de neurotransmetteurs (cholinergique, glutamatergique, etc.) actifs à la fois sur les troubles du comportement et le déficit cognitif; enfin le développement de traitements préventifs (immunisation par β-peptide amyloïde et inhibiteurs de la β-sécrétase et de la γ-sécrétase).

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