Mild cognitive impairment due to Alzheimer disease: Contemporary approaches to diagnostics and pharmacological intervention

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ABSTRACT

Alzheimer disease (AD) and related forms of dementia are among the main medical and social problems in the economically developed countries. It is connected with significant increase in human life span in these regions and with the absence of efficient medicines for treatment and prevention of such diseases. Lack of positive results in the developing of novel drugs for AD treatment stimulates special attention on problem of early diagnosis and drug discovery for pharmacotherapy on the very early stages of dementia, in particular, on mild cognitive impairments (MCI) due to AD. Here we review the state of art in the field of MCI diagnostics and analyze the data on the pharmacological agents developed for MCI treatment, which currently are in preclinical and clinical trials. The conclusion was made that only the agents that act on the very early pathogenetic stages of the disease, when the damage of cholinergic neurons is not observed, can be efficient for pharmacotherapeutic intervention of MCI. Therefore, the focused search and design of “disease-modifying” medicines should be accepted as the most (and may be the only) efficient strategy for treatment and prevention of MCI.

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1. Introduction

Alzheimer disease (AD) was described by Alois Alzheimer in 1906 as a rare form of presenile dementia with a specific developmental scenario and a specific set of neuropathological symptoms. In recent decades, the disease has transformed into the most frequent disabling condition among seniors. It is expected that medical and socioeconomic consequences of AD would grow exponentially in the near future as a result of demographic processes that currently take place not only in more economically developed, but also in developing countries. This results in increasing proportion of seniors and elderly people in the population and, inevitably, in increasing number of dementia patients among them. According to expert prediction of AD International [1], the number of dementia patients all over the world would grow from 36 million in 2010–66...
million in 2030 and then to 115 million by 2050. This means that in the near 30–40 years, almost each person would be affected by dementia throughout the life cycle either as patients or as their caregivers. The highest morbidity rate is expected in so-called low- and middle-income countries. It is predicted that the percentage of dementia sufferers of these countries relative to the whole number of cognitive impairment patients in the world would increase from 58 to 71%.

Despite the enormous financial expenses (about $600 billion was spent for AD research in the USA in 2015) [1] and the effort of the world scientific and medical community, a 30-year period of active research into the neurobiology and neuropharmacology of AD did not result in the development of a therapy. Indeed, these therapies would not merely mitigate the severity of clinical symptoms, but would also reliably modify the course of the disease, i.e., stop or clearly retard its progression. In the skilled professional’s opinion, a key reason for this little progress in the treatment of AD is the late start of therapy. Furthermore, AD is first diagnosed and, hence, the therapy starts only when a patient has developed a dementia syndrome, indicating that the cerebral compensatory reserves have been exhausted because of extensive neurodegeneration. Therefore, currently it is highly recommended to diagnose AD in early, predementia or, perhaps, presymptomatic stage of the neurodegenerative process. According to estimates, this stage may last for at least 10–15 years. Once more, an equally critical task is to search for viable methods for pharmacological interventions able to stop or substantially slow down the development of neurodegenerative process and thus prevent the appearance of dementia or delay it for several years. Without solving this problem, any “super” early diagnosis of AD and/or another progressive neurodegenerative disease causing the dementia becomes a purely scholastic action that is not only unable to help a patient, but can also bring harm, being the source of chronic psychological stress and depression, which are the risk factors for AD development.

2. Diagnostic criteria for AD

A highly important line of scientific research of the last five years has been the development of diagnostic criteria for predementia AD. For this purpose, special workgroups were formed in the USA by the National Institute of Aging and Alzheimer’s Association (NIA-AA) with participation of specialists from France and UK.

The NIA-AA work groups elaborated and published guidelines for AD diagnosis, consisting of two parts. The first part presents a set of clinical criteria that can be used in practical health care and do not require high-tech neuroimaging tests or cerebrospinal fluid (CSF) analysis. The other part is a set of research criteria to be used in scientific institutions and in clinical investigations of new drugs [2]. This second set of NIA-AA criteria is meant for the diagnosis of predementia AD corresponding to the Mild Cognitive Impairment (MCI) syndrome [3]. The research criteria imply the use of biomarkers based on high-tech neuroimaging data or CSF analysis and have four levels of certainty depending on the presence and nature of AD biomarkers. However, further effort is required to validate the criteria that are based on biomarkers and to standardize the biomarker analysis in order to make them suitable for application at patient care services. Perhaps, some aspects of the research criteria would need to be revised. Presumably, this work will be continued on a regular basis as new information becomes available.

The NIA-AA research guidelines use the term “MCI due to AD”, which corresponds to amnestic MCI (aMCI) and it can be treated as symptomatic predementia AD. This means that the cognitive capacity of a patient is below the level corresponding to his hers age, gender and education, although the cognitive decline has not yet reached the dementia level. The guidelines emphasize that, similarly to Alzheimer’s dementia, “MCI due to AD” cannot be diagnosed by laboratory tests alone, but requires the judgment of a clinician. Thus, MCI is considered as a syndrome defined by clinical, cognitive, and functional criteria [4,5]. The NIA-AA diagnostic criteria differ considerably from the NINCDS-ADRDA criteria, which had been used to diagnose AD for more than 25 years [6]. The new diagnostic criteria include definition for not only “dementia due to AD”, but also for the two predementia stages of the disease, namely, the early asymptomatic (preclinical) stage and early symptomatic (clinical) stage (the latter corresponds to the “MCI due to AD” diagnosis). According to the NIA-AA criteria, AD can be diagnosed before the dementia syndrome has formed by considering a combination of the hippocampal amnestic syndrome and specific biomarkers reflecting the nature and location of the Alzheimer neurodegenerative process. These include biomarkers reflecting amyloid-beta (Aβ) accumulation in the patient brain (decreased CSF level of amyloid β-42 and/or amyloid tracer accumulation according to the PIB PET data) and biomarkers that confirm neuronal degeneration. These include increased CSF levels of total and phosphorylated tau protein, reduction of glucose metabolism in the temporoparietal cortex, which may be detected by FDG PET, and the signs of temporoparietal or hippocampal brain atrophy.

The presence of both CSF biomarkers, namely, amyloidosis (CSF Aβ) and neuronal injury (CSF tau/ptau) are regarded as biomarkers of high diagnostic value, i.e., they indicate a high likelihood that an amnestic MCI (aMCI) patient will develop dementia due to AD in the next five years. The presence of one CSF biomarker of AD, either CSF Aβ or CSF tau/ptau, is interpreted as a biomarker of intermediate likelihood [7]. It is noteworthy that biomarkers of both cerebral amyloidosis and neuronal injury are also encountered in other brain diseases. A considerable drawback of these diagnostic criteria is the lack of standardized values for each biomarker.

