Review Article

Herbal and Pharmacological Strategies for Treatment of Ageing Related Disorders

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ABSTRACT

Ageing-associated disorders (Alzheimer's disease, Parkinson's disease, osteoarthritis, atherosclerosis, rheumatoid arthritis, osteoporosis and hypertension) are mostly seen with increasing frequency of senescence. Cholinergic transmission in the basal forebrain innervates the cortex and the hippocampus and is involved in normal learning, memory and attention and in geriatrics. The activity of choline acetyltransferase, a marker enzyme of acetylcholine, is reduced in neocortex due to accumulation of neurotoxic amyloid beta protein and hippocampus due to formation of neurofibrillary tangles and consequently results senile dementia in Alzheimer's disease. Degeneration of neurons in *Nigrostriatal* [substantia nigra pars compacta to neostriatum (nucleus caudatus-putamen)] dopaminergic tract for Parkinson's disease but over-activity (increase in dopamine receptor density) of dopamine, an inhibitory neurotransmitter in *Mesocortical* (ventral tegmental area, substantia nigra, retrorubral nucleus to forebrain limbic and cortical areas) for psychoses and *Mesolimbic* (Medial forebrain bundle to nucleus accumbens and olfactory tubercule in temporal and prefrontal areas) responsible for schizophrenia are studied by positron emission tomography. Anticholinergics: memantine, galantamine, rivastigmine, donepezil for Alzheimer's disease; combination of levodopa with carbidopa or entacapone/tocapone, dopamine agonists: bromocriptine, pergolide, monoamine oxidase (MAO)-B inhibitors: selegiline, rasagaline, NMDA receptor antagonist: amantadine for Parkinson's disease; Statins, fibrates, niacin, bile acid sequestrants, combination therapies (single-pill) for atherosclerosis, combination of opioid with non-steroidal anti-inflammatory drugs & celecoxib for osteoarthritis; estrogen with or without progesterone alendronate, Ibandronate, risedronate, raloxifene for osteoporosis; adalimumab, certolizumab pegol, etanercept, golimumab, infliximab for hypertension are clinically used. Atypical neuroleptics have weak D_2 blocking but potent 5-HT_2 antagonistic activity and are not associated with extra-pyramidal side effects.

Keywords: Alzheimer's disease, Parkinson's disease, Osteoarthritis, atherosclerosis, rheumatoid arthritis, osteoporosis, ageing.

INTRODUCTION

According to Ayurveda, ageing is mentioned in two ways - physiological ageing (Kalaja jara), natural process of ageing and Akalaja jara (premature ageing). Ageing is the accumulation of changes in an organism over time which in humans refers to a multidimensional process of physical, physiological and social changes[1]. The ageing process is of course a biological reality which has its own dynamic, largely beyond human control. Ageing has been defined as a progressive generalized impairment of function resulting in a loss of adaptive response to stress and in a growing risk of age associated disease[2]. Ageing deteriorates memory, retention and recall in human beings and is associated with marked structural and neurochemical changes in the central nervous system. With ageing, the frequency and amplitude of transient corrective movements increase due to age-related reduction in dopamine (D_2) receptors in straitum which controls muscle tone and coordinates movements. An imbalance between dopominergic (inhibitory) and cholinergic (excitatory) system in striatum occurs giving rise to motor defect.

'Ageing-associated disease' term is used here to mean 'diseases of geriatrics (elder people over 65 years of age)'. Nor should ageing-associated diseases be confused with accelerated ageing diseases, all of which are genetic disorders. Alzheimer's disease, Parkinson's disease, osteoarthritis, osteoporosis, rheumatoid arthritis, hypertension and atherosclerosis are aged related disorders. The incidence of all of these diseases increases rapidly with ageing. Cerebral atrophy in rhinencephalon, hippocampus & striatum and cognitive dysfunction are observed in SAMP10, a model of brain senescence. Psychoses are a severe state of hyperactivity with serious distortion of thought, behaviour, capacity to recognize reality and perception: [false belief (delusions) and abnormal sensations (hallucinations)]. Cognitive disorder such as delirium, dementia, confusion and functional disorder characterized by emotion, thought, behavioural alteration such as schizophrenia and paranoid state are types of psychoses. Schizophrenia, splitting of perception and interpretation from reality is a chronic, debilitating psychiatric disorder and a leading social economic burden worldwide with lifetime prevalence. Positive (hallucination, delusion, agitation, and stereotypy behavior), negative (social & emotional withdrawal, lack of pleasure and motivation) symptoms and cognitive dysfunction (impairment in attention & working memory) are symptoms of schizophrenia. Patients with schizophrenia also have reduced glutathione and super oxide dismutase antioxidant enzyme activity, increased level of lipid peroxidation, nitrite as well as monoamine oxidase activity, increased acetylcholinesterase activity and up-regulation of 5-hydroxytriptamine-2A expression

