

Management of the early stage of Alzheimer's disease: a systematic review of literature over the past 10 years

R.A. Cocchiara, F. De Lucia, L. Koci, E. Lisanti, G. Petruccini, G. La Torre

Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

Abstract

Background. Alzheimer's disease is the most widespread senile dementia in the world and diagnoses are on the rise due to the aging of the world's population and this is causing a significant increase in health spending on the care of the disease. Current studies highlight the need for rapid diagnosis in order to prevent the therapeutic approach from being ineffective, and a comprehensive management of the disease, both with pharmacological and integrative therapies (safety of the environment, music therapy, diet, physical activity, recreational activities, etc.). Regarding the care provided by caregivers, the need to educate these figures is fundamental, to support them economically and psycho-socially (especially during the most difficult stages of the disease) and to provide them with technical skills to effectively and safely address the patient's care.

Objectives. Aim of this study was to investigate the current evidence from scientific literature about the early stage of Alzheimer's disease in order to educate and support caregivers with specific technical and practical skills.

Materials and Methods. A systematic review of the scientific literature of the last 10 years, has been conducted in September 2019 through Medline (PubMed), Scopus and Cinahl databases, in accordance with the criteria of PRISMA Statement guideline (Preferred Reporting Items for Systematic reviews and Meta-Analyses). The included studies were related to Alzheimer's disease and patients' management.

Results. Thirty-six articles met the inclusion criteria but only for 26 of these it was possible to retrieve and access the full text.

Conclusions. The evidences from this study provide information on how to effectively address Alzheimer's disease. The studies address different aspects of the disease, with different methodologies, thus providing heterogeneous evidence. Future studies with reproducible methodologies should be undertaken in order to achieve robustness in results. *Clin Ter 2020; 171 (4):e357-368. doi: 10.7417/CT.2020.2239*

Key words: Alzheimer's disease, nursing management, caregivers, review

Introduction

Alzheimer's disease (AD) is a progressive disease, for which healing is not expected, but only a slowdown in the

involution of the patient's health conditions. The evidences call for an early diagnosis to prevent ineffectiveness of the therapeutic approach (1-3).

The research has shown how today is urgent to tackle AD, as it is the most common age-related dementia in the world and the incidence is increasing due to the ageing world population. Moreover, this factor is causing a significant increase in health expenditure (1,2).

The probability of having Alzheimer increases over the years with incidence rates that doubles every 5 years after the age of 65, at least up to 90 years. Age is the main risk factor (3). The world's population of dementia sufferers (including Alzheimer patients) is expected to double in 2050, increasing the cost of care to around 1.2 trillion dollars. Today, for example, the average cost of a patient in the U.S. is about 47,000 dollars (4).

The pathological process of AD usually begins 10 years before signs and symptoms are manifested and has an insidious onset (5). Memory loss for short periods represents the first clinical manifestation of the disease.

Considering the pathophysiology, the brains of AD patients demonstrate cortical atrophy at frontal and temporal lobes and hippocampus, ventricle enlargement with memory impairment. A condition of constant inflammation of tissues causes degeneration, which can lead to form neuronal amyloid plaques, neurofibrillary elbows and granule-vascular degeneration. Neuronal amyloid plaques are proteins that accumulate between brain cells and slow down cell transmission. The plaques mainly affect the hippocampus. The second process, which involves neurofibrillary balls, is characterized by intracellular groups of filamentous proteins that destroy trapped cells: these tangles are mainly found in the cortex and hippocampus. Acetylcholine, which is a neurotransmitter involved in memory maintenance shows to be reduced due to cell loss in the basal area of the cortex where it is produced (6).

The main risk factors, in addition to age, are smoking, unbalanced diet, physical inactivity, loss of loved ones, familiarity, low economic status, low level of education, depression and other psychiatric diseases, previous head injuries and alcohol abuse (5-8).

Correspondence: Dr. Rosario Andrea Cocchiara, Department of Public Health and Infectious Diseases, Sapienza University of Rome - Piazzale Aldo Moro, 5 – Rome. Tel. +39. (0)6.49694308. Fax +39. (0)6.4454845 . E-mail: rosario.cocchiara@uniroma1.it

On the other side we have several protective factors: a balanced diet; physical activity; recreational activities (such as painting, playing or reading, etc.); education; music therapy; having a high social status; not being widowed (5-8).

The tools to deal with the disease are both pharmacological and non-pharmacological, which can range from music therapy to diet, from physical activity to participation in recreational activities, to many others (4,6,7,9).

The main objective of this systematic review was to identify the criticalities of AD and to offer the tools to help the patient during the early stage of the disease, accordingly with the knowledge derived from last 10 years' scientific literature.

Materials and Methods

A systematic review of the scientific literature of the last 10 years was carried out in September 2019 to investigate current knowledge about AD and the patient's management during the early stages of the disease (Fig. 1).