The validity of the proposed diagnostic criteria for early (predementia) AD was evaluated in a five-year cohort study carried out by C.G.B. Vos and co-workers [7]. A large cohort consisting of 227 seniors (the average age was 72.9 ± 6.0), 55% of which were females, was assessed using the MMSE scores and a cognitive test battery and examined for the CSF biomarkers of AD. In terms of the initial cognitive scores and the contents of CSF markers, all participants were distributed among five groups according to the detected cognitive deficit and the presence or absence of one or two biomarkers. During the 5-year prospective observation, the authors estimated the frequency of MCI being diagnosed in the elderly people included in the cohort. The lowest frequency of development of the clinical MCI syndrome was found for participants who were initially classified as normal and for those who were suspected to have a non-Alzheimer pathology. Among the participants who were initially diagnosed with different preclinical AD stages, the rate of progression to MCI steadily increased from stage 1 (11%) to stage 3 (56%).

3. Search for potential biomarkers in AD

Currently, a highly topical issue necessary for application of preventive strategies for AD, is the search for so-called peripheral biomarkers of AD, which can be assessed in blood serum or other body fluids (urine, saliva). Hence, these do not require the use of traumatic invasive procedures (e.g., lumbar puncture) or the use of highly expensive high-tech procedures that are unavailable on a large scale (such as PIB PET, FDG PET etc.). In recent years, certain progress has been achieved in the study of peripheral biomarkers of AD. By means of modern methodological approaches (proteomics, metabolomics, mass spectrometry), a number of panels of proteins and metabolites that could be potential AD peripheral biomarkers were discovered [8,9]. How-
ever, to be confirmed as diagnostic criteria, these markers should be validated in prospective studies. In view of the multifactorial nature and phenotypic heterogeneity of Alzheimer neurodegeneration, it appears more reasonable to create a multimodal panel of biomarkers rather than to expect that a single biomarker able to reliably confirm the Alzheimer nature of an early cognitive impairment would ever be found. The development of AD is known to be determined by integration of numerous factors, including genetic, environmental, constitutional, somatic, and chronogeneic ones. The inhomogeneity of these combinations is responsible for different AD phenotypes (familial, sporadic, presenile, senile, or mixed, i.e., combined with other types of brain pathology). For this reason, a multimodal biomarker panel is expected to better reflect the integrated nature of this disease, although data evaluation is associated with some additional difficulties and algorithm for future analysis of their diagnostic value is yet to be developed.

While evaluating the significance of novel diagnostic techniques meant for diagnosing AD in the predementia stage, or even in the asymptomatic stage, one has to emphasize that this new knowledge, giving researchers a lot of hope, also brings about many new problems. In particular, it is not clear how this can help elderly people who do not yet have clinical symptoms, but whose biomarker tests gave positive results, therefore those clear signs of dementia may be manifested (or not) only several years later. The second problem is rather of moral and ethical nature. In the situation where there is no way to cure AD and/or to stop its development, providing a patient with information about the inevitable disease may have adverse influence on his/hers personal freedom and private life or may even be harmful for health and quality of life. Indeed, the news about inevitable disease may cause a psychologically understandable depressive reaction and disinfection, which can by itself trigger the cascade of pathological events characteristic of AD. In this connection, many scientists wonder to what extent new high technologies should be allowed to affect people’s lives at preclinical stages of the disease. The majority of clinicians believe that there is a need for a thoroughly elaborated procedure of informed consent of patients who are suspected to have the preclinical (predementia) stage of AD for the use of new diagnostic methods that detect the prodromal stage of the disease.

Today, there is an urgent need (at least for research purposes) to identify and then to clinically test reliable peripheral AD biomarkers. The concept of an “ideal” diagnostic marker for AD includes the following criteria: 1) specificity, i.e. the ability to identify particularly the Alzheimer neuropathology; 2) a more than 80% sensitivity; 3) a more than 80% specificity of differentiation from other causes of dementia; 4) reliability; 5) noninvasiveness; 6) experimental simplicity; and 7) relatively low cost. However, none of the biomarkers proposed to date (presumably, except for three genetic biomarkers: APP, PSEN1, and PSEN2, which are responsible for not more than 5–10% of all AD cases) do not meet the “ideal marker” criteria.

A new genetic biomarker candidate for preclinical AD is the recently discovered TOMM40 gene [10] responsible for the mitochondrial dysfunction, which affects the pathophysiological processes inherent in AD via interaction with Aβ and amyloid precursor protein (APP). Recently, it was found that three TOMM40 alleles (rs 157580, rs 2075650 and rs 1165605) are accumulated in the Alzheimer’s patient population, and their level being correlated with the CSF markers of AD. According to the mitochondrial cascade hypothesis, it is assumed that mitochondrial dysfunction controlled by allelic variants of TOMM40 is the primary pathological event in AD, preceding the amyloid cascade initiation [11]. It is hypothesized that TOMM40 variable-length polymorphism predicts the age of late-onset AD and may explain some of the variations in age-at-onset in PSEN2 familial AD. In community-based study the presence a long poly-T proved to be associated with AD neuropathology in persons with APOE3 allele and so determine the risk of developing AD. However, Cruchaga et al. (2011) not only did not replicate these results, but also they found that the poly-T polymorphism was associated with a decreased risk of AD [12].

Currently, P-glycoprotein (P-gp), micro RNA (miRNAs), and free copper ions are considered as candidates for early diagnostic markers of AD [8]. Zhuravlin and coworkers and Alsenko have proposed the decrease in the nepirelin (an amyloid-degrading enzyme) expression level or activity [13] and imbalance of sphingolipids such as sphingomyelin and ceramide [14] to be used as new diagnostic markers. Studies of the sensitivity, specificity, and reliability of the mentioned biomarkers for diagnosing the predementia stage of AD are currently in progress. This is especially important because the study of such markers in the framework of general health examinations during screening of certain population groups for the scientific research or during the prophylactic examination of “vulnerable” population groups does not require high-tech research efforts such as PET with an amyloid ligand neither to carry out the traumatic diagnostic procedures such as an investigation of cerebrospinal fluid markers. In addition, the diagnosis of Alzheimer’s disease at the pre-dementia stage using the peripheral markers is likely to be preferable from an economic point of view. In the same time it should be mentioned that blood biomarkers are technically complex for detection both from analytical and computational point of view.