of serotonin receptor in cortex region. Glutamate, an excitatory neurotransmitter causes excitotoxic neuronal death by inducing Ca^{2+} load through n-methyl-D-aspartate (NMDA) receptor, induces the same metabolic processes that increase free radical production can lead to impaired dopamine-glutamate balance. Ketamine (0.25 mg/kg, i. p.), a metabotropic glutamate NMDA receptor antagonist induces psychotic symptoms (increased locomotor activity, stereotypy, grooming & licking behaviour) and memory impairment in mice. Reduced densities of glutamate receptors in post mortem brain of schizophrenics is confirmed by ketamine induced hyperactivity and catalepsy, a condition in which consciousness and feeling seem to be temporarily lost and the muscles become rigid. An imbalance between dopominergic (inhibitory) and cholinergic (excitatory) system in striatum occurs giving rise to motor defect. Tradive dyskinesia, a late-appearing neurological syndrome after withdrawal of neuroleptic occurs more frequently in elder women or patients with mood disorders than those with schizophrenia. Dopamine blockade in basal ganglia by chlorpromazine and haloperidol neuroleptics appears to cause the extra-pyramidal symptoms such as Parkinsonism, acute muscular dystonias (spasm of muscles of tongue, face, neck, back), akathisia (motor restlessness not anxiety), malignant neuroleptic syndrome (catatonia, stupor, fever, unstable blood pressure, myoglobinemia), perioral syndrome and tradive dyskinesia (purposeless involuntary oral-facial dyskinesia, choreoathetosis or dystonia). Atypical neuroleptics (clozapine, risperidone, olanzapine, quetiapine, aripiprazole & ziprasidone) have weak D_2 blocking but potent 5-HT_2 antagonistic activity and are not associated with extra-pyramidal side effects. Age-associated diseases are to be distinguished from the Ageing process itself because all adult animals age, save for a few rare exceptions, but not all adult animals experience all age-associated diseases. Ayurveda describes various rejuvenatives therapies with the help of special class of medicinal preparations called Rasayana that are believed to rebuild the body, mind, prevent degeneration and postpone ageing or rather reverse the ageing process. Amalakayas Rasayana is one among the many Rasayana formulations mentioned in Ayurvedic classical text Charaka Samhita for the treatment of ageing related disorder and used by Ayurvedic physicians clinically to treat ageing related disorders[2].

Alzheimer's Disease

Alzheimer's disease is a brain disorder named after German physician Aloes Alzheimer, who first described it in 1906[3]. Alzheimer's disease (A. D.) is the most common form of the dementia which occurs among the older people above the age of 60 years. Alzheimer's is characterized by massive loss of neurons and disrupted signalling between cells in the brain. Language, disorientation (include easily getting lost), loss of motivation but not human ageing are Alzheimer's sign and symptoms. The disease can be diagnosed postmortem by observing tangles inside and senile plaques outside cells throughout the brain. The major component of the plaque is a small, 40/42-amino acid peptide amyloid-beta (Aβ). Aβ, causative agent in A. D. was first suggested as the amyloidal hypothesis about 15 years ago and is now widely accepted among scientific community. Aβ is an elusive entity whose chemical and biological action has been difficult to understand. It is not very soluble, cannot crystallize and has highly changeable structure in a solution[4,5]. The studies have indicated that as Alzheimer's disease progresses, neurofibrillary tangles and also the plaques spread throughout the brain starting in the neocortex. Fig. 1 represents that abnormal cluster of protein fragments in between plaques and nerve cell.

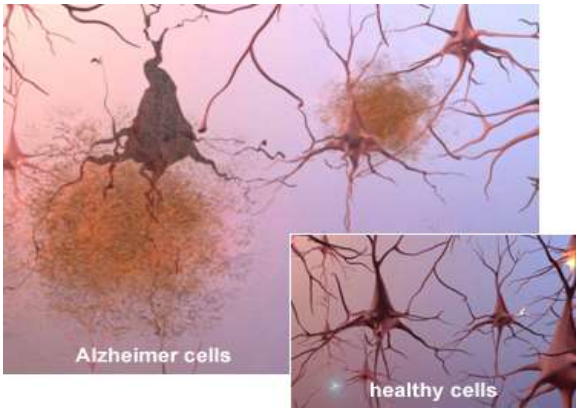

Figure 1: Plaques, abnormal clusters of protein fragments, build up between nerve cells. Dead and dying nerve cells contain tangles, which are made up of twisted strands of another protein. By the final stage, damages widespread and brain tissue shrunk significantly.

Stages of Alzheimer's disease

Stages give a quick assessment of the differences and the various stages of Alzheimer's disease. It typically progresses from early-stage disease characteristics, to middle-stage, to, finally, late-stage[6].

Effects of ageing on memory but not AD

- Forgetting things occasionally
- Misplacing items sometimes
- Minor short-term memory loss
- Not remembering exact details

Early stage Alzheimer's disease

- Not remembering episodes of forgetfulness
- Forgets names of family or friends
- Changes may only be noticed by close friends or relatives
- Some confusion in situations outside the familiar

Middle stage Alzheimer's disease

- Greater difficulty remembering recently learned information

- Deepening confusion in many circumstances
- Problems with sleep
- Trouble knowing where they are

Late stage Alzheimer's disease:

- Poor ability to think
- Problems speaking
- Repeats same conversations
- More abusive, anxious, or paranoid.

Aetiology of Alzheimer's disease

Genetics factors, cholinergic factor, neuroinflammation, neurotransmitter system are the causes of Alzheimer's disease.