Medline (PubMed), Scopus and Cinahl databases were used to perform this research, accordingly with the criteria set out in PRISMA Statement guideline (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (10). The included studies were related to the description of Alzheimer patients' management.

The algorithm for the search string was "Alzheimer AND (begin OR start OR onset) AND patient AND management".

The analysis of the articles was led by four reviewers that independently analysed results and extracted data.

The articles found in the databases were analysed by JabRef software, in order to verify and exclude duplicates and inconsistencies.

After deleting this first assessment, studies were screened for their consistency to the research aims by title, abstract and full text analysis.

The criteria for including the articles was to check whether they dealt with the issue of AD, the management of the early stage of the disease by caregivers, the psychological, social and economic factors related to this issue, the therapeutic (both pharmacological and supplementary) options.

In addition, a quality assessment was carried out using four types of quality scales: Newcastle-Ottawa Scale was used for cohort studies, case-control and observational studies (11); The International Narrative Systematic Reviews scale (INSA) was applied for narrative reviews (12); the AMSTAR scale (Assessing the Methodological Quality of Systematic Reviews) for systematic reviews (13); JADAD scale for (Randomized Clinical Trials) RCTs (14).

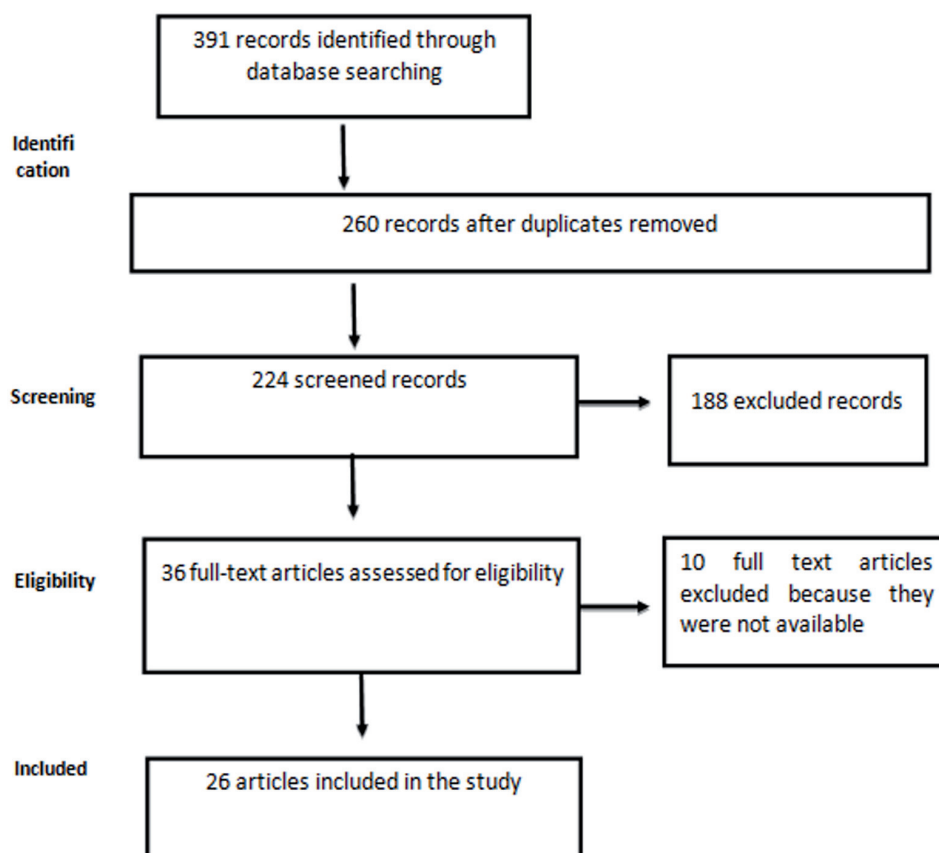


Fig. 1. PRISMA Statement 2009. Flowchart of studies' selection

Results

36 articles were eligible for inclusion in this study. Among them, only 26 were accessible full text and were consequently included. Due to this limitation, the collected results might have been affected by potential bias.

The extrapolated data were classified in 7 categories: first author and year; epidemiology; economics; drug therapy; integrative therapy; psychological and social aspects; diet and environment (Table 1).

Pharmacological therapy

Alzheimer's diagnosis is characterized mainly on memory loss, aphasia, apraxia, agnosia and disorder of executive functions (6,15). The diagnosis includes test for B12 deficiency, hypothyroidism, Apolipoprotein E4 (ApoE4) and genetic test. The instrumental examinations used are MRI, PET and SPECT (16). Diagnosis is one of the most delicate stages in the management of the disease: in fact, in the early stages of dementia doctors fail to recognize AD with a probability of error ranging from 30% to 50% (1,17).