New powerful tool for revealing specific markers for early stages of AD-type MCI is provided by metabolomics research. The study of the metabolic profile of Alzheimer’s disease as a nosological unit, as well as the study of the individual metabolic profile of a patient or phenotypic groups of patients with AD (considering its heterogeneity) seems as a promising approach, both in terms of early diagnosis and in searching for new therapeutic approaches. Metabolomics is aimed at studying chemical processes in the body, in which a low-molecular metabolites are involved. The latter ones are studied using chromatography-mass spectrometry approaches of biological samples (such as urine and tissue extracts). This method more or less has the potential advantage over the currently available diagnostic technologies since it combines the physiological and pathophysiological processes occurring in the body at the molecular level, including the development of Alzheimer’s type neurodegeneration. Besides, it is possible to identify metabolites that are considered as predictors of the susceptibility of a patient to a particular drug and, thus, objectively determine the personified therapy that is necessary for the patient. Metabolomic profiling of the cerebrospinal fluid of AD patients carried out by Kaddurah-Daouk et al. (2011) found disruptions in metabolism of tyrosine, tryptophan, purine, tocopherol, as well as a decrease in the level of noradrenaline and its metabolites, which could be potentially used as a panel of diagnostic markers [15].

4. Protocols for primary and secondary preventive AD therapy

These protocols have been developed since the end of the 20th century and, during the past 15 years; their principles have been substantially modified as regards both selection criteria for populations to be tested and evaluation of the results. A number of potential drug candidates with quite different mechanisms of action (NSAIDs, Ginkgo biloba-based drugs, statins, estrogens, progesterone, vitamins E and C, beta-carotene, folic acid, and selenium) have undergone clinical trials in the last decades; the study design has also been advanced [16]. Unfortunately, none of the studies provided reliable evidence for the efficiency of a given therapy. More recent prospective studies of drugs already approved by FDA and being in wide use for treating AD (Donepezil, Rivastigmine, Galantamine) for their preventive efficiency in aMCI patients
also did not provide reliable evidence for prevention or retardation of the development of dementia by these drugs.

The multicenter comparative clinical open labeled study of cerebrolysin, a peptide drug with proven neurotrophic action (versus vinpocetine), recently conducted in Russia in a group of 110 aMCI patients, who received a course therapy with either of these drugs twice a year over a 3-year period, demonstrated a 3.5-fold decrease in the rate of progression to dementia in the cerebrolysin group [17]. Certainly, these results need to be confirmed in more extensive double-blind placebo-controlled trials.

The search for medications for the pharmacotherapy of aMCI has become considerably more intense in recent years. However, evaluation of the drugs in preclinical trials is complicated by the fact that these trials are often not officially registered. Therefore, in this review, we consider only those drugs that are in the late (officially announced) stages of preclinical trials and have reliably demonstrated in animal models, a beneficial effect on cognitive functions and those drugs that have been under clinical trials according to the Thompson Reuters Integrity database (TR) and the public FDA (Food and Drug Administration, USA) website, www.clinicaltrials.gov.

5. Current therapeutic approaches in AD

As of fall of 2016, the TR database contains four agents defined as anti-MCI drugs and being in the stage of preclinical trials. Potential protective effects of these compounds are discussed below.

DP-NDD is an oligopeptide product developed by D-Pharm Ltd. for the treatment of AD, Parkinson’s disease (PD, and MCI). The lead-compound is aimed at correcting pathological protein aggregation inherent in neurodegenerative disorders. In particular, the agent is under preclinical trials for preventing amyloidosis in AD and MCI [18].

Another compound is BCA909, which is under development by BioCrea GmbH, for the treatment of MCI, AD, anxiety, schizophrenia, and depression. BCA909 is a lead drug candidate of original class of selective phosphodiesterase 2 (PDE2) inhibitors, penetrating the CNS through the blood–brain barrier. The PDE2 inhibition enhances the action antagonists of dopamine-2 receptors, useful for treatment of psychosis, and the action of agonists of dopamine 1 receptors, which decrease the side effect liability and contribute to the pro-cognitive profile. In 2011, preclinical trials of the agent were started, which demonstrated that BCA909 has a significant pro-cognitive activity in models of cognitive impairment caused by disruption of cholinergic as well as glutamatergic neurotransmission [19]. More recent data on the development of this drug are not available.

NNZ-2591 is being developed by Neuren Pharmaceuticals. This is an original pyrrolopyrazine derivative, 8a(R)-allylperhydropyrrolol[1,2-a]pyrazine-1,4-dione. The molecular mechanism of action of this agent has not been clarified; however, it was shown to stimulate cognition and improve motor function in animal models of neurodegenerative disorders [20]. A similar situation occurs for GRE-213 developed by Grespo [21]. GRE-213 is a medical food product that is an oral combination of well-known active ingredients and is under development for the potential treatment of mild cognitive impairment. The first component is generally recognized as safe and the second component is similar to established pharmaceutical products. In preclinical studies, GRE-213 showed an improvement in cognitive behavior, and reinforced neurogenesis and synaptic plasticity in animal models of age-related CNS degeneration. A good safety profile was also demonstrated. No data regarding moving to clinical trials of these agents are currently available.

The DF-302 agent is under preclinical trials for treating MCI. The investigations are underway in Russia in accordance with State Contract 14.N08.12.1027 with the Ministry of Science and Education. The compound was developed at the Institute of Physiologically Active Compounds of the Russian Academy of Sciences [22] and represents a fluorinated analogue of the Dimebon drug, which demonstrated very promising results in phase II clinical trials for Alzheimer’s patients [23], but on phase III trials did not show improvement in comparison with placebo (it has to be mentioned that patients in this trial did not deteriorate significantly in either the drug-treated group or the placebo group, which makes interpretation of the study more difficult [24]). A study of the mechanism of action of DF-302 demonstrated that it reduces uncontrolled protein aggregation in the animal models of proteinopathies. The Thy1mgSN and P301S transgenic mouse was used as experimental models. The Thy1mgSN transgenic mouse on the C57Bl/6J genetic background are characterized by high level of accumulation of the aggregation-prone gamma-synuclein protein and formation of intracellular amyloid type pathological deposits, which in turn promotes the key steps of proteinopathy pathogenesis. The other P301S line of transgenic mice is characterized by overproduction of the aberrant human tau protein, which is a characteristic histopathological structure inherent in tauopathy that seen and/or accompanying AD. According to the trial results, systematic administration of DF-302 considerably reduced the amount of Aβ deposits in the spinal cord tissues of the Thy1mySN transgenic animals. Indeed, prolonged administration of DF-302 led to a statistically significant decrease in the amount of tau positive neurons in the spinal cord of P301S transgenic mice [25]. Recently, it was shown that DF-302 unlike dimebon exerted pronounced pro-neurogenic activity under normal and stressful conditions [26]. Thus, this compound can be regarded as a disease-modifying drug candidate able to affect pathogenetic mechanisms of the disease.

