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ADVANCEMENTS IN DRUG THERAPY AND DELIVERY SYSTEM FOR VASCULAR DEMENTIA

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ABSTRACT

Vascular dementia result from condition that damage your brain blood vessel reducing their ability to supply your brain with the amount of nutrition and oxygen it need to prefer thought processes effectively. Common condition that may lead to vascular dementia include stroke that blocks a brain artery usually cause a range of symptoms that may include vascular dementia. but some stroke do not cause any noticeable symptoms these silent stokes still increase dementia risk with both silent and apparent stroke the risk of vascular dementia increase with the number of stroke that occur over time. The review summarizes the advancements in drug therapy for Vascular dementia.

KEYWORDS: Vascular dementia, Phytoactives, synthetic drugs, delivery systems.

INTRODUCTION

Vascular dementia is caused by brain damage from impaired blood flow to your brain and it develop vascular dementia. and it also develop after a stroke black an artery in your brain but stroke do not always cause vascular dementia. Other conditions that damage blood vessel and reduce circulation depriving your brain of vital oxygen and nutrient. Factor that increase the risk of heart diseases, vascular dementia and stroke including diabetes, high blood pressure, high cholesterol and smoking it also rise your risk of vascular dementia.

Causes

Vascular dementia result from condition that damage your brain blood vessel reducing their ability to supply your brain with the amount of nutrition and oxygen it need to prefer thought processes effectively. Common condition that may lead to vascular dementia include stroke that blocks a brain artery usually cause a range of symptoms that may include vascular dementia. but some stroke do not cause any noticeable symptoms these silent stokes still increase dementia risk with both silent and apparent stroke the risk of vascular dementia increase with the number of stroke that occur over time. One type of vascular dementia involving many strokes is called multi infarct dementia. Narrowed and chronically damaged brain blood vessel. Condition that narrow or inflict long term damage on your brain blood vessels also can lead to vascular dementia. this condition include the wear and tear associated with aging high blood pressure ,abnormal aging of blood vessels (atherosclerosis) diabetes and brain hemorrhage.