Drug management includes agents that improve cognition, treat behavioural abnormalities and manage systemic disorders or complications of AD along with the prescription of medical foods (food supplements e.g. Nutridrink) (18).

The treatment of the AD aims to preserve and defend synaptic functions with the use of two classes of drugs: the class of cholinesterase inhibitors and the class of the NMDA antagonists (6,17,19).

Cholinesterase inhibitor drugs were the first drug treatment to be used against Alzheimer, improving cholinergic nerve transmission and delaying cognitive impairment. This class includes Donepezil, for lighter and more moderate cases, Galantamine, Tacrine and Rivastigmine.

The second class belongs to Memantine, a new generation drug for moderate to severe disease.

There are other types of chemical treatments: antioxidant therapy; hormone replacement therapy; inflammatory agent; herbal supplements (6).

The estrogen and NSAIDs have not proven to be effective in the treatment and prevention of Alzheimer.

To treat depression due to the degenerative effects of Alzheimer's, different types of antidepressants can be prescribed, such as serotonin reuptake inhibitors (SSRI) and norepinephrine reuptake inhibitors (SNRI) (7,17). Cognitive decline produces in a quarter of patient apathy, depression, anxiety, irritability and sleep disorders (20). Depression can be reduced by making the patient participate in pleasant situations, or by increasing social attendance and recreational activities (4). A strong association between the loss of the groom and cognitive decline has been demonstrated.

Table 1. Summary of the characteristics of the selected studies

First author (year; bibliography)	Epidemiology	Economics	Drug therapy	Integrative therapy	Psychological and social aspects	Diet and environment
Alladi S. (2018; 10)	X	X		X	X	
Anstey K.J. (2013; 6)	X	X		X	X	
Armari E. (2013; 1)	X	X			X	
Bakker R. (2013; 12)				X	X	X
Barczak A. (2014; 13)	X			X	X	X
Chi S. (2015; 7)			X	X	X	
Collins L. (2009; 5)	X	X		X	X	X
Daviglus M.L. (2010; 4)	X		X	X	X	X
Diehl-Schmid J. (2018; 14)	X				X	
Downey D. (2018; 3)			X		X	
Van Duinen-van den Ijssel MSc. (2018, 9)	X				X	
Eriksson H. (2014; 32)	X			X		
Fei M. (2013; 31)	X				X	
J.S. Goldman (2015; 11)	X			X	X	
Golimstok A. (2011; 33)	X					
Hershey L. (2019)			X			
Isik A. (2009; 30)			X			
Liu S. (2017; 8)					X	
Mancini M. (2010; 17)			X		X	
Masters C.L. (2015; 18)	X		X		X	
Mc Donald P. (2008; 19)						X
Onieva-Zafra M. D. (2018; 20)				X		
Pauley T. (2018; 21)	X				X	
Riva M. (2012; 22)					X	
Rubbi I. (2016; 23)				X	X	
Solfrizzi V. (2011; 24)	X					X

The small volume of the hippocampus is related to a higher probability of having depressive symptoms. At the same time, the possibility of having a “vascular depression” is greater when dementia is the result of certain risk factors such as hypertension, diabetes, dyslipidaemia, heart disease and heart attack (7,8,21,22).

Some disorders such as screaming, fowl-eyed, repetitions can be the result of cortical disinhibition, but also signs of untreated pain, isolation and sensory deprivation (4). The agitation in patients with AD mainly affects men under the age of 70 and tends to decrease with age due to reduced physical and mental abilities among individuals over 70s (17,23).

Diet

Since the early stage of Alzheimer, it is very important to modify the diet, with lots of fruits and vegetables, low saturated fats and animal proteins (milk, cheese, yogurt, eggs, beef, pork, lamb, chicken and fish). The ApoE4 gene, involved in the transport of fats and cholesterol in the body, increases the cardiovascular risk and AD (24). Providing an adequate intake of folic acid, statins and moderate alcohol consumption is linked with reduced risk of Alzheimer (3).

Poor nutrition is a common risk factor in dementia patients (4). A cohort study concluded that following the Mediterranean diet reduces the risk of Alzheimer (4,25).

The ginkgo biloba associated with vitamin E is not proven to improve and maintain cognitive functioning (3). Despite this, one study claims that the ginkgo taken for 3-6 months gives its antioxidant effects with doses of 120-240mg, but the data are inconsistent (6).

When eating not use coloured tables, as with food designs, because the patient could exchange them as real. Help to eat by providing cups with handle, even the perception of smells and flavours can change, it may be necessary to add sauces for covering the flavours (26).

Dental treatment in the early stages of the disease should be aimed at maintaining a stable oral condition: in fact, in the later stages of the disease, dental treatment can be extremely difficult or impossible.