During 2016, several anti-amyloid drugs underwent phase I trials in recent years. For example, the Sanofi Pharmaceuticals Company is developing SAR-228810—an anti-protofibrillar Aβ monoclonal antibody, for the treatment of MCI due to AD. Protobifibrils are metastable intermediates in the formation of amyloid fibrils, which can alter the electric activity of neurons and cause neurodegeneration in the central nervous system. Thus, the SAR228810 drug candidate affecting the Aβ protobifibrils can be efficient for treating early AD and MCI [27]. In 2013, the drug candidate was under Phase I parallel-group, single and multiple dose escalation study to assess the safety and tolerability as well as pharmacokinetic parameters of SAR228810 administered as intravenous infusions or subcutaneous injections in patients with MCI and mild to moderate AD. The trial results have not been disclosed up to now and, according to the TR database, the agent is still under active development.

Eli Lilly is developing the LY-3002813 agent for the treatment of MCI due to AD. The medication is an N3pG monoclonal antibody targeting Aβ(p3–42), resulting from cleavage of the amyloid precursor protein (APP). The monoclonal antibody is able to cross the blood–brain barrier and is active against both soluble and insoluble Aβ peptide, without causing microhemorrhage. Preclinical trials using PDAPP transgenic mice as AD models demonstrated that a modified antibody was able to clear pre-existing amyloid-beta deposits without toxic side effects. The agent is under Phase I trials covering about 100 participants [28]. One more drug developed by the same company, LY-2599666, is meant for subcutaneous administration for the treatment of MCI due to AD and mild or moderate AD. In 2015, the agent was under Phase I clinical trials [29]. The data on the structure or mechanism of action are not disclosed.

In 2017, Pfizer announced the beginning of Phase I clinical trial of the agent Bosutinib. In 2012, the drug was launched in U.S. for the treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph +) chronic myelogenous leukemia (CML) with resistance, or intolerance to
prior therapy. The agent is a multiple kinase inhibitor (in particular, inhibitor of kinases of Src, Bcr and Abl – family, and also signal transducer and activator of transcription 5) [30]. In in vitro experiments, significant reduction in active Src, MAPK and phosphorylated EGFR and ERK1/2 compared to untreated cells was observed. It is supposed that Bosutinib also prevents formation of abnormal tau-aggregates.

The SAGE-547 agent is being developed by Sage Therapeutics. SAGE-547 is a formulation of allopregnanolone (proges- terone metabolite), a positive allosteric modulator of gamma-aminobutyric acid type A (GABA-A) receptor. The potentiating of GABA-mediated chloride current influx is known to induce hyperpolarization of neurons, resulting in a down-regulation of excitation; hence, this can be considered as a possible neuropro- tective mechanism in some neural disorders [31]. A preclinical study for evaluation of allopregnanolone activity in blocking of Aβ-induced neurodegeneration on animal models of AD showed that allopregnanolone promotes survival of newly generated neural cells, reduces accumulation of the Aβ oligomer. Furthermore, allopregnanolone modulates phosphorylated-tau protein expression in the 3xTgAD mice and regulates liver X receptor (LXR), pregnane X receptor (PXR), and 3-hydroxy-3-methylglutaryl-CoA-reductase (HMGR-CoA-R) expression in 3xTgAD mice. The allopregnanolone treatment inhibits microglial activation and increases a marker of myelination in the brains of the 3xTgAD mice. In July 2014, the University of Southern California in collaboration with the National Institute on Aging (NIA) registered a Phase I and in 2017 it was moved on Phase Ib/2a trials to evaluate the safety and tolerability of allopregnanolone in MCI and early AD [32]. The drug is also under Phase III trials for the treatment of super-refractory status epilepticus and under Phase II phase trials for the treatment of traumatic brain injury, tremor, and for adjunct therapy of severe postpartum depression.

The AbbVie company had performed Phase I clinical trials of the ABT-957 – novel ceplarin inhibitor developed for the treatment of MCI [33] and in parallel, the company started clinical investigations of this agent for AD patients [33]. Both trials have been terminated recently.

For a number of years, Suven Life Sciences Ltd. has pursued the search for and investigation of drug candidates for treating AD and MCI based on selective serotonin receptor (5-HT) antagonists. There are data on several drug candidates (SUVN-501, SUVN-502, SUVN-507, SUVN-512, and SUVN-976), which underwent preclinical studies for the treatment of AD and MCI as selective serotonin type 6 (5-HT6) receptor antagonists. The blockade of this serotonin receptor type is known to enhance neurotransmission in cholinergic and glutamatergic neurons, which is usually disrupted in neurodegenerative diseases. The company does not disclose the chemical structure of the compounds; however, judging by the existing patents, these are arylsulfonfyl-indoles and –carbazoles, and their derivatives. Preclinical studies showed that these compounds are 5-HT6 receptor antagonists increasing the extracellular level of acetylcholine and, hence, improving memory acquisition in experimental animals. According to TP database, SUVN-502 is now under intense development. This selective 5-HT6 receptor antagonist, which readily penetrates the brain upon oral administration [34], is also under Phase II clinical trials for treating early AD when used in combination with Donepezil and Memantine [35,36]. No data about active development of other compounds of this group are available. Another selective 5-HT6 receptor antagonist – quinoline derivative –Itepinephrine was in phase III clinical trials at Axovant Sciences for the treatment of patients with mild-to-moderate Alzheimer’s disease and in phase II clinical trials for the treatment of patients with dementia with Lewy bodies. The product had previously been undergoing clinical evaluation at GlaxoSmithKline for the treatment of Alzheimer’s-type dementia. However, recently Axovant Sciences has announced that the co-primary efficacy endpoints were not met in the phase III MINDSET trial of iteipiridine in patients with mild to moderate Alzheimer’s disease who were receiving background donepezil therapy (ClinicalTrials.gov Identifier NCT02589394).

Yet, another class of medications being developed by Suven Life Sciences Ltd. are carboxamide quinoline derivatives, which are selective agonists of serotonin type 4 (5-HT4) receptors. These receptors are known to be expressed in acetylcholine- innervated CNS regions and to be involved in cognitive function. Being 5-HT4 receptor partial agonists, these agents stimulate the activation of cAMP-response element-binding (CREB) protein and thus provide improved signal transmission and induce neurogenesis. The lead compound in this group is SUVN-D4010 (SUVN-D1108121) which was under Phase I clinical trials for the treatment of moderate cognitive impairment due to AD [37,38]. Recently clinical trials have been completed.

The Takeda company is developing a new muscarinic M1 receptor positive allosteric modulator, TAK-71, for oral administration to treat MCI and early AD [39]. Currently, the drug is in Phase I trials both as a monotherapy and in combination with Donepezil [ClinicalTrials.gov Identifier NCT02769065]. In parallel, the company carries out phase I studies for the treatment of Levy body dementia.