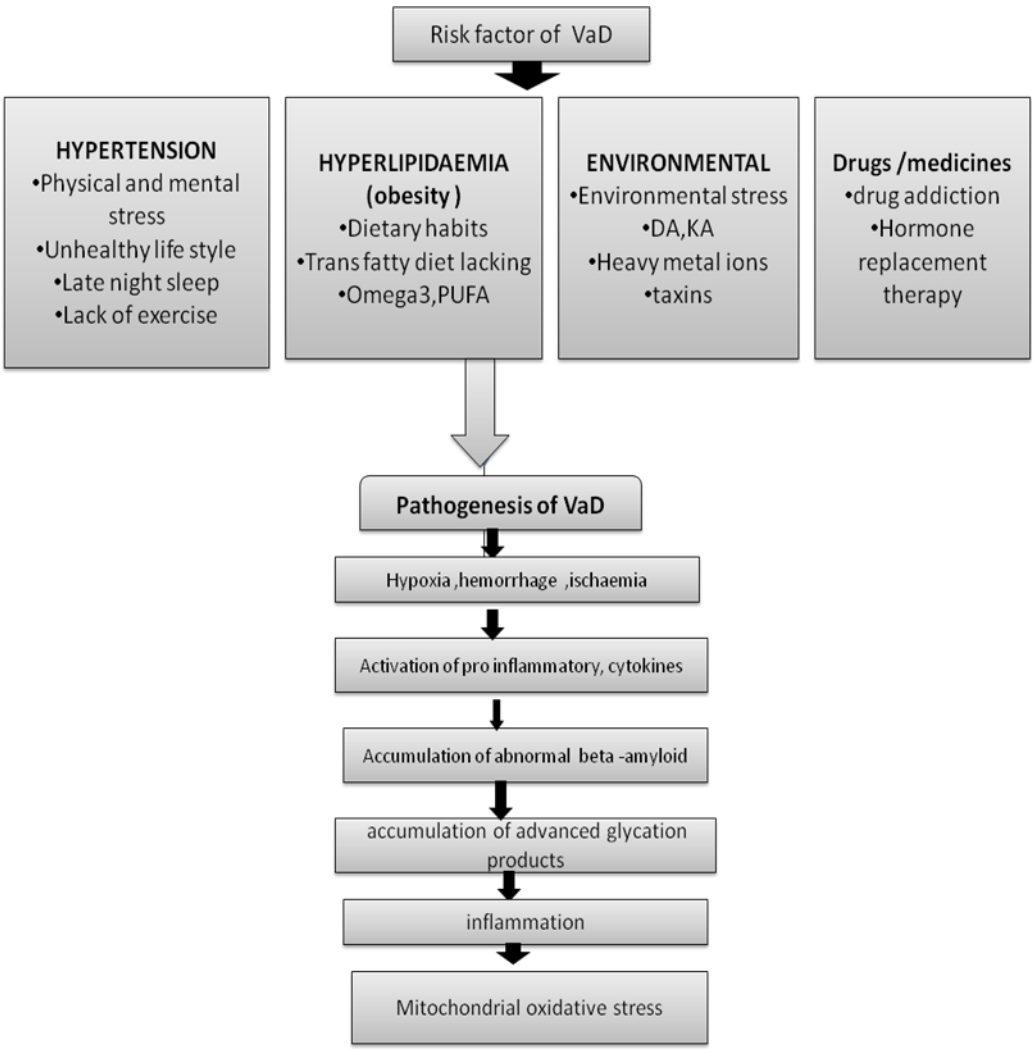
Associated Risk factor

1. Increasing age:-your risk of vascular dementia rise as you is older. This disorder is rare before age 65 and the risk rise substantially by your 90.
2. History of heart attack stokes or mini stoke:- you we had a heart attack you may be at increases risk of having blood vessel problems in your brain .the brain damage that occur with a stroke or a mini stroke(transient ischemic attack) may increases your risk of developing dementia.
3. Abnormal aging of blood vessels (atherosclerosis):- this condition occurs when deposits of cholesterol and other substances (plaques) build up in your arteries and narrow your blood vessels. Atherosclerosis can increases your risk of vascular dementia by decreasing the flow of blood.
4. High cholesterol: - elevated the level of low density lipoprotein (LDL).
5. High blood pressure:-when your blood pressure too high it give extra stress on blood vessels in this stages increases the risk of vascular dementia diseases.
6. Diabetes: - if glucose levels increases then its damage the blood vessels throughout your body damage in brain blood vessels and can increases the risk of stroke and vascular dementia.
7. Smoking: - smoking directly damage your blood vessels and increases the risk of atherosclerosis and other circulatory diseases, vascular dementia.
8. Transient ischemic attack: - its also predispose to increases the risk of stroke and 30% of the patient who suffer stroke develop dementia after a period of 6-12 months. Cerebral autosomal dominant auteriopathy with subcortical infarcts and

leukoencephalopthy an also inherited disorder manifested it's a syndrome of migraine, mood disorder, recurrent transient ischemic attack stoke and early development of dementia is an indepent age related pathogens of AD and VaD.

Pathophysiology of vascular dementia

Vascular dementia is most coomon and widely recognized dementia. and their accurate diagnosis is clinically suspected VaD narrowpsycological and manifestation of cognitive decline which could be attributed to cerebro vascular or cardio vascular dieases. Diagnosis of vascular dementia depend on the risk factor including cerebral autosomal dominant arteriopathy wqith subcortical infaract and leucoencephalopathy and small vascular dieases. two hypothesi have been proposesd for the etiology and pathophysiology of vascular dementia. first hypothesis protein to amyloidal cascade neurodegenration and where as the second protein to the dysfunction of the cholinergic system, tau aggregation metal mediated toxicity and inflammation. according to the amyloidal cascade neurodegeneration hypothesis of vascular. dementia begins with the proteolytic cleavage of the amyloid precrroser protein (APP)and result in the production aggregation and deposition of beta –amyloid and amyloid plaques. when the concentration of betya- amyloid is high insoluble amyloid fibers are formed in the brain. this fiber may be complexed with zinc and copper there by aggravating the neuronal toxicity. According to the cholinergic hypothesis the dysfunction of the cholinergic system is sufficient to produce a memory deficit in animal models and that is similar to AD. and vascular dieases showed the degeneration of cholinergic neurons and a decreas in cholinergic markers where as the activities of choline actyltransferase and AChE was decreases in the cerebral cortex of patient with AD AND VaD.