To maintain good oral health throughout life, the elderly needs a regular dental care. During early dementia, caregivers and family members should ensure that the patient follows scrupulous dental hygiene to eliminate potential sources of pain, illness and infection. It is crucial to anticipate future oral decline by planning treatments together.

Non-pharmacological therapy: environmental management, music therapy and exercise

Non-pharmacological management involves the caregiver's education and the use of techniques that optimize patient-caregiver interaction and minimize behavioural disorders.

It is important to respond to the needs of the family, because Alzheimer affects both the individual and the quality of life of family members. It is therefore fundamental provide them with support, improving the capability of problem solving, technical skills and the strategies to organize and trying to avoid hospitalization.

It is necessary to plan and organize the environment surrounding the Alzheimer patient (26). It should be considered that the patient has visual and auditory impairments and has difficulty walking and orientation (27).

It is necessary to communicate with the subject using a simple, friendly language and speak with the look at eye height, you should have to accompany the patient in everything he does, anticipating the most difficult manoeuvres with the voice instructions. It is necessary to understand the causes upstream of the patient's agitation and to know how to recognize the signals: in fact, it may be enough to modify simple behaviours to calm the patient and gain his confidence (26).

Bakker et al., for example, offer a meticulous model of home management with some practical tips for who faces the AD at home for the first time: remove carpets, door stops, low tables, possible clutter, illuminate rooms, especially corners, provide devices like ramps and comfortable, ergonomic and motorized chairs with lift-up system, handrails to the hallways and to enter the bathtub, shower seats, check programs on TV, if necessary remove the bins from the bathroom, cover photos and mirrors; highlight the steps and slopes. The best bed height for out-of-bed travel is 18 inches (45 cm). Check that the patient has taken the pills in the blister (26).

You can use signals that help the patient not to lose objects, texts written in large characters or use electronic tools to make up for the patient's inabilities. Mark with the contrast of colours to make recognizable the environment and the differences between objects.

To bath: heat the room, use the shower with the moving handle avoiding spraying water in the face, provide towels in contrast to the colours of the bathroom. Use solutions that highlight the bathroom, such as coloured doors, large signals, or leave the light on in such a way as to facilitate the patient's path to his needs (26).

Have 2 or 3 identical clothing to avoid discussion if the patient does not want to change his clothes, leave the clothes to wear during the day outside the closet, make wearing anti-slip shoes (26).

The phenomenon of wandering occurs mainly in the intermediate stage of Alzheimer, but since the early stage it is suggested to control when the patient moves and closes the doors, if necessary (26).

We can use music therapy since the first stage of the disease, that through the emotional affective stimulus of the nervous system manages to preserve language, cognition and learning. It can make rehabilitative activities easier and reduce depression, especially in the first stage of the disease (7,28,29).

Interventions such as asymmetric radioelectric stimulation of the brain or transcutaneous nerve stimulation could have antidepressant effects (7).

It is recognized that physical activity and cognitive stimulation to memory promote neuroplasticity (4), for example rehabilitation strategies can be applied to lead to increased self-confidence and make up for visual and spatial difficulties. These activities instruct the patient and caregivers about the disease and stimulate memory and cognitive function (27).

Participation in clubs, religious groups, painting or gar-

dening, etc., is also related to the preservation of cognitive functions (3).

Psychoeducation aims to increase patients' self-confidence. It highlights the differences between vision and perceptual, and visual recognition processes, therapist helps the sick to identify his everyday problems (27).

Another protective factor is education, which could somehow result in a cognitive reserve for the brain of the AD sufferer (9,28).

Psychological and stress factors for nurses and caregivers

According to the Armari's study, caregivers recognize treatment, diagnosis and research as the most important areas to improve for affected patients: 71% of caregivers support the necessity to obtain an early diagnosis to reduce the costs of managing the disease (1).

Informal caregivers are generally familiars or friends of the sick and are the main source of support in the community. It has been estimated that they provide about 60-90% of the necessary home care. In this context, it is essential to consider the needs of informal caregivers that are often under-prepared in relation to the enormous physical, psychological, emotional, technical and financial requests (30). In a homecare setting it is more difficult to monitor the signs of distress of the caregiver and would be very useful the figure of the community case manager: the RAI-HC (Resident Assessment Instrument - Home-Care) allows a multidimensional and standardized assessment that welcomes and evaluates patients in care, plans care and, finally, generates treatment protocols.

The variables that increase the chances of caregiver's discomfort are the patient's advanced age (65 years and over), sex (mostly men); married or living with the sick family member (30).

A comprehensive assessment of the study shows that people are aware of the main signs of AD but ignore others that are equally important, which are not believed related to the pathology (e.g. depression).