At least four other drug candidates being in Phase 2 trials are positioned as anti-amyloid agents capable of reducing the level of neurotoxic Aβ forms in the brain. For example, BAN2401 is a humanized mAb158 antibody derived from mice immunized with protofibrils, isolated upon the arctic mutation of Aβ42. The mechanism of action includes selective binding, neutralization, and elimination of soluble protofibrils, which are toxic Aβ aggregates involved in the development of neurodegenerative processes in AD [40]. In September 2010, Eisai Co., Ltd. initiated the first clinical study of BAN2401, a new monoclonal antibody developed as a new generation drug for treating AD, with patient enrollment. BAN2401 is the first example of a monoclonal antibody that can selectively bind, neutralize, and eliminate soluble protofibrils–toxic amyloid-beta aggregates. In February 2013, Eisai Inc. completed a Phase I, randomized, double-blind, placebo-controlled, combined single and multiple dose escalation study to assess safety, tolerability, immunogenicity, pharmacodynamic response, and pharmacokinetics of intravenous infusions of BAN2401 in subjects with mild to moderate AD. Since January 2013, Eisai Inc. has started a Phase II study of BAN2401 to evaluate safety, tolerability, and efficacy of BAN2401 in patients with early AD. The study was registered with the US National Institutes of Health. Currently, this drug candidate is in Phase II of development in the USA and EU for treating AD and in Phase I in Japan for treating MCI due to AD and mild AD.

CSP-1103 (CHF-5074) is under development by Cere Spir Inc. as a preventive agent for MCI due to AD and the Batten disease. CSP-1103 is a modulator of gamma-secretase, an enzyme involved in the formation of Aβ, which stimulates neurotrophin expression in primary neurons. The drug candidate has passed preclinical trials, in which it decreased the Aβ deposition in brain tissue and attenuated memory deficit in transgenic mouse models of AD [41]. Phase I trial was performed for three ascending doses of the drug (200, 400, and 600 mg per day for 14 days) in a double-blind, placebo-controlled, parallel-group study involving 48 healthy subjects. No serious or severe adverse effects were reported for any of the subjects. The maximum tolerated dose was about 600 mg per day. Currently, the drug is in Phase II clinical trials for the prevention of MCI due to AD and, according to a parallel drug development program, as an orphan drug for treating the Batten disease.

E-2609 is an inhibitor of beta-secretase (BACE1), an enzyme involved in the formation of Aβ peptide from the APP protein [42]. In 2014, Eisai Co., Ltd. and Biogen Idec signed an agreement on joint
development of this drug. In 2016, this agent successfully passed Phase II and is currently renamed as Elencestat in Phase III clinical trials for the treatment of patients with MCI and mild dementia due to Alzheimer’s disease.

Phenserine, a known AChE inhibitor, underwent Phase III clinical trials involving AD patients for the ability to reduce the APP and Aβ levels in the plasma and CSF of mild to moderate AD patients. The statistical analysis of the results did not show significant improve relative to the placebo group; however, more detailed analysis for separate groups showed a beneficial effect for the highest-dose group of patients. Currently, QR Pharma is performing Phase II clinical trials of (+)-phenserine called Posiphen involving patients with MCI, early Alzheimer’s dementia and PD. The drug is declared as an anti-amylloid agent, which has been shown to reduce the APP, and Aβ levels in preclinical studies on rodents and to cause no significant side effects [43].

Recently, compounds modulating the activity of nicotinic receptors in the brain have also been classified as agents involved in the neurotoxic action mechanism of Aβ peptides. For example, Tropisetron, which is a well-known in clinical practice as an antemetic. In recent years, this compound, which is a 7 nicotinic receptor partial agonist and serotonin receptor type 3 (5-HT3) antagonists, was shown to affect cleavage of the APP, one of the key players in the pathological processes involved in AD. In particular, tropisetron was shown to considerably increase the sAPPα/Aβ1-42 ratio of the normal and pathological peptide formed upon APP cleavage in neuronal cultures of the J20 (PDAPP, huAPP (Swe/Ind)) mice. In in vivo studies involving the J20 mice, tropisetron improved the sAPPα/Aβ ratio and also improved the spatial and working memory in mice, being effective both during the symptomatic and pre-plaque phases [44]. On these grounds, the Buck Institute for Research on Aging initiated, in 2014, Phase I/II randomized, double-blind, placebo-controlled, sequential cohort, multicenter study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics and to estimate the preliminary efficacy of tropisetron in patients with MCI due to AD.

A number of drug candidates in Phase II clinical trials refer to the signal modulating agents, which act at the synaptic transmission level. These are mainly drugs acting on enzymes and receptors and on the second messenger system. Drugs of this type include **UC-2343** (Xanemem), which is a small-molecule amidoisothiazole derivative formulated as capsules. This drug candidate targets 11-beta-hydroxysteroid dehydrogenase type 1 (11-beta-HSD1) that regulates the conversion of glucocorticoids from inactive to active form. Furthermore, the expression of this enzyme results in endothelial-dependent vasodilation. Increased cortisol levels lead to irreversible memory loss and formation of amyloid plaques and neurofibrillary tangles (NFT) in the brain, which aggravates the disease. It is expected that by inhibiting this enzyme, the drug could retard the development of Alzheimer’s dementia. In preclinical 11-beta-HSD1 knockout model studies, the 11-beta-HSD1 level in brain was found to be inversely correlated with cognitive decline, and protection against age-related cognitive impairment was detected. The 11-beta-HSD1 inhibition by UC-2343 reduced the formation of Aβ plaques and decreased the plasma amyloid-beta level in animal models [45]. After successful completion of Phase I clinical trials, Actinogen Ltd., which received a license for the development of this drug, started Phase II clinical trials involving patients with MCI due to AD in 2016 [46].

Another drug is **AN2/AVex-73** being developed by Anavex Life Science. The compound is a multi-target drug, being muscarinic M1 receptor agonist, sigma-1 opioid receptor agonist, NMDA-receptor antagonist, voltage gated sodium channel and tau hyperphosphorylation blocker, and lipid peroxidation inhibitor [47]. Recently, new positive results of Phase II clinical trials of the agent ANAVEX2-73 (AN2/AVex-73) in AD patients have been presented at 10th Clinical Trials on Alzheimer’s Disease (CTAD) [48]. Simultaneously, the company started Phase I clinical trials in order to treat Rett’s syndrome and performs preclinical trials for evaluation of applicability of this drug for the treatment of ADC and epilepsy.