Genetic Factor

The genetic heritability of Alzheimer's disease (and memory components thereof), based on reviews of twin and family studies, range from 49% to 79%. Around 0.1% of the cases are familial forms of autosomal (not sex-linked) dominant inheritance, which have an onset before age 65. This form of the disease is known as early onset familial Alzheimer's disease. Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilins 1 and 2. Most mutations in the APP and present genes increase the production of a small protein called Aβ42, which is the main component of senile plaques. Some of the mutations merely alter the ratio between Aβ42 and the other major forms—particularly Aβ40—without increasing Aβ42 level[7].

Cholinergic Factor

In Alzheimer's disease progress, acetylcholine decreases in the area of brain associated with amyloid deposition. Studies have shown the involvement of neurotransmitter acetylcholine in Alzheimer's disease resulting into disproportionate deficiency of acetylcholine. It has been documented that markers for cholinergic neurons, acetyl choline transferase and acetylcholine esterase are responsible for acetylcholine (ACh) synthesis and its degradation respectively decreases in the cortex and hippocampus area of the brain involved in cognition and memory[8]. The study has demonstrated that the resultant decrease in acetylcholine dependant neurotransmission is associated with the functional deficit of A.D.[9]. The use of cholinesterase inhibitors in the treatment of patient with Alzheimer disease has been found to be better successful strategy[10,11]. Cholinesterase inhibitors are administered to enhance cholinergic function[12].

Neuroinflammation

Inflammation clearly plays critical role in a pathogenesis of Alzheimer's disease. Damaged neurons and neurites and highly insoluble β-amyloid peptide deposits neurofibrillary tangles provide stimuli for inflammation. Studies comparing the effects of the chronic neuroinflammation, produced by infusing the proinflammagen lipopolysaccharides (LPS) into the hippocampus of rats, on memory have supported the theory that effect of the NSAIDs on chronic neuroinflammation are aged dependent.

Neurotransmitter System

Excessive stimulation of Glutamate receptor, in particular the N-methyl-D-aspartate (NMDA), seems intimately involved in the death of brain of forebrain cholinergic neurons. To the degree that abnormal glutamatergic function is causative in Alzheimer's disease, effective pharmacologic antagonism of the NMDA receptor, particularly by open channel antagonists may be able to slow the progression of Alzheimer's disease[13]. Table 1 gives doses, drug classes and mechanism and side effect of medicines for Alzheimer's disease[14].

Curcuma longa L. (Zingiberaceae), *Bacopa monniera Wettst.* (Scrophulariaceae**),** *Centella asiatica L.* (Umbelliferae), *Ginkgo biliba L.* (Ginkgoaceae), *Salvia officinalis (Lamiaceae), Rosmarinus officinalis* (Lamiaceae), *Matricaria recutita* (Asteraceae), *Melissa officinalis L.* (Lamiaceae), *Glycyrrhiza glabra* (Fabaceae), *Euphorbia royleana boiss* (Euphorbiaceae), *Crocus Sativus* (Iridaceae), *Eclipta alba(*Asteraceae)[15], medicinal plants are used for treatment of Alzheimer's disease.

Parkinson's Disease

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder with an estimated prevalence of 31 to 328 per 100,000 people worldwide. It is estimated that more than 1 percent of the population over age 65 are afflicted with PD; incidence and prevalence increases with age. P D is caused by idiopathic degeneration of dopamine-producing cells in the substantia nigra, located in the midbrain. Three "cardinal signs" of PD are resting tremor, cogwheel rigidity, and bradykinesia. Postural instability, typically a late finding in PD, is the fourth cardinal sign. Additional common findings are asymmetrical onset of symptoms and symptomatic response to L-dopa (levodopa). Diagnosis of PD is problematic because of the lack of a dopamine. The diagnosis is generally made clinically, although up to 25 percent of patients with clinical diagnoses of PD have received different pathological diagnoses at autopsy[16]. The elder patient with Parkinson's disease characterized by rigidity, tremor, bradykinesia, and hypokinesia with secondary manifestations like expression less face, defective posture & shuffling gait due to degeneration of neurons in nigrostriatal dopaminergic tract and excessive secretion of saliva (sialorrhoea) and frontotemporal dementia due to increased cholinergic transmission, is more susceptible to the adverse effects (postural hypotension, ventricular dysrhythmias and psychiatric effects) of levodopa[17]. Environmental toxin (4-methyl-4-phenyltetrahydro pyridine) and genetic factors may accentuate induction of lipid peroxidation and

disturbance of Ca^{2+} homeostasis, ageing induced defect in mitochondrial electron transport chain in dopaminergic neurons of nigrostriatal pathway by impairing energy metabolism and manifestations similar to Parkinson's disease. Table 2 provides medicine for Parkinson's disease[18].

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease that is promoted by lifestyle-related diseases, such as hypertension, dyslipidemia, and diabetes. The rennin angiotensin system has been demonstrated to play a critical role in the initiation and progression of atherosclerosis, thereby contributing to development of cardiovascular diseases. Angiotensin II (Ang II), a major substrate in RAS, stimulates atherosclerosis through various deleterious effects such as endothelial dysfunction, cellular proliferation and inflammation. Reactive oxygen species play a major role in the athero-promoting actions of Ang II.