The Riva's studio observes the differences of knowledge, attitudes and concerns about AD between caregivers of different genders and ages. Women caregivers are more informed than men: this highlights that society needs information and education programs specifically adapted for different sections of the population, with a focus on the men and elderly (31).

According to Liu's study, it is necessary to educate and make caregivers understand the symptoms of both psychological and behavioural dementia (BPSD) related to Alzheimer to improve the approach to the patient and understand his behaviours and emotions (20).

Caregivers in more than 40% of cases rate the risk of stress as high or very high level during the care for the person with dementia (including Alzheimer), and 34% of caregivers argues that it would need more help to keep the person safe at home.

The difference in psychological stress between the management of patients in the first stage of the disease and those in the late stage is mainly the irritability of male subjects. Myamoto's study underlines how the nurse, in case of aggression, must both manage the behaviour of the

dangerous person and prevent other patients from being put in danger. The data shows that aggression is more likely to occur in the early stages of dementia, making care for patients with the early stage of disease more difficult and stressful to manage.

The most stressful conditions for caregivers, in addition to aggression, are turbulence, shouting, repeated questions and discussions. All stressors are high level in the early stage of the disease and medium in the final stage.

Approximately 45% of nurses experience sleep disorders, agitation, aggression, and stress disappointment: with these stressful conditions, apathy is the prevailing emotional state for caregivers (20).

In American nursing homes, for example, nursing staff employed on night shifts are usually reduced and this factor often causes problems with the mental and physical health of the nurses themselves (23).

Therefore, some solutions to help caregivers during care could be targeted longitudinally, such as planning activities and redesigning the environment, developing and increasing skills, education (4), greater financial and psychosocial support with the advice of staff trained (32).

Quality judgment

The assessment that emerged through the scales used is poor (table 2).

There are 11 revisions measured with the INSA scale and have an overall average of 5.09/7, a range ranging from 3/7 to 7/7 and a standard deviation of 1.10.

The systematic review is only one and does not offer many elements to verify its reliability by getting a very poor score with the AMSTAR scale of only 2/12.

There are 11 studies (observational, cohort and case control) measured with the Newcastle-Ottawa scale with an average about A (appropriate) 5/11; I (inadequate) 1/11 and N (not clear) 1.6/11, the range ranges between a fully satisfactory A 7 study to a very poor A 0; I 2; N 5, the standard deviation about the judgment A (appropriate) is 2.41.

There are 3 experimental studies measured with the JADAD scale, with an arithmetic mean of 2.3/5, therefore insufficient, with results ranging from 1/5 to 5/5 and a standard deviation of 1.88.

Discussion

Systematic review represent optimal research tools since they allow to gain a complete overview about the previous evidences from the scientific literature and to effectively guide clinical processes and decisions(33,34,35).

About the results, the most frequent form of dementia is AD, pathology that manifests itself with memory loss, screams, foul talk, repetitions, agitation, can lead to isolation, depression, anxiety, sleep disturbances. The probability of presenting this pathology increases with the passing of the years with a peak incidence between 70 and 90 years (1-3).

There are several risk factors that can be changed entirely or partially, since the early stage of the disease, such as nutrition, smoking, sedentary lifestyle, diabetes, high blood