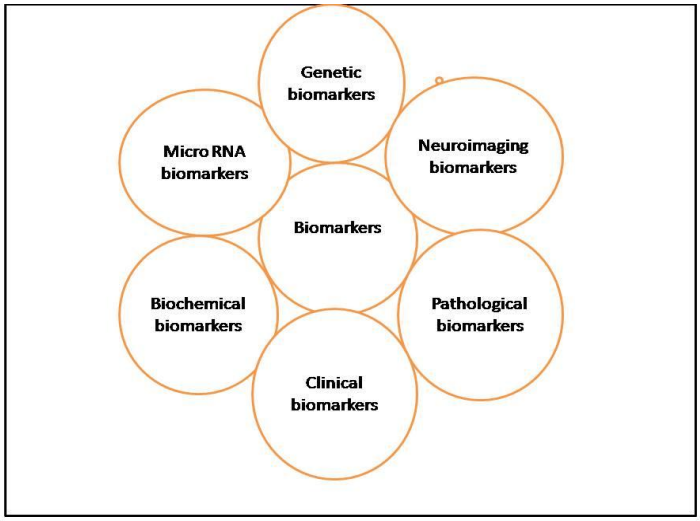
Phospholipas A2(PA2) its enzymes and it responsible for the synthesis of chemicsl mediators of inflammation and is also responsible for the conversion of phosphtidyl choline to choline. if PA2 level have been decreases in the frontal and periatal cortex of vascular dementia their resulting in reduced levels of choline because of choline is converyted to acetyl choline by chAT and AChE its deficit contributes to cholinergic deficiency and vascular dieases progression.

Diagnosis of vascular dementia

Require neuropathological assessment computed tomography, positron emission tomography (PET) magnetic resonance imaging (MRI) and magnertis resonance spectroscophy(MRS). Laboratory test can be used to exclude other possible causes for dementia cerebrovascular dieases cobalamine deficiency syphilis and thyroid dieases .CSF analysis can be very usuful in identifying demenytia caused by other factor such as infection in the CNS like neuroyphis, neuroborreliosis, cryptococcosis

The etiology of dementia based on the biomarker analyes

These biomarker must be easily measured and give accurate result. The surrogate biomarker of vascular dementia mainly based on functional and neuroimaging and CSF and blood –based analysis. The most significant vascular dementia biomarker that could be used for recent clinical diagnosis which are classified as clinical biomarker (neurobehavioural assessment) pathological biomarker (identifying cellular histologicasl change) biochemical biomarker(serum plasma CSF biomarker) neuroimaging biomarker which also include functional multi modality fussion imaging with CT, MRI/MRS PET and single photon emission CT(SPECT) to facilitate the functional and structural information of vascular dementia. biomarker (identifying genes involed in cerebrovascular dieases) and microRNA(subcellular components of vascular dementia. Currently studies on biomarker have emphasized on inflammation hemostasis, oxidation stress hypoxia- ischemia accumulation of biochemical substance compl, ex protein and other metabolites in the hypertensive atheromatous dieases and hyperlipidemia in tissues and CSF. classification of vascular dementia biomarker a diagram give the information of various types of biomarker used to dignos the vascular dementia.



CSF biomarker of vascular dementia:- in this biomarker which measured in various body fluids such as saliva blood and urine and tissue. CSF studied is very important because it drain the ventricular system of the brain and concentration of various metabolits may directly gives various pathological processes in the brain. CSF serum albumin ratio, CSF index, and CSFtotal protein are biomarker having high diagnostic value as these can identify structrul and functional integrity of the blood –brain barrier and microvascular damage. sulfatide it's a biomarker for demyelination is used to identify and the extent of demyelination in the white matter and it is found to be elevated in vacular dementia. Further more the matrix metalloprotease(MMPS) n the CSF can be estimate to identify change in the extracelluar matrix associated with vascular dieases and inflammation. autopsy studies shows that MMP, are increase in patient with vascular dementia. serum to CSF folate ratio can be used to differentiate vascular dementia from AD. This ratio is significantly decreases in vascular dementia. the decreas folate ratio has been found to be charactrstics of the vascular dementia. the protein biomarker represent various physiological process such as protein degradation proteas inhibition (cystatin C and alpha –chymotrypsin) inflammation (C3a,C4a) are kown to be associated with neurodegenerative dieaseas including all form of dementia. these type of marker lack specificity and need to be validated and investigated in large prospective multicentric trails.