In fact, recent basic and clinical studies demonstrated that pharmacological inhibition of renin-angiotensin system is effective in prevention of atherosclerotic diseases.

Elucidation of molecular mechanism of chronic inflammation should lead to development of effective strategies against lifestyle-related diseases[20]. Chest pain, shortness of breath, dizziness, weakness, trouble speaking are sign and symptoms[21]. Dietary lipids, tobacco use, physical inactivity, metabolic syndrome and obesity are the causes of Atherosclerosis Disease. Table 3 shows classes of drugs and ranges of dosage for Atherosclerosis disease[22].

Osteoarthritis

Osteoarthritis, the most common form of joint disease, is characterized by erosion of articular cartilage. The joints most often affected by OA are the knees, hips, spine, and hands, although other joints may be involved. OA is usually classified either as primary (idiopathic) or secondary. Pain, stiffness, and decreased range of motion of affected joints, spasm are the sign and symptoms[24]. Being overweight, getting older, joint injury, joints are not properly formed, a genetic defect in joint cartilage, stress on the joints from certain jobs and playing sport are the cause of Osteoarthritis. Table 4 provides medicines for the treatment for osteoarthritis[25].

Aloe barbadensis (Liliaceae), *Withania somnifera* Linn. (Solanaceae), *Piper nigrum* Linn. (Piperaceae), *Actaea racemosa* Linn. (Ranunculaceae), *Uncaria tomentosa (Rubiaceae), Zingier officinale* (Zingiberaceae), *Calotropis procera* Linn. (Asclepiadaceae), *Ficus bengalensis* Linn. (Moraceae), *Cedrus deodara* (Pinaceae), *Barringtonia racemosa* Linn. (Lecythidaceae), *Mangifera indica* Linn. (Anacardiaceae), *Tinospora cordifolia* Linn. (Menispermaceae), *Ncytanthes arbortristis* Linn. (Oleaceae), *Hemidusmus indicus* Linn. (Asclepiadacea), *Vitex negundo* Linn. (Verbanaceae), *Cissampelos pareira* Linn. (Menispermaceae), *Ammania baccifera* Linn. (Lythraceae), *Terminalia paniculata* Roxb. (Combretaceae), *Justicia gendarussa* Linn. (Acanthaceae), *Cleome gynandra* Linn. (Capparaceae), *Leucas aspera* Linn. (Lamiaceae), *Premna serratifoli* Linn. (Verbenacea), *Strychnos potatorum* Linn. (Loganiaceae) and *Terminalia chebula* Retz. (Combretaceae) are medicinal plants used for treatment of Rheumatoid arthritis disease[33].

Table 1: Medicines for Alzheimer's disease

Drug Name	Doses	Drug Type & Use	Mechanism	Side Effect
Memantine	Tablet: Initial dose of 5 mg once a day • May increase dose to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day) at minimum 1-week intervals. If well tolerated •Extended-release tablet: Initial dose of 7 mg once a day; may increase dose to 14mg/day, 21mg/day, and 28 mg/ day at minimum 1-week intervals if well tolerated.	N-methyl D-aspartame (NMDA) antagonist is prescribed to treat symptoms of moderate to severe Alzheimer's.	It blocks the toxic effects associated with excess glutamate and regulates glutamate activation.	Dizziness, headache, constipation, confusion
Galantamine	Tablet: Initial dose of mg/day (4 mg twice a day) • May increase dose to 16 mg/day (8 mg twice a day) and 24 mg/day (12 mg twice a day) at minimum 4-week intervals if well tolerated •Oral solution: same dosage as above. •Extended-release capsule: same dosage as above but taken once a day.	Cholinesterase inhibitor is prescribed to treat symptoms of mild to moderate Alzheimer's disease.	It prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain.	Nausea, vomiting, diarrhea, weight loss, loss of appetite.

Rivastigmine	Capsule: Initial dose of 3 mg/day (1.5 mg twice a day) • May increase dose to 6 mg/day (3 mg twice a day), 9 mg (4.5 mg twice a day), and 12 mg/day (6 mg twice a day) at minimum 2-week intervals if well tolerated • Patch: Initial dose of 4.6 mg once a day; may increase to 9.5 mg once a day and 13.3 mg once a day at minimum 4-week intervals if well tolerated • Oral solution: Initial dose of 3mg/day (1.5mg twice a day)	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate Alzheimer's (patch is also used for severe Alzheimer's disease)	It prevents the breakdown of acetylcholine and butyrylcholine (a brain chemical similar to acetylcholine) in the brain	Nausea, vomiting, diarrhea, weight loss, loss of appetite, muscle weakness
Donepezil	Tablet: Initial dose of 5 mg once a day. • May increase dose to 10mg/day after 4-6 weeks. If well tolerated, then to 23 mg/day after at least 3 months. •Orally disintegrating tablet: same dosage as above. • 23-mg dose available as brand-name tablet.	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate, and moderate to severe Alzheimer's disease.	It prevents the breakdown of acetylcholine in the brain	Nausea, vomiting, diarrhea