Table 2. Results, type of study and studies judgment

Review

First author (Year)	Results	Type of Study	Quality assessment
Alladi S. (2018)	A comprehensive approach to THE CEO is needed that considers the socio-economic aspects of every nation, people and race. Underdeveloped countries are more exposed to cognitive decline due to resource scarcity, low education and heavier jobs.	Review	INSA 7/7
Bakker R. (2013)	The environment surrounding the patient must be organized through knowledge of the dangers it can present and planning. Several steps are listed to make the environment safe and stimulating for the AD sufferer.	Review	INSA 5/7
Barczak A. (2014)	Psychoeducation is a technique that increases the patient's confidence and self-esteem. Sensitize the patient and his loved ones about what the disease is and its consequences. The exercises aim at the recognition of objects and orientation in visual space.	Review	INSA 5/7
Chi S. (2015)	The non-pharmacological approach such as stimulant therapy, music therapy, multisensory stimulation, diet, have been shown to alleviate AD, especially in the first stage of the disease.	Review	INSA 6/7
Collins L. (2009)	The cost of caring for senile dementia patients will double in 2050. Having a high educational level is a protective factor for cognitive decline. The Mediterranean diet may reduce Alzheimer's risk.	Review	INSA 5/7
Daviglus M.L. (2010)	There is no scientific evidence to support that excluding all modifiable risk factors can reduce AD, despite this physical activity, fruit and vegetable consumption, a low saturated fat diet, the intake of the right amount of folic acid, not smoking and drinking little alcohol are all factors related to reducing the risk of presenting AD.	Review	AMSTAR 2/12
Downey D. (2018)	A correct diagnosis is the basis of the cure of a disease. After excluding reversible causes of dementia and subjected the patient to pathology-specific tests such as hemato-chemical examinations (for the search for vitamin B12 deficiency and folate or deficiencies of electrolytes, hypothyroidism, diabetes) and instrumental examinations (MRI, PET, SPECT), diagnosis and drug therapy are carried on. There are several types of drugs that can be used to slow the progression of Alzheimer's disease (cholinesterase inhibitors, n-methyl-D-aspartate receptor antagonists, along with antioxidants, hormones, herbal supplements). AD is a degenerative disease but through treatment it allows the patient to continue to carry out daily life activities, thus improving the quality of life of the patient and caregivers. Drug therapy is therefore not a cure but remains a fundamental part of the treatment of the patient suffering from Alzheimer's disease.	Review	INSA 4/7
Eriksson H. (2014)	The differences between EOAD and LOAD are based on diagnostic, demographic and drug treatment work. Patients with EOAD were treated with less generic drugs but received more treatments with cholinesterase inhibitors than those with LOAD, while the use of antidepressants and antipsychotics did not differ.	Review	INSA 5/7
Goldman J.S. (2015)	The results point to the main causes of Alzheimer's disease, one of which is genetic. The appropriate test is a genetic test that depends on the confidence of the diagnosis, the symptoms, patients, relatives and the number of genes of the disease. The test is not recommended if it is the only patient who wants it. Treatment is based on two processes, even a good lifestyle and cardiovascular health can reduce the risk of dealing with AD.	Review	INSA 6/7
Mancini M. (2010)	Dental treatment in the early stages of the disease aims to produce a stable oral condition that gives the patient minimal problems in the later stages of the disease, when dental treatment can be extremely difficult or impossible. To maintain good oral health, the elderly needs regular dental care. During early dementia, caregivers and family members should ensure that the patient follows scrupulous dental hygiene to eliminate potential sources of pain, illness and infection. It is crucial to anticipate future oral decline by planning treatments together with the dentist and implementing preventive measures, such as the use of topical fluoride, chlorhexidine or both.	Review	INSA 3/7

Masters C.L. (2015)	Pharmacological management includes agents that improve cognition, treatment of Alzheimer's-related behavioural abnormalities and medical management of systemic disorders or complications of Alzheimer's disease, along with the prescription of Alzheimer's disease medical foods (food supplements e.g. Nutridrink). Non-pharmacological management involves the education of the caregiver, the use of techniques that optimize patient-caregiver interactions and the minimization of behavioural disorders. It is important to respond to the needs of the family as Alzheimer's affects both the individual and the family: providing support, problem solving skills, technical skills, home modification strategies and leveraging support helping the family in its role as caregiver to allow the patient to stay at home longer periods of time possible and avoid hospitalization, if not necessary.	Review	INSA 5/7
Solfrizzi V. (2011)	The prevention of AD also passes through a proper diet preferring a Mediterranean diet, identified as the best for the prevention of cardiovascular diseases and most chronic diseases, rich in fruits with low glycemic level and vegetables, high levels of fish's fat and vegetable oils. Consumption of foods low in added sugars, low consumption of milk and dairy products and with moderate wine intake is recommended. No definitive dietary recommendations are possible but following dietary advice to reduce the risk of cardiovascular and metabolic disorders prevents the onset of dementia and pre-dementia.	Review	INSA 5/7

RCT and not randomized clinical study

First author (Year)	Result	Type of study	Quality judgement
Anstey K.J. (2013)	The AD begins 10 years before it is manifested. Lifestyle interventions can be more effective if implemented in the non-symptomatic phase of the disease. Factors such as alcohol, smoking, poor diet, depression and physical inactivity are common in people with dementia. The Internet is the new frontier of medicine, with a clear cost savings. Network supports increase the personalization.	RCT	JADAD 5/5
Onieva-Zafra M.D. (2018)	The study confirms the effect of music therapy and reminiscence along with reality-oriented techniques in patients with mild Alzheimer's disease. A demographic questionnaire is used that investigates age, gender, marital status, education level and previous profession, years after diagnosis, primary care provider, comorbidity and mobility requirements. The Mini-Mental State Examination (MMSE) is also administered in the Spanish version (Mini-Examen cognitivo). Goldberg's depression and anxiety scales in the validated Spanish version are used for the study results. In the two groups, in the pre-test and post-test, the Tinetti test in the Spanish version is used.	Pilot (not randomized)	JADAD 1/5
Rubbi I. (2016)	32 AD patients treated with 2 cycles of 6 video-music therapy sessions, which consisted of folk music and video, recalling local traditions, which are then given the Quality of Life scale in Alzheimer's Disease (QOL-AD) and Mini Mental State Examination (MMSE). Video and music therapy can increase, in those with AD of grade 1,2,3 (borderline, mild, moderate) according to MMSE, contact with other people (friends, caregivers and other patients), improves communication and contributes people's ability to interact socially; It can reduce anxiety and loneliness and develop positive feelings of vitality and mental well-being, making the person more confident and independent. This non-invasive therapy can improve quality of life, relationships and psychological and mental well-being without side effects.	Pre-post (controlled, not randomized)	JADAD 1/5

