REVIEW

THE DRUG APPROACHES AND THE ROLE OF HEALTHCARE PROFESSIONALS IN THE MANAGEMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

One of the most frequent types of dementia is the Alzheimer's disease (AD). The fundamental concepts of pharmacotherapy valid for AD are substances that increase the cerebral acetylcholine level, intervening in cholinergic neurotransmission through cholinesterase inhibition and N-methyl D-aspartate receptor antagonists. These drugs have the role of slowing down the further evolution of the disease, providing at the same time a symptomatic improvement. The effectiveness of these drugs is clearly limited, both because of several negative side effects and their inefficiency to cure the disease. The therapeutic management is therefore a major challenge in AD, and the non-adherence to treatment often constitutes a serious barrier to an effective therapy. Doctors and pharmacists play a vital role in the pharmacotherapeutic management of AD, contributing to improved clinical results and quality of life of the patient. The current review analysed the challenges in therapeutic management, especially those related to treatment adherence and pharmacist involvement.

RÉSUMÉ

Les approches médicamenteuses et le rôle des professionnels de la santé dans la prise en charge de la maladie d'Alzheimer

L'un des types de démence les plus fréquents est la maladie d'Alzheimer (MA). Les concepts fondamentaux de la pharmacothérapie valables pour la MA sont des substances qui augmentent le niveau cérébral d'acétylcholine, intervenant dans la neurotransmission cholinergique par l'inhibition de la cholinestérase et les antagonistes des récepteurs N-méthyl D-aspartate. Ces médicaments ont pour rôle de ralentir l'évolution ultérieure de la maladie, apportant en même temps une amélioration symptomatique. L'efficacité de ces médicaments est clairement limitée, à la fois en raison de plusieurs effets secondaires négatifs et de leur inefficacité à guérir la maladie. La prise en charge thérapeutique est donc un défi majeur dans la MA, et la non-adhésion au traitement constitue souvent un frein sérieux à une thérapie efficace. Les médecins et les pharmaciens jouent un rôle essentiel dans la prise en charge pharmacothérapeutique de la MA, contribuant à l'amélioration des résultats cliniques et de la qualité

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Keywords: Alzheimer's disease, pharmacotherapy, therapeutic management, treatment adherence, pharmacist involvement.

List of abbreviations:
AD – Alzheimer's disease
Ach – Acetylcholine
AChE – Acetylcholinesterase
Aβ – amyloid beta
APP – amyloid precursor protein
MCI – mild cognitive impairments
NMDA – N-methyl-D-aspartate
WHO – World Health Organization
UAE – United Arab Emirates

de vie du patient. La présente revue a analysé les défis de la prise en charge thérapeutique, en particulier ceux liés à l'observance du traitement et à l'implication du pharmacien.

Mots-clés: maladie d'Alzheimer, pharmacothérapie, prise en charge thérapeutique, observance du traitement, implication du pharmacien

INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia and one of the most frequent mental illnesses, is a disorder that causes cell deterioration in the brain. It is defined by a loss in thinking and independence in everyday tasks. Also, it is a terminal, irreversible, and progressive neurodegenerative condition characterized by neuronal degradation that results in the loss of cognitive abilities such as memory, communication skills, judgment, and reasoning[1]. Actual medications (e.g. acetylcholinesterase inhibitors and N-methyl D-aspartate receptor antagonists) have a modest influence on the condition and target late stages of the disease. All the used therapeutical approaches recommended by the medical protocols have only the role to slow down the course of the disease (by giving symptomatic relief), but they do not provide a real, definitive cure. Pathological processes are widely known to begin decades before the onset of clinical symptoms, during which significant and ultimately irreversible processes have generated widespread destruction at numerous levels, beginning at the molecular and intracellular levels[2].

Frequently, symptoms go undetected, are misattributed, or are disregarded and ignored, resulting in stressful, expensive, and sometimes hazardous delays in seeking appropriate care. Managing treatment is a major challenge in AD, non-adherence to treatment being often a serious barrier for an effective therapy and is associated sometimes with adverse treatment outcomes.

This review presents and briefly details the major challenges encountered in the various aspects of the therapeutic management of AD, emphasizing those related to patient adherence to treatment, respectively the involvement of health professionals (physicians and pharmacists). The most common drug approaches for AD are discussed and analysed.