Table 2: Medicines for Parkinson's disease

Drugs class	Dosage in milligram (mg)	Typical treatment regimen	Adverse effect	Indication
Anticholinergics Benztropine (Cogentin), trihexyphenidyl (Artane)	0.5mg, 1mg, 2mg tablet 2.5mg tablet, 25mg/5ml elixir	0.5mg, 2mg, 2 or 3 times daily 1-2mg, 2 or 3 times daily	Dry mouth, dry eyes, constipation, hypotension, cognitive impairment, urinary retention	They are useful for symptomatic control of Parkinson's disease (benefits are mild to moderate); associated with more adverse effects than other drugs
Carbidopa/levodopa Immediate- and sustained release Carbidopa/levodopa (Sinemet)	10/100mg 25/100mg 25/250mg	150–1000 mg of levodopa total daily dose (divided 3-4 times)	Nausea, somnolence, dyskinesia, hypotension, hallucinations	Levodopa is the most effective medication and remains the primary treatment for symptomatic Parkinson's disease; There is no added benefit for motor complications with sustained release versus immediate-release preparations
COMT inhibitors Entacapone (Comtan) Tolcapone (Tasmar)	200mg 100,200mg	200 mg 4–8 times daily (with each levodopa dose) 100 mg up to 3 times daily	Bright orange urine, Diarrhea; exacerbates levodopa adverse if dyskinesia appears; rare liver failure (liver function monitoring needed).	They are useful for man Ageing motor fluctuations ("wearing-off" effect) in patients taking levodopa; levodopa dose may need to be reduced.
Dopamine agonists Bromocriptine (Parlodel) Pergolide (Permax) Pramipexole (Mirapex) Ropinirole (Requip)	0.25, 0.5, 1, 2, 3, 4, 5mg	9–24 mg total daily dose (divided 3–4 times)	Nausea, headache, dizziness Somnolence; hallucinations; nausea; edema; fibrosis of cardiac valves, lung and retroperitoneum; retroperitoneal and pulmonary fibrosis, Nausea, sleep attacks, edema, hallucinations, hypotension	They are useful for early and advanced disease It is useful for the initial treatment of parkinsonism and as adjunct therapy in patients taking levodopa.
MAO-B inhibitors Selegiline (Eldepryl) Rasagaline (Azilect)	5mg 0.5mg, 1.0mg	5 mg once or twice a day 1 mg once/day	Nausea, insomnia, drug interactions with other MAO inhibitors/tyramine Weight loss, hypotension, dry mouth with Parkinson's disease and motor fluctuations, drug interactions with other MAO inhibitors/tyramine	Useful for symptomatic control of Parkinson's disease (benefits are mild to moderate) and as adjuvant therapy for patients Weight loss, hypotension, dry mouth,
NMDA receptor inhibitor Amantadine (Symmetrel)	100 mg capsules; 50mg/5ml syrup	100 mg 2–3 times Daily	Nausea, hypotension, hallucinations, confusion, edema	It is useful for treating akinesia, rigidity, tremor & dyskinesia.

Mucuna pruriens (Fabaceae) is a medicinal plant used for treatment of Parkinson's disease[19].

Table 3: Medicines for Atherosclerosis Disease

Drugs class	Usual recommended starting daily dosage	Dosage range
Statins		
Lovastatin	20mg	10-80 mg
Pravastatin	40mg	10-80mg
Simvastatin	20-40mg	5-80mg
Fluvastatin	40mg	20-80mg
Fibrates		
Fenofibrate	48-145mg	48-145mg
Gemfibrozil	1200mg	1200mg
Fenofibric acid	45-135mg	45-135mg
Niacin		
Immediate-release	250mg	250-3000mg
Extended-release	500mg	50mg 0-2000mg
Bile acid sequestrates		
Cholestyramine	8-16gm	4-24gm
Colestipol	2gm	2-16gm
Colesevelam	3.8gm	3.8-4.5gm
Combination therapies (single-pill)		
Ezetimibe/simvastatin	10/20mg	10/10mg to10/80mg
Extended-release niacin/simvastatin	500/20mg	500/20 to 1000/20mg

Arjun *(Terminalia arjuna)* and Zafran *(Corcus sativus*) are medicinal plants used for treatment of atherosclerosis[23].

Table 4: Medicines for Osteoarthritis

Drug class	Drug	Dosages	Side effect	Caution & Contraindication
Simple analgesic	Paracetamol	0.5 – 1 gm, 6 – 8hourly Max: 4 gm/day	Rare but hypersensitivity including skin rash may occur	Hepatic impairment Alcohol dependence
Nonselective NSAIDs	Ibuprofen	400 – 800 mg, 6 – 8-hourly Max: 3200 mg/day	Peptic ulcer, GI bleed, Platelet dysfunction, Renal impairment, Hypertension, Allergic reaction in susceptible individuals. It increase in CVS Events.	Gastro duodenal ulcer Asthma Bleeding disorder Renal dysfunction Ischemic heart disease Cerebrovascular disease Inflammatory bowel disease
	Mefenamic acid	250 – 500 mg, 6 – 8-hourly Max: 1500 mg/day		
	Diclofenac sodium	50 – 150 mg daily, 8 – 12-hourly Max: 150 mg/day		
	Meloxicam	7.5 – 15 mg daily Max: 15 mg/day		
	Naproxen	250 – 500 mg, 12-hourly Max: 1500 mg/day		
	Naproxen sodium	275 – 550 mg, 12-hourly Max: 1650 mg/day		