**DAOI-B** acts via indirect activation of NMDA receptors—a subgroup of ionotrophic glutamate receptors of the CNS, which regulate the influx of calcium ions into nerve cells. These receptors are known to play an important role in memory consolidation and cognitive function. Meanwhile, hyperactivation of these receptors contributes to the development of neurodegenerative processes in brain, and NMDA receptors may regulate nerve growth factor expression, thus providing neurotrophic regulation in brain. Hence, moderate activation of NMDA receptors may form a promising strategy for improving cognitive function in patients with early dementia. Although direct data on the DAOI-B structure and molecular mechanism are lacking, presumably, this drug is a D-amino acid oxidase inhibitor, causing accumulation of d-serine – NMDA-receptor glycine binding site co-agonist – and thus enhancing the NMDA receptor. DAOI-B for the treatment of MCI and mild Alzheimer’s disease is under study at the Chang Gung Memorial Hospital (Taiwan). In January 2012, a Phase II trial was initiated to evaluate the applicability of the NMDA-activating agent for treatment of MCI and mild AD. The purpose of the study was to investigate whether DAOI-B would be more efficacious than a placebo for cognitive function in patients with MCI or mild AD. The study was completed in May 2013 [49]. In February 2014, another Phase II trial was initiated in order to investigate the effect of DAOI-B for the treatment of cognitive function and behavioral and psychological symptoms of dementia (BPSD). It was assumed that DAOI-B might show better efficacy than placebo for cognitive function and clinical symptoms in BPSD patients. This study was expected to be completed in the late 2015; however, the results have not been published as yet. Recently, researchers from Takeda Company published new data on DAOI-B structural analogue—the agent PGM030756—on increasing d-serine concentration in experiments in vivo, thus giving promise for further development of this compound as a potential therapeutic for AD and MCI treatment [50].

**Ladostigil** developed by Avraham Pharmaceuticals Ltd. seems to advance the furthest towards clinical use. Ladostigil is a deliberately designed binary drug containing a carbamate moiety, known as acetylcholinesterase and butyrylcholinesterase inhibitor, and a propargyl moiety, which is a selective monoamine oxidase B (MAO-B) inhibitor [51]. Since inhibition of cholinesterase group enzymes is considered as an approach to AD therapy and MAO-B inhibition is a known approach to the development of antiparkinsonian drugs, ladostigil is expected to be efficient for treating both AD and PD. The mechanism of action includes also neuro-protection and immune modulation associated with the ability to reduce oxidative stress. Initially, the drug candidate was tested on AD patients. However, in October 2012, Avraham Pharmaceuticals Ltd. terminated the AD treatment program in Phase II as the drug candidate failed to meet the endpoint. Earlier, Teva (the primary licensee) also stopped Phase II investigations of this drug candidate for treating dementia and AD. Currently, Avraham Pharm. Inc. performs one more multi-center, double-blind, placebo-controlled, randomized study to evaluate the safety and efficacy of low doses of ladostigil in patients with MCI. The trial was designed as an interventional, randomized, parallel-group, double-blind study of the treatment safety and efficacy. The primary outcome measures included the conversion from MCI to AD compared to placebo and the total number of conversions from MCI to AD across the entire 3-year study period. This conversion is defined by a clinical dementia rating (CDR) score of greater than or equal to one. The secondary outcome measures included a change in geriatric depression scale for ladostigil versus placebo admin-
istration, a change in neuropsychiatric test scores for ladostigil versus placebo administration, a change in disability assessment in dementia for ladostigil versus placebo administration, and safety of 10-mg ladostigil versus placebo treatment. These parameters, as well as clinical laboratory safety data, are collected within 3, 6, 12, 18, 24, 20, and 36 months. The data such as the time to development of probable or possible AD, the mean time to development of probable or possible AD, and the time to conversion from MCI to AD are analyzed by means of Kaplan-Meier’s survival method.

Levetiracetam (AGB101) is under development to slow the progression of AD and had been shown to improve the memory of patients with amnestic mild cognitive impairment (aMCI). The compound is an N-type calcium channel blocker (Ca(2+)2.2) and a synaptic vesicle protein 2A (SV2A) ligand [52]. Recently, levetiracetam was found to inhibit the Aβ peptide-induced glutamate release from human astrocytes [53]. Initially, it was brought to the market by the UCB Company for adjuvant therapy of convulsions of various etiologies. The anti-epileptic action is based on targeting the SV2A protein, which is involved in the regulation of secretion in neural and endocrine cells, by selectively enhancing low-frequency neurotransmission. In December 2013, AgeneBio Inc. patented the use of low doses of levetiracetam (AGB101) to treat cognitive impairment and cognitive decline [54]. In March 2014, AgeneBio Inc. and US Food and Drug Administration (FDA) had Pre-IND meeting concerning Phase III clinical trial of AGB101 for the prevention of AD. In July 2014, AgeneBio Inc. announced that they are preparing to initiate a large-scale Phase II/III clinical trial of AGB101 in 2015–2016.

Yet, another target that attracts close attention of companies in the search for drugs for the treatment of MCI and early AD is represented by insulin receptors. The hypothesized neuroprotective mechanism is related to activation of insulin receptors, which are expressed in the brain of AD patients mainly in the desensitized state. Impel NeuroPharma is developing insulin-based INP-102 agent for the treatment of AD and MCI using precision olfactory delivery (POD) technique [55] according to which aerosolized drug is delivered to the upper nasal cavity for direct transport into the brain. The drug candidate is in Phase II development, and the company has performed three Phase II studies and is planning a Phase III program and subsequent commercialization [56].

One more insulin receptor-acting agent that was recently proposed for MCI treatment is a peptide compound—Exenatide [57]. Exenatide (glucagon-like peptide analogue), the first in a new class of drugs known as incretin mimetics, was launched in 2005 as adjunctive therapy to improve blood sugar control in patients with type 2 diabetes who have not achieved adequate control with metformin and/or sulfonylurea therapy. The National Institute on Aging (NIA) is conducting phase II clinical trials with exenatide for the treatment of early-stage Alzheimer’s disease or mild cognitive impairment.

For a number of years, attempts have been made to create efficient vaccines for the treatment of AD and MCI on the basis of various forms of immunoglobulins. Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. Immunoglobulin G competitively blocks gamma-Fc receptors, preventing binding and ingestion of phagocytes and suppressing plateau depletion. It is actively used to treat primary immunodeficiency syndromes such as congenital agammaglobulinemia and hypogammaglobulinemia, severe combined immunodeficiencies, chronic lymphatic leukemia with severe secondary hypogammaglobulinemia, and some other diseases. Octapharma AG is developing Octagam, a drug based on human immunoglobulin in intravenous administration. The drug has been in Phase III clinical trials for the treatment of relapsing remitting multiple sclerosis and in Phase II studies for MCI in the European Union. The grounds were provided by the clinical studies of Octagam in AD patients carried out earlier [58]. Although the study was too small-scale and the duration was too short to draw final conclusions, a [18F]FDG PET examination demonstrated a significant dose-dependent attenuation of the regional reduced glucose metabolism, which is inherent in AD, for all patients who received Octagam 10% compared with the placebo group, low doses being more efficient than high doses. Recent date on results of Phase III clinical trials showed good tolerability of treatment with low-dose human IV Ig for 18 months but did not show beneficial effects on cognition or function relative to participants who received placebo [59].