PHARMACOTHERAPY OF AD

The medications used to treat AD are acetylcholinesterase (AchE) inhibitors and N-methyl-D-aspartate (NMDA) antagonist[3]. Figure 1 presents a summarising scheme in this regard.

Acetylcholinesterase inhibitors

According to the cholinergic theory of AD, cholinergic systems are disrupted early in the disease evolution, including the loss of acetylcholine neurons and enzymatic activity for acetylcholine production and destruction. Acetylcholinesterase inhibitors can thus be used to prevent acetylcholine (ACh) breakdown[4].

Galantamine and donepezil are selective AChE inhibitors, while rivastigmine also inhibits butyrylcholinesterase (BChE). The use of tacrine, the first approved AchE inhibitor, is currently limited because of secondary effects (nausea, vomiting, diarrhoea) and liver toxicity caused by more frequently use (short half-life)[5]. Donepezil is the most prescribed AChE agent. According to several studies, donepezil acts at both molecular and cellular levels in practically every phase of AD development[6]. Some symptoms are alleviated by enhancing cognition and/or behaviour. Insomnia, muscular cramps, tiredness, and anorexia are frequent adverse effects, especially at higher dosages. Most people have minor and temporary side effects that last up to three weeks[7].

Galantamine was first isolated from a variety of plants, including daffodil bulbs. It has been demonstrated to be useful in treating AD cognitive symptoms. Notably, gradually increasing the dose of galantamine may enhance its tolerance. Galantamine's most common adverse effects include convulsions, severe nausea, stomach cramps, vomiting, uneven breathing, and muscular weakness[5].

Rivastigmine has a higher selectivity for AChE in the brain than BuChE, being less effective than
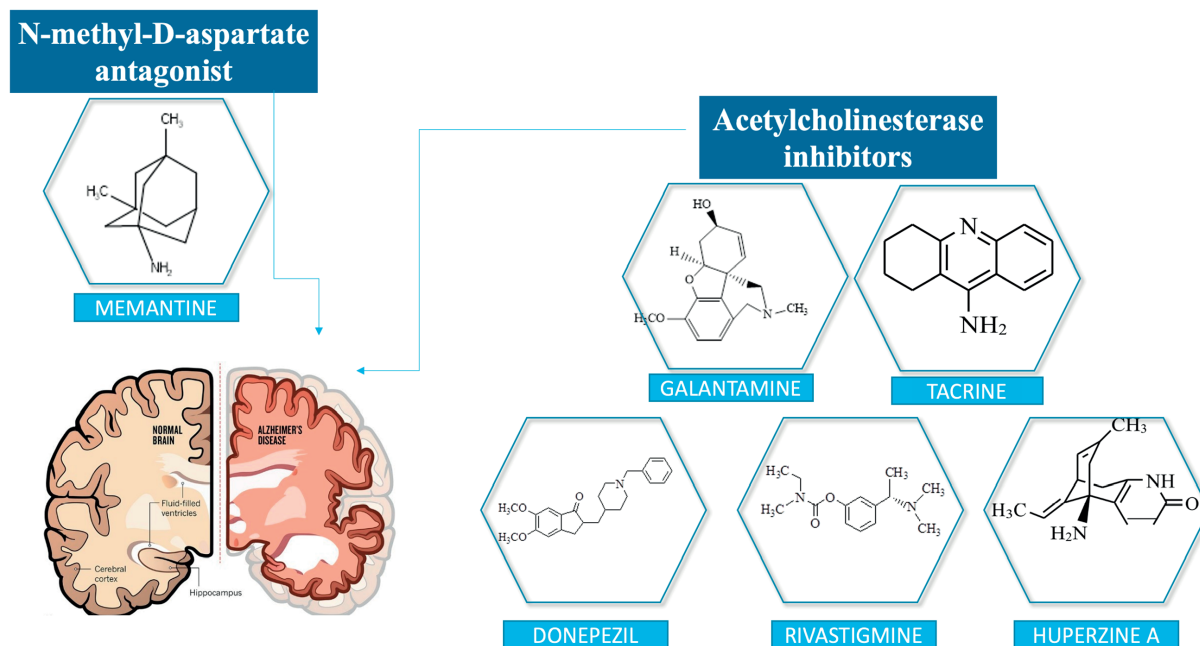
Figure 1. Current treatment options for the Alzheimer`s Disease

physostigmine, the second carbamil derivative and its historical antecedent[8]. The most frequent secondary effects recorded were nausea, vomiting, dizziness, headache, anorexia, stomach discomfort, and tiredness[9].