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Cohort, case control and observational study

First author (Year)	Result	Type of study	Quality assessment
Armari E. (2013)	AD is the most common form of dementia, a misdiagnosis of the first stage of the disease is common in 30-50% of cases. Early detection is the primary goal of AD treatment. Diagnosis is most problematic when young patients have had psychiatric problems. It is necessary to educate caregivers about the disease and the needs of the sick.	Cross-sectional	Newcastle-Ottawa Scale A6; N1
Diehl-Schmid J. (2018)	The Epyloge study consists of four sections: 100 people with YOD and 100 with LOD are analyzed. The purpose of the study is to include 50 people living at home and 50 living in LTC in each group. Families are contacted every 3 months until they die. The results indicate that strategies and interventions are needed to improve palliative care in YOD and LOD.	Cohort	Newcastle-Ottawa Scale A6; N1
Van-Duinen-van den Ijseel C. L. (2018)	All NPS causes distress and stress. Sleep disorders are more likely to cause distress in nurses who treat YODs than LODs.	Case-control	Newcastle-Ottawa Scale A7
Fei M. (2013)	According to a cognitive assessment, 132 diabetics have been diagnosed with dementia. Subjects were elderly in the Chinese population, women had a higher percentage of smoking and took diabetes medication. In multivariate logistic regression analyses, variables such as age, Apo E 4, duration of onset of diabetes, use of oral hypoglycemic agents, HMG-CoA reduction (statins) were significantly associated with an increased risk of dementia with T2DM.	Case-control	Newcastle-Ottawa Scale A6; I1
Golimstok A. (2011)	The study highlights a clear correlation between attention deficit/hyperactivity (ADHD) and dementia with Lewy bodies. ADHD is often confused with depressive and anxious symptoms, but with these it has nothing to do with them.	Observational	Newcastle-Ottawa Scale A3; N4
Hershey L. (2019)	Currently dementia with Lewy bodies can rely on valid diagnostic tools. In addition to the diagnosis of dementia if 2 of 4 of the following symptoms are positive, differential diagnosis is made for DLB (visual hallucinations, parkinsonism, cognitive fluctuations, sleep behaviour disorders (RBD)). The review considers the interaction of different drugs to counteract the symptoms that DLB disease presents with reference to these symptoms.	Observational	Newcastle-Ottawa Scale A4; I1; N2
Isik A. (2009)	Cholinesterase inhibitors for the treatment of Alzheimer's disease (AD) and anti-muscarinic agents for the treatment of urgent urinary incontinence (UUI) can reduce the potential effect in patients with both diseases.	Observational	Newcastle Ottawa Scale A5; I1; N1
Liu S. (2017)	5 groups were formed and matched to the caregiver considering age, status, sex, schooling with patients with the same stage of disease in terms of degree of dementia and cognitive assessment scores. For ADL, caregivers with patients to assist with front-temporal dementia were more emotionally dependent than with NPI. The study highlights how the consequences on caregivers depend on the type of dementia of the patient and the load of care: extravagant motor behaviour and hallucinations in those dealing with FTD, DLB and apathy were the symptoms in those dealing with dementia.	Longitudinal	Newcastle-Ottawa Scale A6; N1
McDonald P. (2008)	Structure a diet low in saturated fats and animal protein (milk, cheese, yogurt, eggs, beef, pork, lamb, chicken and fish) as the Apo E gene, involved in the transport of fats and cholesterol in the body, increases the risk of developing diseases devastating diseases such as AD.	Longitudinal	Newcastle-Ottawa Scale A0; I5; N2
Pauley T. (2018)	Informal caregivers, who are generally family or friends of the sick, are the main source of support in the community as state-provided home care is limited, providing about 60-90% of home care necessary. In this context, it is essential taking care the needs of caregivers because, even if they readily accept this role, they are often unprepared to face the physical, psychological, emotional, technical and financially to do so. In a homecare setting it is more difficult to monitor the signs of distress of the caregiver and in this case the figure of the community case manager is central. In this study, the RAI-HC (Resident Assessment Instrument Homecare) is administered, which allows a multidimensional (VMD) and standardized assessment that can accommodate and evaluate patients in care, planning care and generating treatment protocols. The variables that increase the likelihood of the caregiver's discomfort are the elderly patient (65 years and older), sex (mostly men); being married or living with the family member sick.	Case-control	Newcastle-Ottawa Scale A6; I1; N1