Selective COX-2 inhibitors	Celecoxib	200 mg daily Max:200mg/day (Recommended daily maximum dose is 200 mg or 400 mg Q.I.D for inflammatory arthritis)	Renal impairment Allergic reaction in susceptible individuals It increases in CVS events.	Ischemic heart disease Cerebrovascular disease Contraindicated in hypersensitivity to sulfonamides
	Etoricoxib	60 mg daily Max: 90 mg/day	Hypertension Renal impairment It increases in CVS events.	Uncontrolled hypertension Ischemic heart disease and Cerebrovascular Diseases.
Weak Opioid	Tramadol	50 – 100 mg, 6 – 8-hourly Max: 400 mg/day	Dizziness, Nausea, Vomiting Constipation and Drowsiness	Risk of seizures in patients with history of seizures & with high doses, In elderly, start at lowest dose (50 mg) & maximum of 300 mg daily.
Combination of opioid & paracetamol	Paracetamol 325 mg + tramadol 37.5 mg (Ultracet)	1 – 2 tablets, 6 – 8-hourly Max: 8 tablets/day	Nausea, Vomiting and Drowsiness	Hepatic impairment, Renal impairment, Alcohol dependence and Epilepsy.

Zingiber officinale Roscoe. (Zingiberaceae), *Emblica officinalis, Withania somnifera, Tribulus terrestris* Linn. (Zygophyllaceae) are medicinal plants used for treatment of osteoarthritis[26].

Table 5: Medicines for osteoporosis

Medication	Typical dosage	Route	Fracture type
Estrogen, with or without progesterone	0.625 mg daily	Oral	Hip, vertebral, Non vertebral
Alendronate (Fosamax) Ibandronate (Boniva) Risedronate (Actonel Raloxifene (Evista)	70 mg weekly 150 mg monthly 35 mg weekly 60 mg daily	Oral Oral Oral Oral	Hip, vertebral and Non vertebral Vertebral Hip, vertebral, Non vertebral and vertebral
Ibandronate Zoledronic acid (Reclast) Calcitonin (Miacalcin) Teriparatide (Forteo)	3 mg every three months for four doses 5 mg annually for three doses 200 IU daily 20 mg daily up to two years	Intravenous Intravenous Nasal subcutaneous	It increases bone mineral density, but fracture end point is not evaluated Hip, vertebral and non vertebral Vertebral Vertebral and Non vertebral

Astragalus membranaceus, Cornus officinalis, Commiphora mukul, Dioscorea batatas, Drynaria baronii, Glycyrrhiza glabra, Lycium chinense, Epimedium leptorrhizum, Glycine max, Nigella sativa, Notopterygium forbesii, Zingiber officinale, Withania somnifera, Terminalia arjuna, Psoralea corylifolia, Sambucus williamsii, Panax ginseng, Sambucus nigra, Punica granatum, Podophyllum emodi are medicinal plants used for treatment of osteoporosis[29].

Table 6: Medicines for Rheumatoid arthritis

Drug	Doses	Route
Adalimumab	40mg every other week	subcutaneous (under the skin) injection
Certolizumab pegol	400mg at weeks 0, 2 and 4 (given as two injections of 200mg) , and then 200mg every other week	subcutaneous injection
Etanercept	25mg twice a week, or 50mg weekly	subcutaneous injection
Golimumab	50mg monthly	subcutaneous injection
Infliximab	3mg per kg of body weight, repeated 2 weeks and 6 weeks after the first infusion, then every 8 weeks	subcutaneous injection

Table 7: Medicines for hypertension

Medication	Initial dose	Recommended maximum dose
Thiazide diuretics		
Hydrochlorothiazide	12.5 mg daily	25 mg daily
Chlorthalidone	12.5 mg daily	25 mg daily
ACE inhibitors		
Lisinopril	10 mg daily	40 mg daily
Combination lisinopril/HCTZ	20/12.5 mg x ½ tab daily	20/12.5 mg x 2 tabs daily
Angiotensin receptor blockers		
Losartan	25 mg/day in 1–2 doses	100 mg/day in 1–2 dose
Calcium channel blockers		
mlodipine	2.5 mg daily	10 mg daily
Beta blockers		
Metoprolol IR (tartrate)	25 mg twice daily	100 mg twice daily
Metoprolol LA (succinate)	50 mg daily	200 mg daily
Atenolol	25 mg/day in 1–2 doses	100 mg/day in 1–2 doses

Allium sativum (Alliaceae), *Annona muricata* (Annonaceae), *Apium graveolens* (Apiaceae), *Castanospermum austral* (Fabaceae), *Daucus carota* (Umbelliferae), *Fuchsia magellanica* (Onagraceae), *Avena sativa* (Gramineae), *Blond psyllium* (Plantaginaeae), *Capparis cartilaginea* (Cappaaraceae), *Cassia absus* (Caesalpiniaceae), *Carum copticum* (Umbelliferae), *Cassia occidentalis* (Caesalpiniaceae), *Glycine max* (Fabaceae), *Hibiscus sabdariffa* (Malvaceae), *Lavandula stoechas* (Lamiaceae), *Lycopersicon esculentum* (Solanaceae), *Commelina virginica* (commelinaceae), *Musanga cecropiaceae* (Cecropiaceae), *Ocimum basilicum* (Lamiaceae), *Pinus pinaster* (Pinaceae), *Uncaria rhynchophylla* (Rubiaceae), *Vitex doniana* (Verbenaceae), *Zingiber officinale* (Zingiberaceae), *Rauwolfia serpentine* (Apocynaceae) and *Sesamum indicum* (Pedaliaceae) are medicinal plants used for treatment of hypertension[39].