N-methyl-D-aspartate antagonist

Glutamate is the brain's primary excitatory neurotransmitter, where one of the receptors – NMDA – has been linked to long-term potentiation (process involved in learning and memory). The excessive stimulation, on the other hand, induces excitotoxicity due to excessive intracellular calcium concentrations, which promotes neuronal malfunction. When neuronal activity rates are high, memantine inhibits the NMDA receptor and prevents calcium influx[10]. It has been approved for the therapy of moderate to severe AD. In patients with moderate Alzheimer's disease, memantine improved cognition, global assessments, and behaviour more than placebo. It is a well-tolerated medication, with the following adverse effects occurring in more than 2% of patients: dizziness, headache, constipation, vomiting, back pain, disorientation, somnolence, hallucination, coughing, dyspnoea, agitation. When used in combination treatment, memantine has been shown to have antagonistic effects on type 3 serotonin receptors, which can protect against the gastrointestinal adverse effects of AChE inhibitors[11].

Potential drugs for future management

New approaches have been included to reduce the amyloid burden. Amyloid beta (Aβ) is generated from amyloid precursor protein (APP), being digested by both β-/γ- secretases (the secretase's inhibitors are considered the targets for innovative drug development). An appropriate treatment strategy is Aβ removing, through immunotherapy. Also, few enzymes degrade Aβ, considering neprilysin as well, that is included in the newest therapy approach[12].

Modulating the β-/ γ- secretases enzymes is an extreme searched direction in controlling the APP protein amyloid processing, allowing to understand the secretase inhibitors mechanism in blocking the enzymes which cleave APP, resulting senile plaques formation and Aβ peptide toxic forms.

Published data revealed that isophthalic amide's few bio isosteres provide good cell-free/ cell-based β-secretase inhibitory role. Such compounds (like GRL-7234/-8234) have highlighted an increased reduction regarding the toxic Aβ peptides production. Additionally, in different stages of some clinical trials small molecule of BACE inhibitors (E2609, LY2811376, and LY2886721) are mentioned[13].

Five studies were carried out on crenezumab, solanezumab, aducanumab, gantenerumab and on an association between solanezumab and gantenerumab, in 2019, using monoclonal antibody against Aβ. Aducanumab attacks the aggregated forms of Aβ. At the brain level, it particularly binds to parenchymal in contrast to vascular amyloid. In all study groups it was indicated that amyloid deposits were diminished at 26 weeks and continued to diminish until the end of the first year. Furthermore, the amyloid was removed from six cortical regions of interest (lateral

temporal, frontal, sensorimotor, parietal, anterior, and posterior cingulate)[14,15].

In the pathogenesis of AD, based on the currently recognized amyloid cascade hypothesis, Aβ deposits are the leading force, that afterwards generate transformation in tau protein, triggering a neurodegenerative cascade throughout the evolution of the illness. As various previous investigations on drugs that intended to inhibit Aβ development were unsuccessful in proving effectiveness, microtubules and tau were brought into attention as notable downstream points[16]. The immune reaction is determined by AADvac1 active formulation that acts against several main epitopes in pathological types of tau protein (denoted with τ letter of the Greek alphabet), thus suppressing tau accumulation and reducing neurofibrillary tangles production. Beginning with March 2016, it was initiated a phase 2 trial of AADvac1, planned to run until June 2019. The trial was designed for the assessment of the efficiency, as well as the reliability of AADvac1 administration over 24 months in subjects with moderate AD[17].

In the therapy of inflammatory neurodegenerative diseases like AD, among the new developing therapy goals are mentioned PLA_2 inhibitors. In normal circumstances, PLA_2 interferes in the production of lipid mediators closely connected to neurotransmitter release, ion channel function, phospholipids turnover, membrane repair, long-term potentiation, gene transcription and memory processes. Thus, the PLA_2 triggering generates greater deterioration of phospholipids. This causes alteration in the permeability of the membrane, as well as in the lipolysis involved enzymes stimulation, leading to membrane structure disarrangements, in specific pathological conditions[18,19].