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Riva M. (2012)	A comprehensive assessment of the study shows that people are aware of the main signs of AD, but ignore others that are equally important, but less established in popular belief related to Alzheimer's disease and its manifestations (e.g. depression). The study looked at differences in knowledge, attitudes and concerns about AD between caregivers and non-caregivers of different genders and ages, and it appears that women in the subgroup of caregivers are more informed than other subgroups. Society needs accurate information, but education programs should be specifically adapted for different sections of the population, precisely because of the differences between the different subgroups, with a focus on men and elderly people.	Correlation, descriptive	Newcastle-Ottawa Scale A0; I2; N5
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pressure (5-8); immutable risk factors are age (>65 years) and race (such as Hispanic and African race). It is easily noticeable that most of risk factors are superimposed on those related to the cardiovascular disease.

Diagnosis is the most delicate phase and there is a probability of error between 30% and 50%. The tools used to diagnose the AD include the B12 deficiency test, hypothyroidism test, genetic test and Apolipoprotein E 4 test (Apo E4) (1,5,6,16,17). Apo E4 gene is involved in determining the carriers of fats and cholesterol in the body, increasing the risk of developing cardiovascular disease and Alzheimer (24). For this reason, since the early stage of disease a balanced diet is recommended providing adequate intake of folic acid, statins and a moderate consumption of alcohol (4,25).

Drug therapy accompanies the patient since the beginning of AD, and is characterized by the class of cholinesterase inhibitors (the first treatment used for AD which delays cognitive impairment), and the class of NMDA antagonist such as Memantine (second-generation drugs used in cases where the disease is at a moderate-to-severe stage) (6,17,19).

To provide greater quality to patient care, all non-pharmacological treatments that provide for the patient's cognitive and relational health are included and promoted as soon as possible when the AD is diagnosed, such as music therapy and video therapy, pet therapy and aroma therapy (3,14,27,28).

The research analyses the psychological stress of caregivers during the care provided to the patient. It would be desirable that caregivers could be supported, since the early stage of Alzheimer at economic and psycho-social level and provide them with the technical and practical expertise to effectively and safely deal with the assistance of the individual (30,31). The moment a person is diagnosed with AD, the entire family is affected. Although informal caregivers, especially family members and friends, respond promptly to the request for family care, but they are not always adequately educated about the pathology and aware of the physical, emotional workload, technical and financial issues (30).

The phenomenon of distress is frequent, especially when patients are old (65 years or older), men and live with a sick family member. For this reason, it is recommended the figure of the community case manager, who can use validated tools to monitor and assess the onset of distress (20,23).

Nowadays 60-90% of care is provided at home, therefore it is essential to educate caregivers about drug therapy and teach them to order the house according to the needs of the patient, such as avoiding low furniture, carpets, possible clutter, place ramps and signs inside the house especially for the bathroom inside which it is useful to remove baskets and place a shower chair (26,31).

Managing an Alzheimer's patient is more difficult in the early stages of the disease due to the presence of irritability, turbulence and the ease of starting diatribes that could lead to him being violent (17,23). In response, caregivers, like parents or professional nurses, can develop feelings of apathy, agitation and aggression.

The population needs an education about AD, to be able to recognize signs and symptoms and effectively manage the patient, the environment and drug therapy. Education must be targeted and differentiated by gender and age, focusing more on men and the elderly.

In emerging countries, people with poor schooling, low economic status and strong gender disparity in access to care are more prone to dementia (9). Statistically In these countries we have more early-stage Alzheimer patients, given low life expectancy, reduced access to diagnostic tools and advanced therapies and communication difficulties, such as using neuro-psychological tests written in English, because they require translation and adaptation to the local context and are aimed at patients, often, illiterate (9).

It is important to consider the new ways of accessing information about the disease. In recent years the percentage of information and interventions carried out through the internet has soared. The "network" has brought lower costs and greater usability of knowledge with the aim of developing a more sophisticated and effective personal service model (5).

The strengths of this study are the heterogeneity of the aspects addressed on AD and the maturity that emerged in the studies in dealing with the pathology.

The weaknesses of the research are represented by the differences in the applied methodologies within the included studies that do not allow to quantitatively synthesize the retrieved results.

Other limitations are the impossibility of obtaining the full text of 10 studies and that only one study is an RCT. The overall quality rating is poor.

Conclusions

The retrieved scientific articles have shown the importance of facing the AD promptly and the importance of providing the caregivers with all the necessary tools to effectively manage the disease. It is suggested that new studies with reproducible methodologies should be undertaken to achieve meaningful results.

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Annex 1. PRISMA Statement 2009. Checklist [27]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11-12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5;12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression (see Item 16)).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20