Verubecestat (MK-8931) developed by Merck & Co is in Phase III clinical trials for the treatment of MCI. The drug is classified as an anti-amyloid agent, as it has been shown to inhibit beta-secretase 1 (BACE1), which ensures cleavage of APP to give the Aβ peptide. The compound is also in Phase II/III clinical trials for the treatment of Alzheimer type dementia [60]. Already in February 2017 Merck announced that they will stop EPOCH trial of verubecestat in mild to moderate AD. A pre-specified interim analysis by an external data-monitoring committee reportedly judged the chance of a clinical benefit to be near zero, according to Merck press release. Another Merck’s trial (APECS) in people with prodromal AD will continue; results are expected by 2019.

One more strategy in the search for new drugs is investigation of novel applications for the drugs that have already been introduced in the medical practice for some other indication. This approach, which is called drug repositioning, is actively used in the search for drugs for the treatment of various forms of dementia, in particular, AD and MCI [61]. Below we present data from the Thomson Reuters Integrity database on known drugs that have undergone clinical trials for the possible use in MCI therapy.

Pioglitazone (Actos, Glustin, Zactos) was brought to the market in the 1990s by Lilly, Novo Nordisk, and Takeda for treating type 2 diabetes. Currently, Takeda together with Zinifandel Pharmaceuticals performs Phase III clinical trials of this drug in combination with the TOMM40 biomarker to treat MCI. The hypothesized mechanism of neuroprotective action is related to the ability of this compound, as a peroxisome proliferator-activated receptor γ (PPAR γ) agonist, to affect the CRMP2 phosphorylation level disrupted at early stages of Alzheimer’s dementia preceding the formation of Aβ-structures [62].

Three other drugs that are currently in use for the treatment of AD were investigated as preventive agents for MCI patients. Eisai performed Phase III clinical trials of Donepezil but no evident beneficial effects were noted [63]. No data on further development of these studies are available. Clinical investigations of Galantamine for the treatment of MCI patients did not show any promising good results either [64]. The Schwabe company, which has developed a Ginkgo Biloba extract-based agent, carried out Phase III trials involving patients with MCI; however, later, the investigations were terminated. Nevertheless, recently it was reported that Ginkgo Biloba Tablet (GLT) improves some memory characteristics of MCI patients, especially in recognition, regeneration, understanding, and recitation tests [65].

Tasamorelin, a growth hormone releasing factor (GRF) developed by Serono, which was approved in the USA in 2010 for treating HIV-associated lipodystrophy syndrome, is now in Phase II studies. The clinical trials involving MCI patients are currently performed by the National Institute of Aging [66].

There are data about initiation of clinical trials of Sagrastomim (Leukine) [67], which is a glycoprotein consisting of 127 amino acids and resembling the granulocyte-macrophage colony-stimulating factor (GM-CSF), with the only difference being arginine instead of leucine in position 23. The Genzyme Company performs Phase II clinical trials of this agent for the therapy of MCI.
Table 1
Drug candidates for MCI treatment in clinical and preclinical trials.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>Main type of action</th>
<th>Trials phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAR-228810</td>
<td>Sanofi</td>
<td>Anti-amyloid</td>
<td>I</td>
</tr>
<tr>
<td>LY-3002813</td>
<td>Eli Lilly</td>
<td>Anti-amyloid</td>
<td>I</td>
</tr>
<tr>
<td>LY-2599666</td>
<td>Eli Lilly</td>
<td>Anti-amyloid</td>
<td>I</td>
</tr>
<tr>
<td>SAGE-547</td>
<td>Sage Therapeutics</td>
<td>Anti-amyloid</td>
<td>I/IIa</td>
</tr>
<tr>
<td>ABT-957</td>
<td>AbbVie</td>
<td>Signal modulation</td>
<td>I</td>
</tr>
<tr>
<td>SUVN-502</td>
<td>Suven Life Sci Ltd.</td>
<td>Signal modulation</td>
<td>I</td>
</tr>
<tr>
<td>SUVN-D4010</td>
<td>Suven Life Sci Ltd.</td>
<td>Signal modulation</td>
<td>I</td>
</tr>
<tr>
<td>TAK-71</td>
<td>Takeda</td>
<td>Signal modulation</td>
<td>I</td>
</tr>
<tr>
<td>Guanfacine*</td>
<td>NIA (NIH)</td>
<td>Anti-inflammatory</td>
<td>I</td>
</tr>
<tr>
<td>Montelukast*</td>
<td>IntelGenx</td>
<td>Anti-inflammatory</td>
<td>I</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Pfizer</td>
<td>(Anti-tau?) Decreases MAP phosphorylation</td>
<td>I</td>
</tr>
<tr>
<td>Exenatide</td>
<td>NIH</td>
<td>Insulin secretion modulator</td>
<td>II</td>
</tr>
<tr>
<td>BAN-2463</td>
<td>Eisai</td>
<td>Anti-amyloid</td>
<td>II</td>
</tr>
<tr>
<td>CSP-1103</td>
<td>Cere Spir Inc.</td>
<td>Anti-amyloid</td>
<td>II</td>
</tr>
<tr>
<td>Posipen</td>
<td>QR Pharma</td>
<td>Anti-amyloid</td>
<td>II</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>Back Inst. Res. Aging</td>
<td>Signal modulation</td>
<td>II</td>
</tr>
<tr>
<td>UE-2343</td>
<td>Actingen Ltd.</td>
<td>Signal modulation</td>
<td>II</td>
</tr>
<tr>
<td>ANZ/A/Avex-73</td>
<td>Anavex Life Sci.</td>
<td>Signal modulation</td>
<td>II</td>
</tr>
<tr>
<td>DAOI-B</td>
<td>Kaohsiung Chang Gung Memorial Hospital, Taiwan</td>
<td>Signal modulation</td>
<td>II</td>
</tr>
<tr>
<td>Ladostigil</td>
<td>Avraham Pharmaceuticals Ltd.</td>
<td>Signal modulation</td>
<td>II</td>
</tr>
<tr>
<td>Levitiracetam</td>
<td>Agene Bio Inc.</td>
<td>Signal modulation</td>
<td>II</td>
</tr>
<tr>
<td>NVN-102</td>
<td>Impel NeuroPharma</td>
<td>Insulin receptor modulation</td>
<td>II</td>
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<tr>
<td>Octagam</td>
<td>Octapharma AG</td>
<td>Immunocorrector</td>
<td>II</td>
</tr>
<tr>
<td>Tesamorelin*</td>
<td>NIA (NIH)</td>
<td>Neurotrophic</td>
<td>II</td>
</tr>
<tr>
<td>Sagamostim*</td>
<td>Genzyme</td>
<td>Neurotrophic</td>
<td>II</td>
</tr>
<tr>
<td>Melatonin*</td>
<td>1. NeuriumPharm.</td>
<td>Neuroprotective</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>2. Facultad de Medicina, Universidad de Buenos Aires</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-2609</td>
<td>Eisai &amp; Biogen</td>
<td>Anti-amyloid</td>
<td>III</td>
</tr>
<tr>
<td>Verubecestat</td>
<td>Merck&amp;Co.</td>
<td>Anti-amyloid</td>
<td>III terminated</td>
</tr>
<tr>
<td>Pioglitazone*</td>
<td>Takeda &amp; Zinfandel Pharm.</td>
<td>Neuroprotective</td>
<td>III</td>
</tr>
<tr>
<td>Ginkgo Leaves Tablet (GLT)*</td>
<td>Schwabe &amp; Huadong Hospital, Fudan University, Shanghai, China</td>
<td>Neuroprotective</td>
<td>III</td>
</tr>
<tr>
<td>DP-NDD</td>
<td>D-Pharm Ltd.</td>
<td>Anti-amyloid, anti-Tau</td>
<td>preclinic</td>
</tr>
<tr>
<td>BCA909</td>
<td>BioCrea</td>
<td>Signal modulation</td>
<td>preclinic</td>
</tr>
<tr>
<td>NNZ-2591</td>
<td>Neurwn Pharmaceuticals</td>
<td>Not disclosed</td>
<td>preclinic</td>
</tr>
<tr>
<td>GRE-213</td>
<td>Grespo</td>
<td>Not disclosed</td>
<td>preclinic</td>
</tr>
<tr>
<td>DF-302</td>
<td>IPAC Rus Acad Sci.</td>
<td>Anti-aggregative</td>
<td>preclinic</td>
</tr>
</tbody>
</table>