Several positive results in the treatment of neurodegenerative diseases comprising AD were demonstrated in case of metformin, a first-line medication in the treatment of type 2 diabetes mellitus (T2DM). Clinical trials revealed that metformin administration reduces the risk of AD and improves cognitive function that can be altered by factors like the presence of APOE-ε4 and diabetes. The metformin impact on the pathophysiology of AD, comprising chronic neuroinflammation, neural dysfunction, neuronal loss, mitochondrial dysfunction, altered glucose metabolism, insulin resistance, tau phosphorylation and amyloid-β (Aβ) deposits, was demonstrated by previous mechanistic studies. However, current data are confusing and contradictory. Therefore, the recent evidence regarding metformin action in AD pathology is analysed while resuming recent data from clinical trials[20].

Alzheimer's disease pharmacotherapy management

The management of the AD includes early diagnosis and initiation of pharmacological treatment, accompanied by counselling provided by health professionals (medical doctors and pharmacists), as depicted in Figure 2. The first step is to identify the illness, its stages and severity. An early diagnosis allows
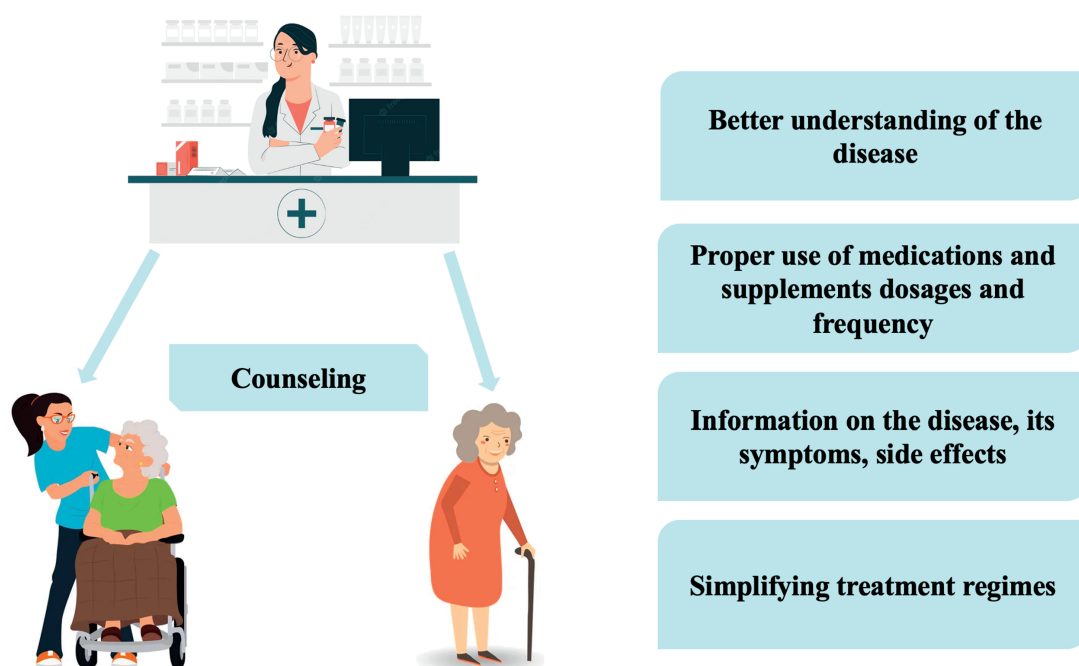

Better understanding of the disease

Proper use of medications and supplements dosages and frequency

Information on the disease, its symptoms, side effects

Simplifying treatment regimes

Counseling

Figure 2. The role of healthcare professionals in dealing with the disease

the family the necessary time to get used to the disease, to acquire basic knowledge (at least) in how to care for the AD patient, respectively to manage the disease in the best possible way, under medical supervision. Some studies confirm that even mild cognitive impairments (MCI) can be accurately diagnosed, but the definitive, clearest and real diagnosis can only be made at the end, after the patient's death, by histological examination of the brain tissue[21] by the forensic doctor, respectively by the histopathologist.

In AD, managing treatment is a major challenge, and non-adherence to medication is frequently an obstacle to effective treatment. Certain steps must be included as part of the care of patients with dementia so that the patient sticks to the prescribed drug hours, but as cognitive abilities deteriorate, patients' adherence to treatment decreases. Non-adherence involves aspects such as non-use of drugs, a minimal or no therapeutic response, increasing the incidence of side effects, or hospitalization. Treatment adherence is determined by the safety and effectiveness of treatment. On the other hand, the subject's non-adherence to the recommended treatment is caused by multiple factors (such as not using the drugs at all or not using them regularly, a minimal or completely absent therapeutic response, increased risk of side effects, hospitalization or repeated hospitalizations, etc)[22].