Osteoporosis

Osteoporosis is defined as a bone mineral density of 2.5 standard deviation or more below the mean peak bone mass. The risk of osteoporosis fractures can be reduced with lifestyle changes and in those with previous osteoporosis related fractures medications[27]. Osteoporosis is called the "silent disease" because bone is lost with no signs. Table 5 shows medicines for treatment of osteoporosis[28].

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is chronic, progressive, disabling autoimmune disease characterized by systemic inflammation of joints, dam Ageing cartilage and bone around the joints. It is a systemic disease which means that it can affect the whole body and internal organs such as lungs, heart and eyes. Although numbers of synthetic drugs are being used as standard treatment for rheumatoid arthritis but they have adverse effect that can compromise the therapeutic treatment. Unfortunately, there is still no effective known medicinal treatment that cures rheumatoid arthritis as the modern medicine can only treat the symptoms of this disease that means to relieve pain and inflammation of joints. It is possible to use the herbs and plants in various forms in order to relieve the pain and inflammation in the joints. Joint swelling, pain, morning joint stiffness, poor sleep, fatigue, loss of weight and feeling of having flu are the sign and symptoms of rheumatoid arthritis[30]. The exact causes of RA are unknown, but research has shown that several factors may contribute to its development: family history, gender, hormones, age, environment and smoking[31]. Table 6 provides medicines for the treatment of rheumatoid arthritis[32].

Hypertension

Hypertension or high blood pressure is a condition in which the blood pressure in the arteries is chronically elevated. With every heart beat, the heart pumps blood through the arteries to the rest of the body. Blood pressure is the force of blood that is pushing up against the walls of the blood vessels. The normal level for blood pressure is below 120/80, where 120 represent the systolic measurement (peak pressure in the arteries) and 80 represents the diastolic measurement (minimum pressure in the arteries). Blood pressure between 120/80 and 139/89 is called pre-hypertension (to denote increased risk of hypertension), and a blood pressure of 140/90 or above is considered hypertension[34]. Hypertension (HTN) or high blood pressure (BP) is a chronic medical condition in which the BP in the arteries is elevated. It is classified as either primary (essential) or secondary.

About 90 to 95% of cases are termed primary HTN, which refers to high BP for which no medical cause can be found[35].

The remaining 5 to 10% of cases, called secondary HTN, are caused by other conditions that affect the kidneys, arteries, heart, or endocrine system[36].

Smoking, obesity or being overweight, diabetes, sedentary lifestyle, lack of physical activity, high levels of salt intake (sodium sensitivity), insufficient calcium, potassium, and magnesium consumption, vitamin D deficiency, high levels of alcohol consumption, stress, Ageing, medicines such as birth control pills, genetics and a family history of hypertension and chronic kidney disease are the causes of hypertension[37].

Table 7 provides medicinal treatment of hypertension[38].

This article summarizes the nature and extent of the changes with ageing and neural system, possible treatment approaches and a potential mechanism involving chronic neuroinflammation to explain the pattern of neuropathologic changes in old ages.