Serum and plasma biomarker of vascular dementia

The serum and plasma from the blood sample of patient with vascular dementia, AD. and other neurodegenerative dieaseas C reactive protein it is a inflame, matory biomarkaer and its level are elevated in vascular dementia. hyperhomocystinemia is a well estabilishd vascular dementia risk factor and increases level of serum homocysteine prove and relationship with vascular recent studies have been shown that I ncreas in serum of homocysteine is associated with hippocampal and cortical atropy in patient with vascular dementia due to deficiency of vitamin B12 and folate cause

hperhomocystenimia the supplementation of these vitamin failed to produce any improvement in patient with dementia hence role of homocysteine remain contaversial. dehydroepiandrostrone (DHEA) a neurosteroid and its metabolites DHEA, sulfate (DHEA-(MDA), thyroid stimulating hormones (TSH), calcium and magnism have been found to be non specifically elevated in patient with dementia suggesting vascular etiopathogensis in illnesses. The receptor for advanced glycation and product (RAGE) is a cell- bound receptor of the immunoglobuline superfamily that may be activated by proinlammatory ligand including advanced glycol-oxidation end product and amyloid –beta peptide, clinical studies have shown that hiher plasma levels of RAGE are associated with decreased risk of coronary arteroy dieaseas, hypertension, metabolic syndrome, arthritis and AD similarly atherosclerotic cerebrovascular dieases is a significant cause of vascular dementia.

Pathological biomarker of vascular dementia:- pathological biomarker which is used for diagnosis of vascular dementia and this biomarker, facilited and clasiifying the dieases process at the cellular and molecular level. this biomarker are divided into six parts, biomarker of CADASIL, biomarker of microvessel angiopathy, biomarker of hypertensive vasculopathy, biomarker of cerebral amyloid angiopathy, biomarker of atherosclerosis or thrombotic diseases.

Nanotechnology –Based Drug Delivery System For The Treatment Of Vascular Dementia Disease

Treatment of vascular dementia dieases are limited mainly due to the inability of drugs to cross the blood – brain barrier or their poor solubility by oral route. many strategies Have been developed to overcome the BBB, such as the drug delivery system, liposomes, polymeric and solid lipid NPs, solid lipid carrier, liquid crystal, microemulsion and hydrogei. the physiochemical properties of drug including hydrophilicity or lipophilicity , ionization ,high molecular weight, poor bioavailability adverse effect, extensive metabolization which result in its failure as a pharmacotherapeutic. These limitation can be overcomes by the use of intranasal administration which offer an alternative, noninvensive means of the drug delivery to the brain because drug delivered this way can bypass the blood brain barrier and directly transport drugs to the central nervous system.

Polymeric NPs:-NPs are defined as particulate dispersions or solid particles with size ranging from 1 to 1000 nm.the structurally organization of a nanosystem and it is based on composition: the presence of compartment within nanocapsules and nanocapsules lad to oily or aqueous cores surrounded by thin polmer membrane. NPs have been prepared by using different method, such as polymer polymerization, ionic gelation and coacervation, spontaneous emulsification, emulsion solvent evaporation solvent diffusion, nanoprecipitation, spray drying, superficial fluid technology and particle S) have neuroprotective effect and their levels in central nervous system are raised in neurodegenerative dieaseses however the reason for their alterd level in blood as a cause or as an effect remain uncertain. similarly oxidative stress or such as malondialdehyde replication in non-wetting templates. drug delivery across the BBB to the brain may provide a significant advantage over currently used strategies without damaging the BBB. the transport mechanism of NPs across the BBB can be explained by the increased retention of the NPs in the brain blood capillaries in combination with the adsorption of the NPs to the capillary walls. These events leads to a higher concentration gradient. which increases the transport across the endothelial cell layer and thus enhances the delivery to the brain. transport can also be facilitated through the inhibition of the efflux system by using polysorbate80 as the coating agent. NPs may induce local toxic effect on the brain vasculature, leading to a limited permeabilization of the brain endothelial cells. the use of a surfactant to solubize the lipid of the endothelial cell membrane can enhance drug permeability across the BBB. The NPs can permeate the BBB through the tight junction, which are open between the endothelial cells of the brain blood vessels. other technology include, coating NPs with polyethylene glycol, polmers, or antibiotic to improve nasal absorption.