Obtaining visible results after treatment depends primarily on the regular administration of the medication, the continuity of treatment being indispensable and essential for the best results. The chronic nature of the disease, as well as the memory loss associated with it and which becomes more and more accentuated with the passage of time, also interfere with the patient's adherence to the medication regimens and can make these subjects not (anymore) responsive[23].

Strategies for increasing adherence

Procedures that lead to adherence to treatment, simplification as much as possible of medication regimens, or the use of a most suitable dosage formulation to facilitate regular dosing administration are among the most important factors which intervene in offering the patient the best therapeutic options[24]. Medication adherence is one of the concepts that has become more and more recognized as a *sine qua non* factor in treating patients. Studies published in the literature have demonstrated that a poor adherence reduces the effects of prescription drugs and, obviously, leads to a high probability of obtaining poor results following the administration of therapy[25]. In a study conducted between January 1, 2006, and December 31, 2007, adherence to oral medication and potential predictors of adherence were assessed in a cohort of Alzheimer's patients who used rivastigmine, donepezil, galantamine, or memantine; in this study, only 58% of patients adhered to oral medications, of whom 86-year-old patients had a higher adherence than 75-year-old patients. Although older adults are thought to have lower levels of medication adherence than younger adults, most studies have shown the opposite[26]. Adherence is also increased among the elderly because they have fewer activities and are more aware of the potential impact that the medication can have on their health[27,28].

Family members have a vital role, not to be neglected, in the care of the AD patient, starting from the correct and regular administration of the treatment to the global management of the disease, in all its stages. It is essential that the caregivers of the subject to be educated and have at least minimal knowledge regarding the general aspects of AD as well as how to optimize patients' adherence. The correct understanding of the benefit-risk profile of the medicines prescribed by the doctor, the professional guidance of a pharmacist, the use of medicine organization boxes, are just some of the elements that can intervene and help to comply with the therapy and to guide the AD patient, to increase the quality of life.

Considering the above-mentioned facilities for AD subjects, the transdermal patches have a better potential in being more effective than traditional oral drugs. Literature data specify that over 70% of people prefer rivastigmine patches to pills, according to a survey of 1059 persons, performed in 2020. With the patch vs. the capsule, the relatives reported better overall pleasure, more satisfaction of the patients related to drug administration, and less interference with everyday life. However, no research has been done yet on the impact of patch preference on long-term adherence[29].

New ways of medication administration (such as prolonged-release, oral disintegration, or sublingual, intranasal or intramuscular tablets with short and extended action, transdermal versions, and newest nanotechnology-based delivery systems) are among the strategies recognised to improve subject's adherence[30]. Prolonged-release tablets (in the case of galantamine) and trans-dermal application (in the case of rivastigmine) are among the options, with the transdermal application of the rivastigmine patch having several benefits over capsules due to its higher tolerance and efficacy at lower dosages[31].

In one study cholinesterase inhibitors were administered to 1,086 individuals, with a mean age of 79.87 years. Donepezil was given to 94.4% of the patients, whereas rivastigmine was given to the rest of them. More than 80% of patients stopped using the medication, only 33.6% of them continuing its

administration after a year. When only patients who have been off the medicine for a year have been included, the risk of discontinuation within a year remains high (58.6%). According to observational studies, more than half of total number of included patients drop out the treatment during the first year. Other findings include patients in long-term care institutions having greater levels of persistence and adherence, with no significant variations in persistence and adherence amongst AChE inhibitors[32].

Treatment adherence, according to the World Health Organization, is a dynamic process impacted by a range of circumstances, that necessitates medical professionals and family members' close supervision of the patient. In chronic illnesses, adherence is measured by watching the dosages and frequency of the doctor's prescription, and non-adherence is displayed because of excessive drug consumption or, in the majority of cases, the patient's neglect of treatment. Patients' adherence to treatment is aided by the emotional support they get from family and friends. These subjects are usually on a multi-drug regimen; therefore, family monitoring is very important in preventing forgetfulness and regulating drug treatment administration[33].

The variables that contribute to non-adherence to medications are equally significant and must be carefully monitored. One example is of cholinesterase inhibitors; individuals receiving rivastigmine had a greater chance of discontinuation than those taking other inhibitors, but galantamine, according to certain research, had a higher incidence of persistence. When compared to cholinesterase inhibitors, memantine had a reduced risk of cessation, with 45% of patients stopping after 12 months, compared to 67% of individuals taking rivastigmine[34].