* agents that were launched earlier for another application.

In recent years, **Melatonin** and its analogues have attracted considerable attention as safe drug candidates for the treatment of MCI. This is an endogenous compound produced in the body by the secretory cells of epiphysis and normalizing the circadian rhythms. Previously, it was found in a number of studies that melatonin and its biological precursor, N-acetylserotonine, exhibit clear-cut neuroprotective properties [68,69]. Therefore, the study of this compound for the therapy of MCI initiated by Neurium Pharm. was

![Fig. 1. Known structures of agents for MCI treatment currently in preclinical and Phase I clinical trials.](image-url)
reasonable. No data about results of this study are available in the TR database; however, the results of another study were published [70], indicating that melatonin is promising as an open label add-on drug for the therapy of MCI.

Two other drugs that have been used previously for a different indication are in Phase I clinical trials. The first one is Guanfacine, which was first proposed by Novartis for the treatment of hypertension and later approved by the FDA for the therapy of attention deficit hyperactivity disorder in children was under investigation initiated by the US National Institute of Health involving MCI patients [71]. Recently, the clinical trials have been completed. The participants in both the investigational agent group and the placebo group showed statistically significant improvement in their symptoms and functioning over the course of the trial. The mechanism of action of this drug is attributable to neurotransmission modulation, as this compound is an alpha-2-adrenergic receptor agonist and hyperpolarization- and cyclic nucleotide-gated (HCN) channel blocker [72].

Another drug, Montelukast, was developed by Merck in the late 1990s to treat asthma and allergic rhinitis. The mechanism of anti-allergic action is related to its action as an antagonist of leukotriene receptors, in particular, LTD4. According to TR data, IntelGenx is developing an oral film formulation of the compound, which is in phase I a clinical trial for the treatment of mild cognitive impairment and Alzheimer’s disease. Presumably, the cognitive stimulation action of this drug is associated with the possible positive modulation of leukotriene receptor inhibition of cyclooxygenase- (COX) and lipoxygenase-mediated (LOX) inflammatory processes [73]. The key data on the compounds that have undergone preclinical and clinical trials as drug candidates for the treatment of MCI are summarized in Table 1. Known structures of agents for MCI treatment currently in preclinical and Phase I, II and III clinical trials are displayed in Figs. 1 and 2.

6. Conclusions

Analysis of the state-of-the-art studies in the diagnosis and therapy of the predementia stages of AD provides the conclusion that early diagnosis and pharmacological correction of MCI is currently one of the most important strategies for the therapy of Alzheimer dementia. Numerous failures in the development of efficient drugs for the treatment of AD at the dementia stage draw particular attention to the possibility of pharmacotherapy of early predementia stages of neurodegenerative changes in the human brain. Today many pharmaceutical companies revise their anti-Alzheimer strategy towards correction of the earliest stages of the disease. A number of drugs, for example, Ladostigil, Posiphen (Phenserine isomer), which did not show beneficial results in Phase II or III clinical trials for AD are repositioned for the treatment of MCI. Meanwhile, it cannot be regarded that any drug that has proved useful for treating clinically diagnosed AD would automatically prevent the development of dementia in MCI patients. As noted above, AChE inhibitors used to treat AD—Donepezil, Galan- tamine, and Rivastigmine—proved inefficient in the therapy of MCI [64]. Evidently, a disease-modifying, i.e., preventive effect in the predementia stages, can be expected only of the agents that can act on the earliest stages of pathogenesis where no considerable damage of cholinergic (and possible glutamatergic) neurons has
taken place. Of particular attention are the biotargets and biological pathways that are believed to be primarily involved in early stages of neurodegenerative processes, in particular, mitochon- 
drial functions, tau phosphorylation processes, and formation of
soluble oligomeric products of pathological proteolysis of APP. 
Therefore, the search for disease-modifying drugs for the therapy 
and neuroprotection for MCI patients is the most efficient strategy 
for pharmacotherapy.

Another quite prospec tive approach related to reposi tioning of
earlier known drug for this (anti-MCI) new application, is the
known toxicological profile of such compounds. In series of the
described above agents about 1/3 have been launched earlier for
another application, in particular, there are: Guanfacine, 
Mentelkast, Levitirametam, Tesamorelin, Sargramostin, Pioglitazone,
Ginko extracts.

One more key issue of the studies of MCI treatment is the
search for adequate markers for early stages of neurodegenerative
processes. It is evident that without reliable (qualitative and
quantitative) methods for diagnosing the predementia AD stages,
efficient application of any ways of pharmacotherapy is impossible.
A balanced solution of these two problems can provide grounds for
a considerable progress in the theory of AD and MCI caused by the
early neurodegenerative AD process.

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dimercaptopropanolhydrochlorides as Agents Decreasing Uncontrolled Protein 
Aggregation in Nervous System, Based Pharmaceutical Preparation and Method of Using It, 
of dimercaptopropanolhydrochlorides as Agents Decreasing Uncontrolled Protein 
Aggregation in Nervous System, Based Pharmaceutical Preparation and Method of Using It, 


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