Solid lipid carrier:- SLNs are typically spherical, with average diameters between 10 and 1000 nm when dispersed in water SLNs possess a solid lipid core matrx that can solubilize lipophilic molecules. SLNs are formed by a matrix lipid, a new generation of NPs can be produced using a blend of solid lipid with a liquid lipid, termed nanostructured lipid carrier (NLCs), in order to minimize the drug expulsion associated to SLAs. SLNs or NLCs are prepared from lipid, an emulsifier, and water or solvent by using different methods such as high pressure homogenization, an ultrasonication/high-shear technique, the solvent evaporation method, the solvent emulsification-diffusion method, the supercritical fluid method, the ME-based method, the spray-drying method, the double emulsion method, or the precipitation technique. the BBB can be overcome through the use of SLNs or nanocarriers lipids for the delivery of drug to the brain, as these formulation can penetrate the BBB or be used itranassaly to bypass the BBB. the use of cationic lipids can be a strategy to improve mucoadhesion in the nasal cavity by promoting electrostatic interaction with mucus in addition to mediating the adsorptive –mediated transcytosis cationic NPs across the BBB. Piperine SLNs with a polysorbate 80coating were prepared by the emulsification-solvent diffusion technique. these NPs were experimentally assessed in ibotenic acid-induced vascular dementia in mice. The results showed an increases in AChE activity and improvement in cognition. which were superior to the result shown for donepezil. histopathology studies also revealed a reduction in plaques and tangles.

Developed curcumin /donepizil- loaded NCLs for delivery to the brain via the intranasal route. The results demonstrated a higher concentration of the drug in the brain via intranasal delivery compared to intravenous administration a mouse model showed improved memory and learning compared to the group treated with the free drug. Never the less, the level of acetylcholine were improved and oxidation damage was reduced in the groups treated with NLCs.

Liposomes:-liposomes are vesicles consisting of one or more phospholipid bilayer concentrically oriented around an aqueous compartment that serves as carriers of lipophilic or hydrophilic drugs. Various processes can be used to prepare liposomes, such as hydration of a thin lipid film followed by agitation, sonication, extrusion, high pressure homogenization, or reverse-phase evaporation.

Liposomes may contain a single lipid bilayer or multiple bilayers around the inner aqueous compartment and are therefore classified as unilamellar and multilamellar, respectively. liposomes are classified by their lamellar size as small unilamellar vesicles with diameters of 20-100 nm, large unilamellar vesicles with diameters exceeding 100nm, giant unilamellar vesicles with diameters up to 1 um, oligolamellar vesicles with diameters of 0.1-1 um, and multilamellar vesicles with diameters up to 500 nm.

Liposomes are classified as niosomes, transfersomes ethosomes and phytosomes. niosomes are formed by self- assembly of nonionic surfactant in an aqueous dispersion and they are flexible and more stable than liposomes. which reduces the flux of drug in comparison to conventional liposomes. transfersomes are deformable vesicles composed of phospholipids that are usually administered via the transdermal route.

Rivastigmine liposomes and cell-penetrating peptide (CPP)- modified liposomes to improve the distribution of rivastigmine in the brain, enhance the pharmacodynamic via intranasal administration, and minimize side effects. the results showed that the concentration of rivastigmine across the BBB were significantly different after 8 hours, reaching higher concentration values when CPP liposomes and liposomes were used compared to the free drug. The biodistribution of rivastigmine in the are not transparent and less thermodynamically stable then MEs. the two systems are very different because NEs are formed by mechanical shearing and ME phase are formed by self-assembly.

Other parameter cerebellum was not found when free drug was administered intranasally or intravenously. The average rivastigmine concentration in CNS cerebral tissues was higher following intranasal administration of modifiedliposomes compared with liposomes, and the average rivastigmine concentration was significantly higher for the modified liposomes in the hippocampus, cortex andolfactory region at 15 minutes to 60 minutues. That rivastigmine –loaded liposomes especially-modified liposomes, improve the brain delivery and enhance pharmacodynamics with respect to BBB penetration and the nasal olfactory pathway into the brain after intranasal administration. were obtained using the thin-film hydration technique. Thermal studies showed that the beta-sheet blocker was located in the hydrophobic core. Many method used to target liposomes across the BBB. These strstegies techniques include the conjugation of drugs and monoclonal antibodies against endogenous receptors in the BBB or liposomes or other nanomolecules, peptides or antibodies against BBB receptors or a beta peptides tocross the BBB and to be targeted to the brain.