According to the study by Haider et al., 34% of patients who stopped taking their prescription medication did so after 6 months, and the remaining after 12 months[35]. Co-administration of at least four medications at the same time increased non-adherence by more than 2.5 times. Women had a lower persistence rate and a 20% increased risk of early discontinuation of cholinesterase inhibitors. Age is one of the factors which lead to medication discontinuation, although according to a published survey the seniors adhered to medications, whilst women had a lower persistence rate and a 20% increased risk of early discontinuation of cholinesterase inhibitors. Males, on the other hand, were shown to be strongly linked with the chance of adherence to Alzheimer's medications[29].

AD greatly influences, like any chronic disease, the everyday quality of life of the patient and his family. Given the short life expectancy and the progressive nature of the disease, treatments that stabilize symptoms or delay their progression, even for 6-12 months, can have valuable benefits on the quality of life of these patients[31].

THE ROLE OF THE HEALTHCARE PROFESSIONALS

Physicians and pharmacists play a vital role in the pharmacotherapeutic management of AD, and their involvement leads to improved clinical results and quality of life of the patients and their caregivers. Because the number of patients with AD is rapidly growing, professionals in the health field should be prepared through training courses and ongoing educational assistance[36].

The doctor and pharmacist's responsibilities are to counsel both the patients and their family members on the safe and proper use of medications and/or supplements for symptoms including anxiety and insomnia. Most health experts play a critical role in detecting the early symptoms of AD, and they should urge and advise patients to get the testing they need. Patients and family members frequently seek information on the disease, its symptoms, side effects, drug-drug interactions, and, to a lesser extent, psychological assistance. There is a group of individuals (30%) who have trust in them, believing that they have adequate knowledge of the ailment or that the pharmacist is not adequately educated about it[37].

Community pharmacists can help in educating individuals on the risk and protective factors for AD, as well as encouraging early intervention for the best outcomes. Even though pharmacists are unable to diagnose AD, they can give real information related to the accessible services. There may be a barrier owing to their lack of understanding of the disease, its course, and the pharmaceutical therapy of cognitive impairments and behavioural symptoms, as well as their limited awareness of AD[38].

Once AD is identified, patients and/or their caregivers often have a poor understanding of the condition, its course, and treatment options. Drug interactions and adverse effects must be managed well, and as few drugs as possible should be used.

In the United Arab Emirates (UAE), Alzubaidi et al. investigated community pharmacists' knowledge of AD and their capacity to treat various circumstances in patients with AD[39]. When asked about their family's history of AD, 24% of pharmacists answered they asked their relatives. The most common types of advice given by pharmacists were prescription instructions (48%), medicinal indication (32.9%), and probable adverse effects (30.8%), with most pharmacists hardly giving advice. Pharmacists reported verbal communication of information to families in 36% of cases, written and verbal communication in 30% of cases, and no response in 33.5% of cases[40].

During counselling, pharmacists should be on the lookout for indicators of disease, such as trouble learning or remembering pharmaceutical information, difficult family duties, spatial disorientation, and difficulty communicating. Patients, for the most part, wish to keep their independence, but their families worry about their safety and well-being[41]. Moreover, in the future, drug companies and researchers in the field will have to pay special attention to nutraceuticals/ bioactive substances of plant-based origin, which have shown promising potential in the therapy of diseases in general, and neurodegenerative diseases in particular, this trend of „return to nature" being a very topical one[30, 42-47].

CONCLUSIONS

AD is an incurable disease, and the primary goals of the treatment are to reduce symptoms and increase patients' quality of life. In general, AChE inhibitors are administered in the first phase of disease. In the later stages of the disease, dual treatment is recommended by adding memantine. Healthcare professionals' role in managing AD is essential and it mainly consists in establishing the diagnosis, optimal treatment, follow-up of the patient and evolution of the disease, careful checking of prescriptions and counselling of patients, but also of their caregivers. Pharmacists have an increased frequency of interaction with the patient or his caregiver, a more open relationship with the patient (probably since in the pharmacy the patient is more relaxed than in the medical office environment), and in case of adverse reactions or drug-drug interactions, the possibility to intervene faster than the doctor, being more accessible. Consequently, pharmacists should be well-informed about this disease, with solid knowledge, having a good view of the methods and tools through which they can intervene to increase adherence to the treatment recommended by the doctor, and with counselling options for both the patient and those who take care of him.

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