REFERENCES

1. Kirkwood T, Ebrahim S Kalache A, Mechanism of ageing in epidemiology in old age, (BMJ Publishing group, London), 3, 1999, 275-291.
2. Ian SH, The psychology of ageing; an introduction, Jessica Kingley Publishers, London, 1, 1998, 47-56.
3. Samarakoon SMS, Chandola HM, Ravishankar B, Ashok BK Gupta Varun B, Evaluation of adaptogenic activity profile of a compound Ayurvedic formulation-Amalayakas Rasayana, Indian journal of Traditional Knowledge, 2011, 661-667.
4. Singh N, Pandey BR, Verma P, An overview of phytotherapeutic approach in prevention and treatment of Alzheimer's syndrome and dementia, International Journal of Pharmaceutical Science Drug Research, 3, 2011, 162-72.
5. Rauk A, The chemistry of Alzheimer's disease, International Journal of Ayurveda and Pharma Research, 38, 2009, 2698-715.
6. Evaluating prescription drugs used to treat: Alzheimer's disease comparing effectiveness, safety and price, Consumer Reports Drugs Effectiveness Review Project [cited 2012 May].
7. Selkoe DJ, Podlinsy MB, Deciphering the genetic basis of Alzheimer's disease, Annual Review of Genomics and Human Genetics, 3, 2002, 67-99.
8. Nordberg A, Svensson AL, Cholinesterase inhibitors in the treatment of Alzheimer's disease: A comparison of tolerability and pharmacology, Drug Safety, 19, 1998, 465-80.
9. Weinstock M, Selectivity of cholinesterase inhibition: Clinical implication for the treatment of Alzheimer's disease, CNS Drugs, 12, 1999, 303-7.
10. Francis PT, Palmer AM, Snape M, The cholinergic hypothesis of Alzheimer's disease: A review of progress, Journal of Neurology Neurosurgery and Psychiatry, 54, 1999, 137-47.
11. Wright CI, Geula C, Mesulam MM, Neurological cholinesterase in the normal brain and in Alzheimer's disease: Relation to plaques, tangles and patterns of selective vulnerability, Annals of Neurology, 34, 1999, 373-84.
12. Gary L. Wenk, Neuropathologic Changes in Alzheimer's Disease, Journal of Clinical Psychiatry, 64 2006, 7-10.
13. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, Finch CE, Frautschy S, Griffin WS, Hampel H, Hull M, Landreth G, Lue L, Mrak R, Mackenzie IR, McGeer PL, O'Banion MK, Pachter J, Pasinetti G, Plata-Salaman C, Rogers J, Rydel R, Shen Y, Streit W, Strohmeyer R, Tooyoma I, Van Muiswinkel FL, Veerhuis R, Walker D, Webster S, Wegrzyniak B, Wenk G, Wyss-Coray T, Inflammation and Alzheimer's Disease Neurobiology Ageing, 21, 2000, 383-421.
14. Alzheimer's disease education and referral (ADEAR) Center, *www.nia.nih.gov/alzheimers* NIH Publication No. 08-3431, 2014.
15. Patel K, Pramanik C, Patil S, Vibha C, Ayurvedic approach with a prospective to treat and congitive disease: a review, World Journal of Pharmacy and Pharmaceutical Science, 3, 2014, 234-252.
16. Cindy B. Levine, Kyle R, Fahrabch A, Diagnosis and treatment of Parkinson's disease: a systematic review of the literature, 2003.
17. Rao SS, Laura A, Hofmann, Shakil A, Parkinson's disease: diagnosis and treatment, 74, 2006, 12.
18. Houghton D, Hurtig H, Metz S, Brandabur M, Parkinson's Disease Medication, 2012, 5-64.
19. Christian M, Huisden, Modern-day naturopathic medicine and traditional Ayurveda in a combined attack against Parkinson's Disease, Academic Journal of Suriname, 1, 2010, 53-58.
20. Sata M, Fukuda, D. Chronic inflammation and Atherosclerosis: a critical role for renin angiotensin system that is activated by lifestyle-related disease, Inflammation and Regeneration, 31, 2011, 3.
21. An international atherosclerosis society position paper: Global Recommendations for the Management of Dyslipidemia, 8, 2014, 29-60.
22. Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW, Shepherd MD, Seibel JA, American association of clinical endocrinologists guidelines for management of dyslipidemia and prevention of atherosclerosis, 18, 2012, 18.
23. Rabbani AS, Unani drugs in the management of cardiovascular disease: a review on Pharmacological Studies of arjun and zafran, International Journal Research in Ayurveda and Pharmacy, 4, 2013, 463-467.
24. Keith S, Osteoarthritis: diagnosis and treatment, American Academy of Family Physicians, 85, 2012, 49-56.
25. Management of osteoarthritis (Second Edition). www.moh.gov.my
26. Chopra A, Saluja M, Tillu G, Venugopalan A, Sarmukaddam S, Raut KA, Bichile L, Narsimulu G, Handa R, Patwardhan BA, Randomized controlled exploratory evaluation of standardized Ayurvedic formulations in symptomatic osteoarthritis knees: a Government of India NMITLI Project, 2010-12.
27. Rajagopal PL, Premaletha K, Kiron SS, Sreejith KR, Medicinal plants in osteoporosis-a review, International Journal of

Advances in Pharmacy, Biology and Chemistry, 4, 2013, 605.

28. Sweet GM, Sweet JM, Jeremiah MP, Galazka S, Diagnosis and treatment of osteoporosis, American Academy of Family Physicians, 3, 2009, 201-202.
29. Rajagopal PL, Premaletha K, Kiron SS, Sreejith KR, Medicinal plants in osteoporosis-a review, International Journal of Advances in Pharmacy, Biology and Chemistry, 4, 2013, 605-608.
30. Kaur A, Nain P, Nain J, Herbal plants used in treatment of rheumatoid arthritis: a review, International Journal of Pharmacy and Pharmaceutical Sciences, 4, 2012, 44.
31. The rheumatoid arthritis society causes, symptoms and treatment, 2015. arthritis.ca/publications.
32. The Biologics Story So Far, 2013, www.nras.org.uk.
33. What is hypertension? What causes hypertension? Available from: URL: www.medicalnewstoday.com/articles /150109.php.2012.
34. Carretero OA, Oparil S, Essential hypertension, Part I: Definition and etiology, Circulation 101, 2000, 329-35.
35. Beevers G, Lip GY, O'Brien E. ABC of hypertension: The pathophysiology of hypertension. British Medical Journal, 322, 2000, 912-6.
36. What is hypertension? What causes hypertension? Available from: URL: www.medicalnewstoday.com/articles/150109.php.2012.
37. Hypertension Diagnosis and Treatment Guideline. Group Health Cooperative 2014.
38. Sharma I, Parashar B, Kumar, DH, Sharma R, An ayurvedic arena for hypertension treatment, Asian Journal of Pharmaceutical Research, 2, 2012, 54-58.

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