Liposomes were prepared by the lipid hydration method to sustain the effect of rivastigmine in the brain. Rivastigmine-loaded liposomes and rivastigmine solution were administered via the subcutaneous route in an aluminum chioride-induced vascular dementia. And Alzheimer,s model. Both formulation improved the deterioration of spatial memory induced by aluminum chloride, with liposomes having a superior effect.

Surfactant-based systems:-surfactant-based drug delivery system are different drug delivery systems in which surfactant molecules are self-aggregated, usually in the presences of water, to form structure with variable parameters depending on the concentration of the surfactant, the presence of salt, or the temperature. These aggregates becomes more organized even when oils or other components such as other surfactant are added to the surfactant- water systems. Thus, microemulsion (MEs), nanomolecues (NEs), and lyotropic LC mesophases with different geometries can be generated. Microemulsion are usually thermodynamically stable isotropic liquids formed by mixing oil, water, and surfactant together NEs, by contrast, are conventional emulsion that contain very small particles. the droplets sizes of microemulsion are between 10and 140 nm which results in optically transperant and thermodynamically stable systems. NEs are up to 140 nm in diameters and can also described the MEs from NEs : MEs are more stable in long-term storage then NEs; MEs can be agitated cooled, or heated and then returned to their original condition, whereas NEs cannot return to their original condition; MEs have a homogenous droplet size while NEs have range of heterogeneously sized droplets; and MEs may or may not contain spherical droplets due to the lower interfacial tension while NEs consist of spherical droplets due to the large laplace pressure acting upon them.

MEs are formed from spontaneous mixture of oils, water, and surfactant, though it is often necessary to apply stirring or heating to facilitate the formation of MEs due to kinetic energy barriers that must be overcome or mass transport limitation that inhibit their spontaneous formation. NEs are formed using the input of some

external energy provided by high-pressure homogenizers, microfluidizers. and sonication method to convert the mixture into a colloidal dispersion or phase inversion spontaneous emulsification method can then be used to form NEs.

NEs containing curcumin were developed for intranasal delivery, and the results from behavioural experiments showed improved memory and learning in the group treated with curcumin –loaded NEs compared with the group treated with the pure drug MEs were developed for transdermal delivery in order to mange vascular dementia and AD.

Table 1: Representation of various drugs used in Vascular Dementia with their delivery systems.

Drug	Drug delivery system	Protein binding	Mechanism of action	Route of administration	uses
Donepezil	Solid lipid nanoparticles	96%	Donepezil is a peparidine derivaties. It is a reversible inhibitor of cholinesterases, like actylcholinesterase, which help to prevent the hydrolysis of actylcholine and which lead to increases the concentration of acetylcholine at cholinergic synapses.	Intranasal, oral route	Mild cognitive impairment ,schizophrenia,, attention deficit disorder, multiple sclerosis,VaD. Diffuse lewy body disease, mild dementia Alzheimer's
Rivastigmine	Polymeric nanoparticles, liposomes	40%	Rivastigmine is a carbamate derivatives and its reversibly with and inactivates cholinesterase(eg. Butyrylcholiesterases) its also help in preventing the hydrolysis of acetylcholine, and increases the concentration of acetylcholine at cholinergic synapses.	Oral route and intranasal and transdermal patch, intravenous	Parkinsion cortex and olfactory region.
Galantamine	Liposomes	18%	Galantamine is a phenanthrene alkaloid and a reversible acetylcholinsterase inhibitor.and galantamine binds to allosterically with nicotinic acetylcholine receptor.	Oral route	Improve memory , awareness, mild to moderate confusion(dementia).

CONCLUSION

Thus, it can be concluded that vascular demntia is a syndrome associated with progressive impairments in memory and learning ability, cognitive skills, behaviour, activities of daily living, and quality of life. There are more than 47.5 million people with dementia worldwide and 7.7 million new cases are added to the dementia pool each year. In addition to prescription medication, many individuals with dementia, Supplemental nutrition, or other alternative therapies could also help to treat the disease's progression and symptoms. Diet, physical activity, and mental activities may help slow the progression of the illness. In conclusion, the existing evidence to support the use of single and complex herbal preparations is promising but requires further development.

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